APTI Women's Forum

# Newsletter

## The Science of Inflammation: Triggers, Impact, and Management



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## The Science of Inflammation: Triggers, Impact, and Management

# Editor's Note


## Prof. Vandana B. Patravale

Chief Editor,
APTI Women's Forum Newsletter


**Dear Readers,**

This edition of our newsletter is dedicated to shedding light on inflammation, a biological response intended for protection, which oscillates between promoting healing and causing damage depending on duration and intensity. The theme for May-August 2025 APTI women's newsletter is "**The Science of Inflammation: Triggers, Impact, and Management**". This edition of our newsletter examines the functions of inflammation across various circumstances, ranging from dermatological to systemic diseases, and from cellular signaling to overall health.

The newsletter provides comprehensive information on the signaling pathways, the inflammation cascade, and management strategies. There are articles uncovering the role of environmental pollutants, damage - associated molecular patterns (DAMPs), immune dysregulation, and linoleic acid in causing or exaggerating inflammation. Articles exploring inflammation in specific diseases like dry eye disease, Huntington's, Polycystic - Ovary Syndrome (PCOS), and gout are also present for the benefit of researchers working in such areas.

The editorial board is certain that you will get equal interest from reading this issue focused on inflammation as you did from reading our prior APTI Women Forum Newsletters. We express our utmost gratitude to all the authors for their diligent work in making this newsletter very enlightening. I express my gratitude to the whole editorial team for their tireless efforts, which included both the conceptualization and editing of the reviews provided by authors from different parts of the country. I would like to convey my thanks and gratitude to Dr. Vanaja K, Dr. Preeti Suresh, Dr. Shubhini Saraf, Dr. Rashmi Trivedi, Dr. Rakhi Khabiya, and Dr. Suneela Dhaneshwar for providing editorial comments for the articles. Also, thanks to Dr. Clara Fernandes for providing puzzles for the newsletter.

Also, I wish to thank VBP research group, especially Preeya Negi and Vikas Kamble, for all the support rendered for this newsletter.

# APTI Women's Forum
# Editorial Board

# Unseen threats: The inflammatory pathways linking environmental pollutants to chronic diseases

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## Abstract

Toxic environmental contaminants including airborne toxins, heavy metals, and endocrine-disrupting chemicals (EDCs) are among the key causes of the worldwide burden of chronic disease that involves shared mechanisms of inflammation leading to disease onset. These contaminants induce low-grade, chronic inflammation through numerous mechanisms, including the production of reactive oxygen species (ROS), activation of inflammatory signaling pathways, immune dysregulation, and epigenetics. Chronic inflammation has been linked with various conditions such as cardiovascular disease, diabetes, asthma, neurodegenerative disorders, autoimmune diseases, and certain cancers. The review describes how the pollutants trigger inflammatory mechanisms, that is, oxidative stress, immune alterations, and epigenetic alterations. It emphasizes raising awareness of this relationship to allow effective public health measures and regulation to control environmental health hazards.

**Keywords:** Chronic disease, epigenetic changes, environmental toxins, immune dysregulation, inflammation, oxidative stress

## 1. Introduction

Environmental toxins are now significant drivers of chronic disease burden globally, but short of being exceedingly valued for their role as causative agents of systemic inflammation. Massive exposure to harmful contaminants like particulate matter (PM), heavy metals, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), and EDCs through increased urbanization and industrialization over the years has impacted hundreds of millions of human beings around the globe (1). They contaminate air, water, earth, food, and consumer items and form chronic low-level exposure that

that generates disturbance in biological homeostasis. Chronic, low-grade inflammation is one of the most important mechanisms through which the pollutants cause disease pathology. Unlike the reversible protective response of acute inflammation, chronic inflammation results in tissue damage, cellular dysfunction, and disease progression (2). Pollutants may initiate and sustain such an inflammatory response through oxidative stress, activation of pro-inflammatory signaling pathways like Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Mitogen-Activated Protein Kinases (MAPKs), and immune suppression. They also regulate gene expression through epigenetic mechanisms and kill the mitochondria, further increasing inflammation (3). There is emerging evidence of environmental exposure linked with inflammatory conditions such as asthma, cardiovascular disease, diabetes, neurodegenerative disorders, autoimmune disorders, and certain cancers. Yet the molecular mechanism through which it happens has yet to be found (1,2). Understanding of the mechanisms by which environmental poisons cause and sustain inflammation will guide prevention and treatment strategies that are effective, and environmental health will become increasingly pertinent to the prevention of chronic disease as well as to public policy (3).

## 2. Types of environmental pollutants

The environmental pollutants expose human health and the environment to severe risks and effects through air, water, soil, and organism effects. The pollutants as particulate matter in microscopic form, to toxic chemicals, cause remote health effects by way of inflammation, endocrine balance disruption, and long-term disease induction (1).

### 2.1. Air and water contaminants

Air and water contaminants pose important public health dangers by exacerbating systemic as well as cellular-level chronic inflammation and oxidative stress. The four most dangerous air pollutants are fine particulate matter (PM2.5), nitrogen oxides (NOx), ground-level ozone ($O_3$), and carbon monoxide (CO). PM2.5 can infiltrate deep within the lungs, up to a level near alveoli, and into the blood, where it gets absorbed, and activate toll-like receptors (TLRs). This induces NF-κB signaling, which causes the release of pro-inflammatory cytokines like interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α). Prolonged inflammation induced by PM2.5 initiates respiratory disease like asthma and systemic cardiovascular disease (3). NOx gases contribute to smog formation and airway inflammation through MAPKs pathways. Ozone is a strong oxidant that causes damage to lung epithelial cells and enhances cytokine release, impairing lung function. CO has a high affinity for hemoglobin, which binds it to form carboxyhemoglobin and impairs oxygen transport and mitochondrial respiration, and leads to hypoxic injury (1).

In water bodies, toxins such as heavy metals (lead, mercury), pesticides, and drugs become deposited and damage the nervous system and endocrine functions. The toxins disrupt neurotransmitter and hormone receptor transduction of signals, cause mtROS, and maintain NF-κB activation. This causes chronic immune dysregulation and tissue damage and is associated with neurodevelopmental retardation, kidney damage, and hormonal interference in long-term exposure (4).

### 2.2. Endocrine-disrupting chemicals (EDCs)

Endocrine Disrupting Chemicals are outside chemicals that interfere with hormonal homeostasis through the mimicry or opposition of natural hormones. Bisphenol A (BPA), phthalates, and some pesticides are traditional EDCs, which directly bind to nuclear receptors such as estrogen receptors (ERα/β), androgen receptors (AR), and peroxisome proliferator-activated receptors (PPARs). Binding to the receptors causes the regulation of gene expression for reproduction, growth, and metabolism (5). BPA is an agonist on a subset of the estrogen receptor and induces aberrant gene transcription, causing precocious puberty, infertility, obesity, and hormone-sensitive cancer. . EDCs also induce epigenetic modifications such as DNA methylation and histone modification that lead to aberrant gene patterns and probable intergenerational transfer. Exposure elevates mtROS and activates inflammatory signaling (NF-κB, MAPKs), producing chronic low-grade inflammation with increased cytokines IL-6 and TNF-α,

suppressing immune function. Because of extensive application in plastics, cosmetics, and packaging, exposure to EDCs is ubiquitous, with their lipophilicity leading to bioaccumulation and augmented health impacts (2).

### 2.3. Persistent organic pollutants (POPs)

POPs such as polychlorinated biphenyls (PCBs) and DDT are chemically inert, degradation-resistant, and lipophilic chemicals. They are bioaccumulated by the food chain and globally dispersed through atmospheric transport, polluting remote regions. POPs interfere with endocrine systems by binding to receptors like the aryl hydrocarbon receptor (AhR) and thyroid hormone receptors, regulating gene expression for metabolism and immunity. POPs induce mitochondrial damage, increasing mtROS levels, and activating inflammatory signaling pathways like NF-κB and AP-1, leading to chronic inflammation. Long-term exposure to POPs has been linked to cardiovascular disease, diabetes, cancer, neurodevelopmental disorders, and immunotoxicity—dysfunctioning T cells and macrophages, and risking infection and autoimmunity. Far from eliminated despite international efforts such as the Stockholm Convention, POPs are a continuing environmental and health concern since they are stable and long-lasting (6).

## 3. Mechanisms of inflammation induced by pollutants

Environmental toxins play a significant role in the pathogenesis of chronic disease by a number of different biological mechanisms. Figure 1 shows the oxidative stress, induction of pro-inflammatory cascades, immune dysregulation, epigenetic modification, and mitochondrial damage culminating in inflammation and disease pathogenesis (2).

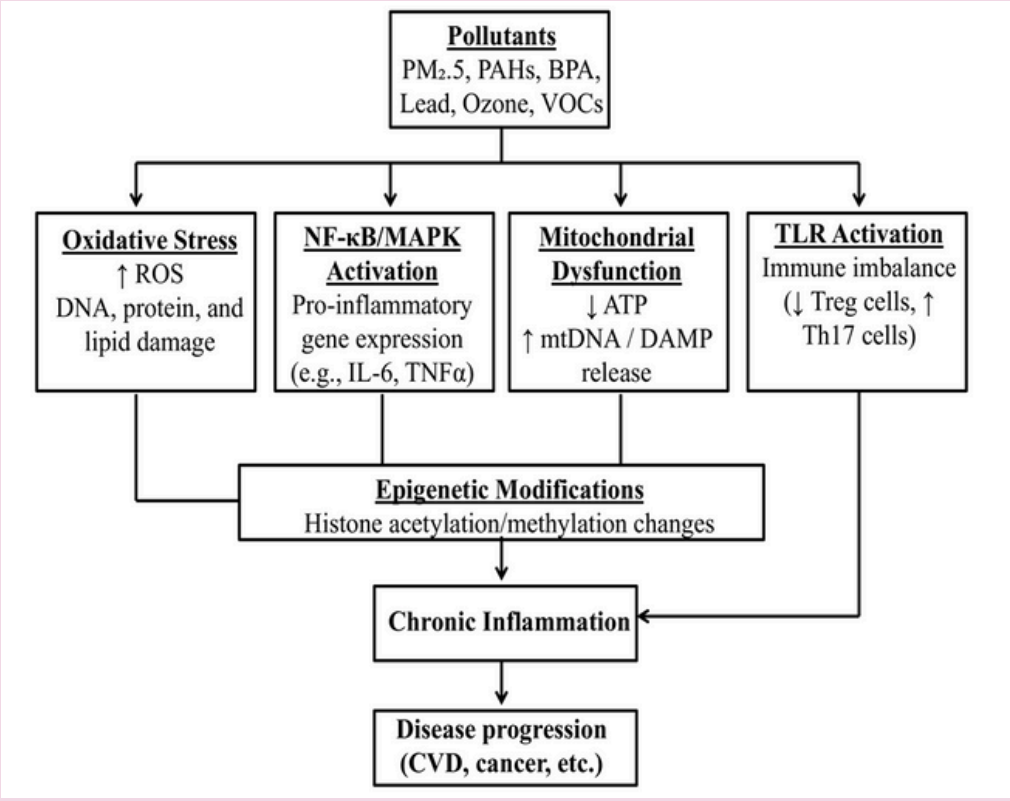


**Figure 1.** Mechanisms of inflammation induced by environmental pollutants

### 3.1. Oxidative stress and reactive oxygen species (ROS) production

We went on to study in more detail how the ambient air pollutants, such as particulate matter (PM), ozone, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) form ROS. ROS are tightly regulated under resting physiological conditions through the antioxidant defense system. However, on exposure to pollutants, this balance is destroyed, and there is oxidative damage to DNA, lipids, and proteins. . This

triggers a cascade of inflammatory signaling and cytokine secretion. Chronic oxidative stress is highlighted now as a shared pathologic mechanism to explain cardiovascular, neurodegenerative, and metabolic disorders. Mitochondrial vulnerability to oxidative damage and resultant positive feedback vicious cycle of ROS production and inflammation were also addressed. Targeted antioxidant therapy is highlighted as an emerging therapy (4,5).

### 3.2. Activation of pro-inflammatory pathways

The section now contains a more elaborate molecular explanation of how pollution leads to NF-κB and MAPK signaling pathways. We explicitly described that activation of NF-κB is mediated through IκB degradation, thus enabling translocation to the nucleus and expression of inflammatory genes. We delineate cross-talk between MAPK cascades and NF-κB, which synergistically augment inflammatory responses. Pathological activation of pathways is linked to asthma pathogenesis, autoimmune diseases, and cancer (2,4,6).

### 3.3. Immune system dysregulation

We expanded the explanation of how toxicants disrupt immune system homeostasis. Heavy metals and PM over-activate immune cells like macrophages and dendritic cells and induce exaggerated cytokine production. We also describe how toxicants disrupt antigen presentation, reduce regulatory T cell (Treg) populations, and induce pathogenic T cell responses (Th17 and Th2) and amplify autoimmunity and allergic diseases. We also added information on how repeated activation of innate immune receptors, such as Toll-like receptors (TLRs), results in autoimmune and inflammatory disease conditions like asthma, rheumatoid arthritis, and multiple sclerosis (1,7).

### 3.4. Mitochondrial dysfunction

This subsection now explains in greater detail how mitochondrial toxicity due to such poisons as diesel exhaust and heavy metals results in dysfunctional electron transport, increased ROS, decreased ATP production, mtDNA release, and damage-associated molecular patterns (DAMPs). These stress signals from mitochondria activate immune receptors and initiate inflammation. We also observe how abnormal mitochondrial dynamics (fusion and fission) result in apoptosis and cellular stress. The interconnectedness of mitochondrial pathology, oxidative stress, and epigenetic deregulation is emphasized to underscore the system-wide impact of environmental toxicants (5,8).

## 4. Environmental pollutants and chronic diseases

Environmental pollutants are the culprits for toxin exposure, and this adds up to chronic inflammation, a major mediator of the disease pathogenesis of such conditions as cardiovascular disease, type 2 diabetes, asthma, Chronic Obstructive Pulmonary Disease (COPD), and neurodegenerative disorders. Table 1 shows the environmental toxins whose elevated inflammatory markers include C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which are like pollutants PM2.5 (9). These inflammatory markers lead to endothelial dysfunction, insulin resistance, and tissue injury. Epidemiologic evidence indicates of higher chronic disease burden among exposed groups. Prevention of health risk due to long-term effects from environmental exposure includes decreasing the pollutant-induced inflammation and reasserting public health policy to curb these risks (7).

**Table 1.** Impact of environmental pollutants on chronic diseases: Unraveling the mechanisms of inflammation

| S. N. | Environmental pollutant | Associated chronic diseases | Molecular mechanisms of inflammation | Ref. |
|---|---|---|---|---|
| 1 | Particulate matter (PM2.5) | Cardiovascular diseases (e.g., hypertension, atherosclerosis), asthma | ROS generation, oxidative stress, endothelial dysfunction, activation of NF-κB and MAPK pathways, cytokine production (IL-6, TNF-α), vascular inflammation | (8) |

| | | | | |
|---|---|---|---|---|
| 2 | Ozone ($O_3$) | Asthma, COPD, and pulmonary fibrosis | Oxidative stress, lipid peroxidation, activation of NF-κB, neutrophilic airway inflammation, increased IL-8, GM-CSF | (9) |
| 3 | Tobacco smoke | COPD, lung cancer, cardiovascular diseases | Chronic oxidative stress, DNA adduct formation, pro-inflammatory cytokines (I1β, TNF-α), activation of MAPK/NF-κB, impaired macrophage function | (10) |
| 4 | Heavy metals (e.g., Lead, Cadmium, Mercury) | Neurodegenerative diseases,renal dysfunction,and cancer | Mitochondrial dysfunction, oxidative DNA damage, misfolded proteins, epigenetic modifications (histone deacetylation), Th17/Treg imbalance, microglial activation | (11) |
| 5 | Polycyclic aromatic hydrocarbons (PAHs) | Cardiovascular disease, lung cancer, and reproductive toxicity | Aryl hydrocarbon receptor (AhR) activation, ROS generation, DNA damage, NF-κB signaling, CYP450 enzyme induction, inflammation-driven carcinogenesis | (12) |
| 6 | Bisphenol A (BPA) | Obesity, type 2 diabetes, and hormone-dependent cancers | Estrogen receptor binding, insulin resistance, adipose inflammation, Th1/Th17 skewing, reduced Tregs, oxidative stress | (13) |
| 7 | Phthalates | Endocrine disorders, reproductive abnormalities, and obesity | PPAR-γ activation, epigenetic modulation, IL-6 and CRP elevation, macrophage infiltration into adipose tissue, and immune dysregulation | (14) |
| 8 | Dioxins | Cancer, autoimmune diseases, and developmental disorders | AhR activation, sustained TLR signaling, IL-6/IL-17 induction, Th17 polarization, immune suppression, and chronic inflammation | (15) |
| 9 | Arsenic | Diabetes, skin and lung cancer, cardiovascular disease | ROS overproduction, mitochondrial dysfunction, NF-κB/STAT3 activation, inflammasome (NLRP3) induction, apoptosis and chronic inflammation | (16) |
| 10 | Formaldehyde | Asthma, nasopharyngeal cancer, leukemia | Direct epithelial toxicity, protein cross-linking, DNA-protein adducts, ROS-mediated airway inflammation, activation of inflammatory transcription factors | (17) |
| 11 | Trichloroethylene (TCE) | Autoimmune diseases, liver and kidney toxicity, cancer | ROS generation, ER stress, hepatocellular inflammation, dysregulation of mitochondrial bioenergetics, altered immune tolerance | (18) |
| 12 | Tetrachloroethylene (PERC) | Hepatic injury, CNS toxicity, reproductive toxicity | Oxidative stress, glutathione depletion, mitochondrial respiration inhibition, cytokine release, disruption of neuronal homeostasis | (19) |

## 5. Future perspective

Follow-up research will attempt to elucidate the intricate molecular mechanisms by which toxins induce chronic inflammation. Biomarkers for previous-in-time exposure will enable improved surveillance and targeted intervention (20). Combining environmental exposure with genetic data can enable precision medicine to inform the prevention of disease. New treatments, such as inflammasome inhibitors and mitochondrial protectants, have the potential to reverse damage from contaminants (21). Increased control of polluting emissions and promotion of clean technology are necessary now more than ever. Special attention has to be paid to vulnerable populations under increased risk of exposure. There has to be public health action in the form of prevention, education, and awareness of environmental health. Increased global collaborative action in science, policy, and community is required to reduce long-term health consequence that goes hand in hand with environmental pollutants (22).

## 6. Conclusion

Environmental toxins are insidious initiators of chronic disease and inflammation everywhere in the world. Through induction of oxidative stress, immune dysregulation, epigenetic modification, and mitochondrial damage, toxins initiate and perpetuate inflammation and cause cardiovascular disease, diabetes, respiratory disease, neurodegenerative disease, autoimmune disease, and cancer. Understanding the toxin-inflammation link redirects our approach to disease prevention, catalyzing a paradigm shift from treatment of symptoms to treatment of environmental causatives. Action next year has to include the integration of scientific knowledge, protection of the environment, health reform, and education to mitigate this pressing global threat. An all-out, interdisciplinary assault on protecting human health and avoiding a disastrous future must be undertaken.

## References


1. Zhang RD, Chen C, Wang P, Fang Y, Jiang LQ, Fang X, Zhao Y, Ni J, Wang DG, Pan HF. Air pollution exposure and auto-inflammatory and autoimmune diseases of the musculoskeletal system: a review of epidemiologic and mechanistic evidence. Environ Geochem Health. 2023;45(7):4087–105.
2. Lee PH, Park S, Lee YG, Choi SM, An MH, Jang AS. The impact of environmental pollutants on barrier dysfunction in respiratory disease. Allergy Asthma Immunol Res. 2021;13(6):850.
3. Tsai HJ, Wu PY, Huang JC, Chen SC. Environmental pollution and chronic kidney disease. Int J Med Sci. 2021;18(5):1121.
4. Guillotin S, Delcourt N. Studying the impact of persistent organic pollutants exposure on human health by proteomic analysis: a systematic review. Int J Mol Sci. 2022;23(22):14271.
5. Dushyant, Balram, Singh G, Kumar N, Narwal S, Dhingra AK. Oxidative Stress in Cardiovascular Diseases: Mechanisms and Exploring Advanced Therapies. Cardiovasc Hematol Agents Med Chem. 2025.
6. Sun L, Sun Z, Wang Q, Zhang Y, Jia Z. Role of nuclear receptor PXR in immune cells and inflammatory diseases. Front Immunol. 2022;13:969399.
7. Reddam A, McLarnan S, Kupsco A. Environmental chemical exposures and mitochondrial dysfunction: a review of recent literature. Curr Environ Health Rep. 2022;9(4):631–49.
8. Leland EM, Zhang Z, Kelly KM, Ramanathan M. Role of environmental air pollution in chronic rhinosinusitis. Curr Allergy Asthma Rep. 2021;21:1–4.
9. Rivas-Arancibia S, Miranda-Martínez A, Rodríguez-Martínez E, Hernández-Orozco E, Valdés-Fuentes M, De la Rosa-Sierra R. Ozone environmental pollution: relationship between the intestine and neurodegenerative diseases. Antioxidants. 2023;12(7):1323.
10. Vilcins D, Cortes-Ramirez J, Currie D, Preston P. Early environmental exposures and life-long risk of chronic non-respiratory disease. Paediatr Respir Rev. 2021;40:33–8.
11. Haidar Z, Fatema K, Shoily SS, Sajib AA. Disease-associated metabolic pathways affected by heavy metals and metalloid. Toxicol Rep. 2023;10:554–70.
12. Yu YY, Jin H, Lu Q. Effect of polycyclic aromatic hydrocarbons on immunity. J Transl Autoimmun. 2022;5:100177.
13. Della Rocca Y, Traini EM, Diomede F, Fonticoli L, Trubiani O, Paganelli A, Pizzicannella J, Marconi GD. Current evidence on bisphenol A exposure and the molecular mechanism involved in related pathological conditions. Pharmaceutics. 2023;15(3):908.
14. Li R, Zheng B, Zhang Y, He L, Ren C, Guan L, Yang H, Tian J, Chen X, Shi D, Zhao L. The impact of phthalates on asthma and chronic obstructive pulmonary disease: a comprehensive analysis based on network toxicology and molecular docking. Front Pharmacol. 2025;16:1566965.
15. Tan J, Gao Y, Xia Y, Sun P, Qin W. Investigating the impact of dioxins, furans, and coplanar polychlorinated biphenyls on mortality, inflammatory states, and chronic diseases: An integrative epidemiological analysis. Ecotoxicol Environ Saf. 2025;289:117463.
16. Haidar Z, Fatema K, Shoily SS, Sajib AA. Disease-associated metabolic pathways affected by heavy metals and metalloid. Toxicol Rep. 2023;10:554–70.
17. Rana I, Rieswijk L, Steinmaus C, Zhang L. Formaldehyde and brain disorders: a meta-analysis and bioinformatics approach. Neurotox Res. 2021;39:924–48.
18. Lash LH. Trichloroethylene: An Update on an Environmental Contaminant with Multiple Health Effects. Annu Rev Pharmacol Toxicol. 2024;65.
19. Ogbodo JO, Arazu AV, Iguh TC, Onwodi NJ, Ezike TC. Volatile organic compounds: a proinflammatory activator in autoimmune diseases. Front Immunol. 2022;13:928379.
20. Estevinho MM, Midya V, Cohen-Mekelburg S, Allin KH, Fumery M, Pinho SS, Colombel JF, Agrawal M. Emerging role of environmental pollutants in inflammatory bowel disease risk, outcomes and underlying mechanisms. Gut. 2025;74(3):477–86.
21. Obeng-Gyasi E, Obeng-Gyasi B. Association of combined lead, cadmium, and mercury with systemic inflammation. Front Public Health. 2024;12:1385500.
22. Cheng Y, Yang Y, Bai L, Cui J. Microplastics: an often-overlooked issue in the transition from chronic inflammation to cancer. J Transl Med. 2024;22(1):959.

# Inflammation in dry eye disease: From pathogenesis to promising therapeutic avenues

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**Abstract**

Tear film dysfunction is a unifying characteristic of dry eye disease (DED), propelled by an intricate interplay of intrinsic and extrinsic drivers. This article explores the complex pathophysiology of tear film instability, including abnormalities in the lipid, aqueous, and mucin layers. The involvement of inflammation and neurosensory changes in disease pathology is also discussed. Current and future therapeutic modalities are addressed, emphasizing targeted therapies designed to restore tear film homeostasis and enhance patient outcomes in managing DED.

**Keywords:** Tear film dysfunction, ocular inflammation, pro-inflammatory cytokines, dry eye disease

## 1. Introduction

Dry Eye Disease (DED) is a common, multifactorial illness characterised by tear film instability leading to visual disturbances and eye discomfort, and largely affecting quality of life. Initially considered trivial, DED today is recognized as a condition entailing hyperosmolarity, inflammation, and neurosensory abnormality. The tear film is the eye's vital environmental interface, maintaining corneal lubrication, clarity, and immunological protection. The increasing worldwide prevalence of DED is attributed to aging, environmental stress, and the use of digital devices. This review discusses the pathophysiology, triggering factors, and treatment options for DED and emphasizes the latest research breakthroughs and new strategies to enhance patient outcomes.

## 2. Pathophysiology of DED

The progression and severity of DED are greatly affected by the inflammation that is a component of the pathophysiology of this condition. Either decreased tear secretion (aqueous-deficient dry eye) or elevated tear evaporation (evaporative dry eye) is the typical etiology of dry eye, and results in hyperosmolarity and instability of the tear film (1). These ocular surface epithelial cells are under stress due to tear hyperosmolarity, which leads them to produce pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Dendritic cells and CD4+ T lymphocytes, particularly the Th1 and Th17 subsets, are some of the immune cells that are attracted and activated by the inflammatory cascade initiated by these cytokines. These activated T cells secrete more pro-inflammatory cytokines, such as interleukin-17 (IL-17) and interferon-gamma (IFN-γ), that reduce tear film stability, inhibit mucin formation, and further damage the ocular surface by inducing loss of goblet cells (2). The underlying immunoinflammatory mechanisms in the pathophysiology of the eye are illustrated in Figure 1.

In addition, the barrier function of the cornea is disrupted, epithelial tight junction proteins are degraded, and further damage to the epithelium is induced by inflammatory mediator-induced upregulation of enzymes like matrix metalloproteinase-9 (MMP-9). The outcome is a cycle of escalating inflammation, unstable tear film, and ocular surface injury. The injured sensory nerves release neuropeptides like substance P and calcitonin gene-related peptide (CGRP), which induce vasodilation, recruitment of immune cells, and cytokine release (2,3). Inflammation eventually extends to the lacrimal glands, impairing their ability to produce tears. The chronic inflammation ultimately leads to a self-perpetuating cycle in which immunological activation, damage to the epithelium, and tear deficiency reinforce each other. This cycle explains the progressive and chronic nature of DED and highlights the importance of anti-inflammatory therapies such as lifitegrast, corticosteroids, and cyclosporine in managing the disease and restoring ocular surface homeostasis (3).

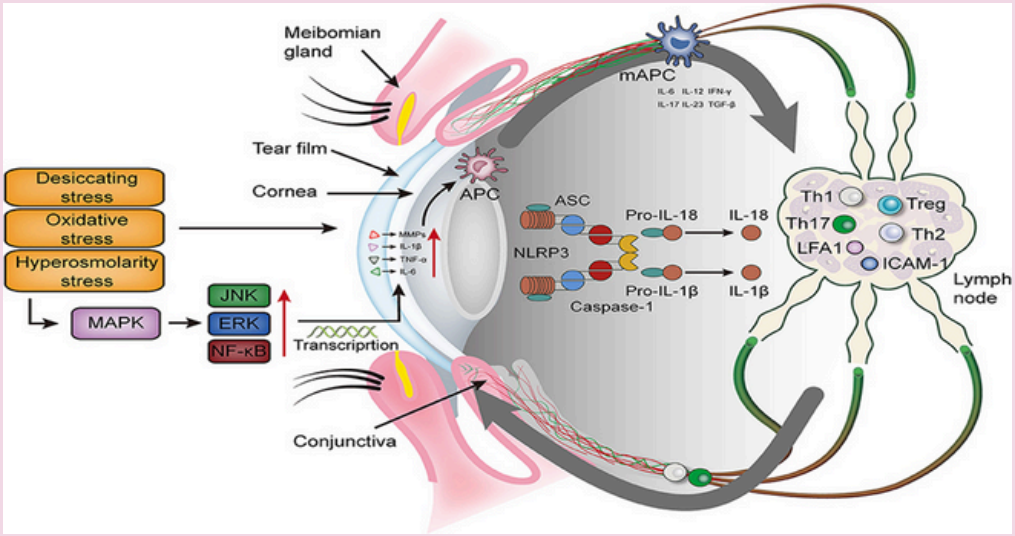


**Figure 1.** Immunoinflammatory mechanisms in dry eye disease (4)

## 3. Triggers of tear film dysfunction

The tear film, crucial for healthy eyes, can be compromised by a variety of influences, leading to dry eye (5) (Table 1). Systemic diseases like Sjögren's syndrome, rheumatoid arthritis, and lupus are known conditions, as are specific drugs like antihistamines and diuretics. Environmental factors like low humidity and prolonged screen time can also contribute in tear film failure (6).

**Table 1.** Triggers of tear film dysfunction

| S. No. | Risk factors for dry eye disease | Description | Ref |
|---|---|---|---|
| 1. | Meibomian gland dysfunction (MGD) | MGD is a prevalent cause of dry eye and results from the meibomian glands (located in the eyelids) secreting too little or altered oil, which is critical for the tear film's lipid layer. | (7) |
| 2. | Autoimmune diseases | Rheumatoid arthritis, lupus, sarcoidosis, and Sjögren's syndrome are autoimmune diseases that can harm the tear glands and decrease their ability to produce tears. | (8) |
| 3. | Medications | Several drugs, including diuretics, antihistamines, and antidepressants, can decrease tear production. | (9) |

| | | | |
|---|---|---|---|
| 4. | Environmental factors | Dry or windy conditions may cause more tears to evaporate. Smoky atmospheres: Irritants may lead to dry eye by damaging the surface of the eyes. | (10) |
| 5. | Aging | The tear ducts may constrict or obstruct as people age, resulting in excessive tears. | (11) |
| 6. | Hormonal changes | Tear production may be affected by hormonal changes that occur during menopause, pregnancy, or thyroid disorders. | (12) |
| 7. | Contact lens wear | Contact lenses can damage the tear film. | (13) |
| 8. | Infrequent blinking | Blinking infrequently, such as while looking at displays, causes evaporation to rise and tear film stability to decrease, leading to tear film dysfunction. | (14) |
| 9. | Eye surgery | A specific kind of eye surgery may impact tear film stability. | (15) |
| 10. | Neurologic conditions | Tear film dysfunction or dry eye can result from neurological disorders that interfere with the tear film. | (16) |

## 4. Therapeutic strategies for dry eye disease

Therapeutic approaches to DED focus on restoring tear film stability, diminishing inflammation, and alleviating symptoms (17). Therapy involves artificial tears, punctal occlusion, anti-inflammatory medications such as cyclosporine, and treatment of meibomian gland disease. New therapies include autologous serum, platelet-rich plasma, and surgery, with new biologics and gene therapies representing potential for the future (18). Some of the current therapeutic approaches are presented in Table 2.

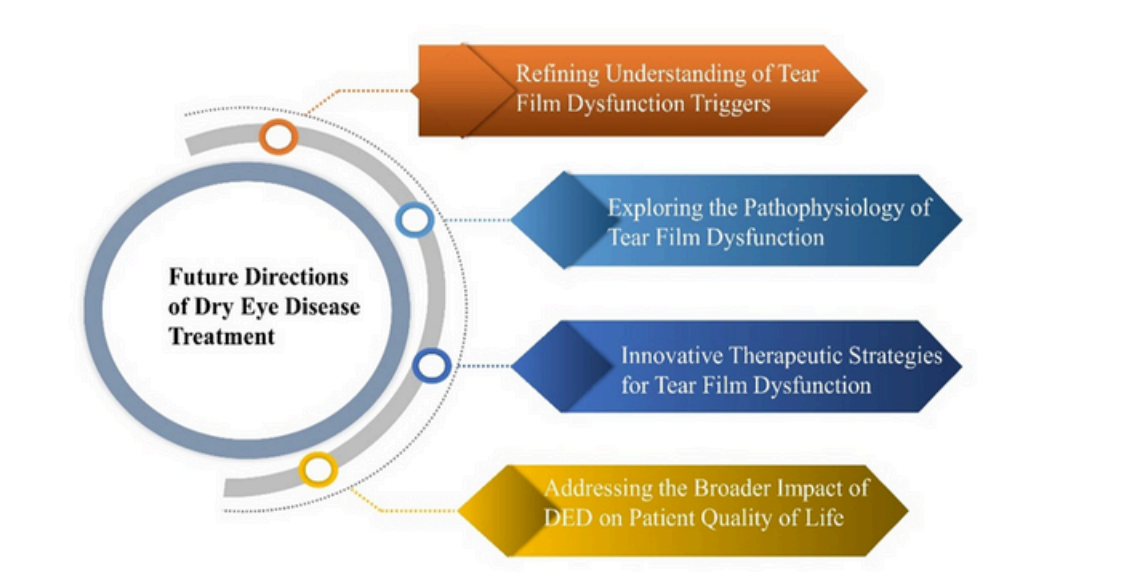


**Figure 2.** Future direction and research gaps of dry eye disease treatment

**Table 2.** An overview of therapeutic strategies for dry eye disease

| S. No. | Therapy Class | Examples | Mechanism of Action | Ref |
|---|---|---|---|---|
| 1. | Anti-inflammatory agents | Cyclosporine A, Lifitegrast, Corticosteroids | Suppress T-cell activation, prevent the production of cytokines, and stop the interaction between LFA-1 and ICAM-1 | (19) |
| 2. | Immunomodulatory agents | Tacrolimus, Anakinra | Calcineurin inhibitor (Tacrolimus); IL-1 receptor antagonist (Anakinra) | (20) |
| 3. | Lubricants (Artificial tears) | Carboxymethyl-cellulose, Hyaluronic acid | Stabilization of tear films; mechanical protection | (21) |
| 4. | Secretagogues | Diquafosol,Pilocarpine | Stimulate aqueous and mucin secretion via P2Y2 receptors (Diquafosol) | (22) |
| 5. | MMP inhibitors | Doxycycline (low-dose oral) | MMP-9 inhibition and anti-inflammatory properties | (23) |
| 6. | Biologic agents | Autologous serum, Platelet-rich plasma | Provide growth factors and mediators that reduce inflammation | (24) |
| 7. | Punctal occlusion | Plastic plugs/Silicone | Decrease tear leakage and improve tear retention | (25) |
| 8. | Thermal pulsation / Lid hygiene | Lipi Flow, Warm compresses | Boost meibomian gland activity and lower evaporative DED | (26) |
| 9. | Novel therapies | RGN-259 (Thymosin β4), Mesenchymal stem cells | Promote the repair of epithelium; reduce inflammation | (27) |
| 10. | Adjunctive measures | Omega-3 supplements, Environmental modifications | Anti-inflammatory dietary support; reduce evaporative stress | (28) |

## 5. Conclusion

In recent years, the understanding of DED has evolved beyond the traditional view of DED as merely a deficiency in tear production, and studies have established that inflammation is a central component in its pathogenesis. Elucidating the initiating factors, developing further understanding of mechanisms underlying inflammation and tear film dysfunction, and formulating novel treatment strategies that specifically address the fundamental causes of the disease should remain the primary research objectives. From identifying triggers and clarifying the pathophysiological mechanisms to designing

more specialized and effective treatment strategies, future research on DED is to bridge the gaps in tear film failure knowledge (Figure 2). In moving the field forward, a multidisciplinary approach involving immunology, regenerative medicine, molecular biology, and personalization of therapy will be necessary. Additionally, improving diagnostic procedures and expanding investigations into the extended impact of DED will ultimately lead to better patient outcomes, improved quality of life, and more effective management of this incapacitating condition.

## References


1. Harrell CR, Feulner L, Djonov V, Pavlovic D, Volarevic V. The Molecular Mechanisms Responsible for Tear Hyperosmolarity-Induced Pathological Changes in the Eyes of Dry Eye Disease Patients. Cells. 2023 Dec 1;12(23):2755.
2. Periman LM, Perez VL, Saban DR, Lin MC, Neri P. The immunological basis of dry eye disease and current topical treatment options. Journal of ocular pharmacology and therapeutics. 2020 Apr 1;36(3):137-46.
3. Bhujel B, Oh SH, Kim CM, Yoon YJ, Chung HS, Ye EA, Lee H, Kim JY. Current Advances in Regenerative Strategies for Dry Eye Diseases: A Comprehensive Review. Bioengineering. 2023 Dec 29;11(1):39.
4. Ling J, Chan BC, Tsang MS, Gao X, Leung PC, Lam CW, Hu JM, Wong CK. Current advances in mechanisms and treatment of dry eye disease: toward anti-inflammatory and immunomodulatory therapy and traditional Chinese medicine. Frontiers in Medicine. 2022 Jan 17;8:815075
5. Abed EK, Abbood AA. Risk Factors and Management Strategies for Dry Eye Syndrome: A Comparative Study. Sriwijaya Journal of Ophthalmology. 2024 Jul 29;7(2):333-44.
6. Kwon J, Moghtader A, Kang C, Bibak Bejandi Z, Shahjahan S, Alzein A, Djalilian AR. Overview of Dry Eye Disease for Primary Care Physicians. Medicina. 2025 Mar 6;61(3):460.
7. Sheppard JD, Nichols KK. Dry eye disease associated with meibomian gland dysfunction: focus on tear film characteristics and the therapeutic landscape. Ophthalmology and therapy. 2023 Jun;12(3):1397-418.
8. Shan H, Liu W, Li Y, Pang K. The autoimmune rheumatic disease related dry eye and its association with retinopathy. Biomolecules. 2023 Apr 23;13(5):724.
9. Guo M, Diaz GM, Yu Y, Patel CA, Farrar JT, Asbell PA, Ying GS, Assessment DE, Management Study Research Group. Association between systemic medication use and severity of dry eye signs and symptoms in the DRy eye assessment and management (DREAM) study. The Ocular Surface. 2024 Apr 1;32:112-9.
10. Patel S, Mittal R, Kumar N, Galor A. The environment and dry eye manifestations, mechanisms, and more. Frontiers in toxicology. 2023 Aug 23;5:1173683.
11. Fan M, Hung JL, Hung SH, Chen LC, Horng CT. Improvement of Presbyopia, Dry Eye, Intraocular Pressure, and Near Vision Through Cassiae Tea Consumption. Medicina. 2024 Dec 29;61(1):35.
12. Kaštelan S, Hat K, Tomić Z, Matejić T, Gotovac N. Sex Differences in the Lacrimal Gland: Implications for Dry Eye Disease. International Journal of Molecular Sciences. 2025 Apr 18;26(8):3833.
13. Kareem M, Agbaje T, Alam F, Butt H. A review of thin films used in smart contact lenses. Advanced Engineering Materials. 2024 Feb;26(4):2300363.
14. Romeo MA, Coco G, Taloni A, Carnovale-Scalzo G, Scorcia V, Giannaccare G. Digital Applications for Videoterminal-Associated Dry Eye Disease. Vision. 2024 Nov 28;8(4):67.
15. Pac CP, Munteanu M, Sánchez-González JM, Rocha-de-Lossada C, Mercea N, Ferrari F, Stanca HT, Cosnita DA, Ionica M, Boruga O, Danielescu C. Long-Term Impacts of Intense Pulsed Light Therapy on Ocular Surface Health and Tear Film Dynamics in Patients with Dry Eye Disease: Detailed Analysis and Observations Over a 1-Year Follow-Up Period. Ophthalmology and Therapy. 2024 Oct;13(10):2715-30.
16. Luib E, Demleitner AF, Cordts I, Westenberg E, Rau P, Pürner D, Haller B, Lingor P. Reduced tear fluid production in neurological diseases: A cohort study in 708 patients. Journal of neurology. 2024 Apr;271(4):1824-36.
17. Sheppard J, Shen Lee B, Periman LM. Dry eye disease: identification and therapeutic strategies for primary care clinicians and clinical specialists. Annals of medicine. 2023 Dec 31;55(1):241-52.
18. Suleman A, Aluyi-Osa G, Ashipa F, Spadea L, Gagliano C, D'Esposito F, Zeppieri M, Musa M. Autologous blood in the management of ocular surface disorders. World Journal of Experimental Medicine. 2024 Dec 20;14(4):96412.
19. Huang D, Li Z. Multidimensional immunotherapy for dry eye disease: current status and future directions. Frontiers in Ophthalmology. 2024 Nov 1;4:1449283.
20. Sahay P, Kumawat D. An Overview of Topical Immunomodulators used in Ophthalmology. Delhi Journal of Ophthalmology. 2022 Jan 1;32(3):104-10.
21. Aragona P, Benítez-del-Castillo JM, Coroneo MT, Mukherji S, Tan J, Vandewalle E, Vingrys A, Liu H, Carlisle-Wilcox C, Vehige J, Simmons PA. Safety and efficacy of a preservative-free artificial tear containing carboxymethylcellulose and hyaluronic acid for dry eye disease: a randomized, controlled, multicenter 3-month study. Clinical Ophthalmology. 2020 Oct 1:2951-63.
22. Tan CQ, Wu D, Toh XY, Lim BX, Shih KC, Tong L, Lim CH. Applications of Diquafosol Sodium in Ophthalmology: A Comprehensive Review of Therapeutic Utility. Life. 2025 Mar 17;15(3):484.
23. Perez VL, Mah FS, Willcox M, Pflugfelder S. Anti-inflammatories in the treatment of dry eye disease: a review. Journal of ocular pharmacology and therapeutics. 2023 Mar 1;39(2):89-101.
24. Metheetrairut C, Ngowyutagon P, Tunganuntarat A, Khowawisetsut L, Kittisares K, Prabhasawat P. Comparison of epitheliotrophic factors in platelet-rich plasma versus autologous serum and their treatment efficacy in dry eye disease. Scientific reports. 2022 May 26;12(1):8906.
25. Singh RB, Yung A, Coco G, Sinha S, Dohlman TH, Yin J, Dana R. Efficacy and retention of silicone punctal plugs for treatment of dry eye in patients with and without ocular graft-versus-host-disease. The ocular surface. 2020 Oct 1;18(4):731-5.
26. Blackie CA, Murakami D, Donnenfeld E, Oliff HS. Vectored thermal pulsation as a treatment for meibomian gland dysfunction: a review spanning 15 years. Ophthalmology and Therapy. 2024 Aug;13(8):2083-123.
27. Sosne G, Kleinman HK, Springs C, Gross RH, Sung J, Kang S. 0.1% RGN-259 (thymosin ß4) ophthalmic solution promotes healing and improves comfort in neurotrophic keratopathy patients in a randomized, placebo-controlled, double-masked phase III clinical trial. International Journal of Molecular Sciences. 2022 Dec 29;24(1):554.
28. Cong Y, Zhang Y, Han Y, Wu Y, Wang D, Zhang B. Recommendations for nutritional supplements for dry eye disease: current advances. Frontiers in Pharmacology. 2024 May 30;15:1388787.

# Mind body connection: Stress, inflammation, and health

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**Abstract**

The mind and body are profoundly connected, and this association strongly affects our health. This chapter explains how psychological stress can lead to inflammation in the body and how that impacts physical health. Stress activates systems in the body that release hormones like cortisol and inflammatory chemicals. When stress last long-term, it can lead to chronic inflammation, which is linked to diseases such as heart problems, autoimmune disorders, and depression. Research from psychoneuroimmunology shows that managing stress through techniques like mindfulness and healthy behavior can reduce inflammation and improve overall health. By understanding how stress causes inflammation in the body, we can develop better and more complete healthcare strategies to treat and prevent long-term illnesses.

**Keywords**: Inflammation, stress, mind, psychological, mental health, mindfulness

## 1. Introduction

A stress response is triggered by any psychological or physical events that upset equilibrium. The stress response is the term used to describe the physiological and behavioral alterations brought on by stressors. A stress reaction might be psychological or environmental, such as an impending deadline at work. Anxiety, hormones, and the immune system all contribute to a stress response by triggering the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic-adrenomedullary (SAM) axis, and the immunological system. Chronic stress has lasting impact on both the body and the mind. Prolonged stress causes high blood pressure, and encourages the development of arterial plaque, anxiety, depression, and addiction (1).

The brain initiates the stress reaction starts. When our sense organs, such as our eyes and earssee danger, they communicate with the brain's Amygdala, which controls how emotions are processed. The Amygdala processes it, controls involuntary action, and sends it throughout the body through the ANS. It activates the sympathetic nervous system and the "fight and flight" response. The signal travels to adrenal gland which release epinephrine into the bloodstream. Epinephrine causes physiological changes like increase heart rate,increase blood supply to muscles, heart and another organ. $O_2$ supply increases which increase

alertness in the brain. The body enters a second phase of the stress response after the immediate effects of epinephrine (adrenaline) wear off, and this is regulated by the Hypothalamic-Pituitary-Adrenal axis (HPA axis), a complex network that includes the pituitary gland, the adrenal glands above the kidneys, and the brain's hypothalamus.When the brain continues to interpret a situation as threatening, the hypothalamus responds by releasing a chemical signal called corticotropin-releasing hormone (CRH). This hormone reaches to the pituitary gland, which then releases adrenocorticotropic hormone (ACTH) into the bloodstream. In turn, ACTH signals the adrenal glands to produce and release cortisol, the body's main stress hormone. The hormone cortisol keeps the body alert. It elevates blood sugar (glucose) levels to provide quick energy, enhances brain function, and suppresses non-essential functions like digestion and reproduction so the body can focus entirely on dealing with the threat. This is part of the "fight-or-flight" survival mechanism.



However, prolonged higher cortisol levels caused by chronic stress can have negative consequences like reduced immunity, elevated blood pressure, disturbed sleep, and even mental health conditions like depression or anxiety. This emphasizes how crucial it is to properly manage stress in order to avoid long-term harm to the body and mind (2).

## 2. Chronic stress influence inflammation

Although stress is a normal component of life, persistent stress can have very negative effects on our bodies. Regularly experiencing stress triggers the neuro-endocrine pathway that results in stress reactions. The stress hormone cortisol is to blame for this, as it acts on glucocorticoid receptors all over the body. When stressor is strong in intensity or duration it over activate the immune system and causes the imbalance between inflammatory and anti-inflammatory responses. Normally cortisol reduces the inflammation but when chronic stress increases it leads to increase inflammation and supress the immune system. Over long time these chronic stress makes glucocorticoid receptor resistance to inflammatory hormones like cortisol. Chronic stress activates the HPA axis and sympathetic nervous system which causes release of stress hormone in the blood and causes systemic inflammation. Stressful events also triggers the person to adopt unhealthy lifestyles like alcohol consumption,unhealthy food and lack of physical activity which causes chronic inflammation. When cortisol and epinephrine are increased it triggers the chronic stress which damages blood vessels and arteries and causes increase blood pressure and sometimes heart attack. Chronic stress also affects the brain and causes neuroinflammation, neuronal plasticity and affect neurotransmitter release which have a harmful effect on cognitive function and mental health (3).

### 2.1. Role of cortisol in stress induced inflammation

Cortisol is a natural hormone made by the body that is commonly used (or mimicked by drugs) to reduce inflammation. However, this study takes a fresh look at how cortisol works and shows that it can both increase and decrease inflammation depending on the situation.

**2.1.1. Daily cortisol levels don’t always reduce inflammation:** Normal levels of cortisol in the body throughout the day don’t seem to reduce inflammation much. This suggests that the relationship between cortisol and inflammation isn’t simple or straightforward.

**2.1.2. In surgery patients, cortisol can reduce inflammation:** When the body is under stress, like during surgery, cortisol can help reduce inflammation but only within a certain range. Too little or too much might not help (4).

**2.1.3. Short-Term cortisol treatment has a two-phase effect:** Giving healthy people cortisol before exposing them to inflammation later on showed an interesting pattern: Moderate levels of cortisol made inflammation worse. High levels of cortisol had no clear effect neither helping nor hurting (5).

## 3. Inflammation link between stress and disease

Inflammation is the body's natural defense against various threats, including infections, cancer, organ

rejection, and even psychological stress. In response, the immune system releases chemicals called pro-inflammatory cytokines to combat these threats. Stress triggers inflammatory responses throughout the body, both in the brain and peripherally. In other words, stress not only activates inflammation in the brain but also in other parts of the body. This inflammation can occur through various mechanisms, including the release of inflammatory mediators and the activation of immune cells (6).

Stressors of varying types and intensities activate both pro-inflammatory and anti-inflammatory pathways in the immune system. Acute stressors tend to enhance immune function, while chronic stressors can suppress it. Intense stressors can lead to an imbalance in these pathways, with pro-inflammatory effects becoming more prominent. This pro-inflammatory response, confirmed by numerous studies, involves markers like C-reactive protein (CRP), IL-6, TNFα, IL-1β, and the transcription factor NF-κB. Stress can significantly contribute to a range of diseases, including cardiovascular problems like hypertension and atherosclerosis, metabolic issues like diabetes and NAFLD, mental health conditions such as depression, and neurodegenerative disorders like Alzheimer's and Parkinson's disease.

### 3.1. Rheumatoid arthritis (RA)

It is an autoimmune disease where inflammation damages joints and tissues, causing pain and stiffness. This inflammation, partly triggered by stress-induced cytokines, can lead to long-term joint and bone damage.

### 3.2. Atherosclerosis

An overly active sympathetic nervous system, the body's "fight or flight" response, constricts blood vessels, increasing blood pressure and heart workload. This, along with inflammation, contributes to atherosclerosis, a major risk factor for heart disease.

### 3.3. Depression

Depressive symptoms like low mood, fatigue, and a lack of enjoyment. In individuals with existing depression, inflammation can exacerbate these symptoms. Essentially, stress-induced inflammation can mimic or worsen depressive symptom (7).

## 4. Physiological effect of inflammation: The mind response to stress

Under psychological or physical stress, sensory nerve fibers release neuropeptides, notably Substance P, triggering inflammation. This inflammation is further enhanced by the activation of mast cells, which release inflammatory mediators. Stress leads to the release of neuropeptides, such as substance P, and other inflammatory mediators from sensory nerves, which in turn activate mast cells, leading to an inflammatory response. Inflammatory stimuli activate the HPA axis and sympathetic nervous system, triggering the release of stress hormones like cortisol and adrenaline, which can exacerbate inflammation. Psychological stress can also initiate an inflammatory response through the release of neuropeptides from peripheral neurons and the activation of mast cells. A key inflammatory stimulus is lipopolysaccharide (LPS). The brain actively regulates inflammation, and stress responses and inflammatory responses share overlapping mechanisms. Both are mediated by similar neuropeptides like CRF and possibly SP, and cytokines released during stress or inflammation can signal the brain via similar sensory pathways. Inflammation evolved within the context of the broader stress response. (8).

## 5. The gut brain axis: Stress inflammation and digestive health

The gut brain axis is the pathways that provide signalling between nervous system and gastrointestinal tract (GIT) bidirectionally. This pathway is also linked with vagus nerve, immune system, hormones, neurotransmitters and microbial metabolites. That means the signal transmits from gut to brain and from brain to gut via vagusnerve, hormones , neurotransmitters, and other chemical mediators etc (9)

Whenever the Physical and psychological stress produced in our body, it causes the release of inflammatory mediators like cytokinins and release of catecholamine and glucocorticoid respectively. This affect the permeability of blood brain barrier (BBB) and intestinal barrier resulting in movement of

gut microbiota from gut lumen into blood. This causes change in composition of gut microbiota (Microbiota are the microorganisms like fungi, bacteria, virus etc that are present in human GIT) leading to dysbiosis. Microbiota is responsible for controlling the gut brain axis and inflammatory responses. When microbiota from blood enter into brain through blood brain barrier in response to physical and psychological stress, they causes neuroinflammation. This gut inflammatory response can be reduced by taking high fibre rich food, probiotics, prebiotics. All these food products are beneficial against this gut dysbiosis associated brain disorder (10).

## 6. Mindfulness and stress reduction: Breaking the cycle of inflammation

Mindfulness means paying full attention to what's happening right now where you are,what you are doing, without getting too caught up in thoughts or emotions - Although in simple terms "training your attention" to achieve a mental calm and positive emotions. Various health related problems like anxiety and depression caused due to stress could be cured doing meditation (11).

MBSR (mindfulness based stress reduction) is a meditation therapy it is being used to treat many different illnesses such as depression, anxiety, cancer, diabetes mellitus, hypertension, immune disease. MBSR also teaches people how to increase mindfulness through yoga and meditation. It can improve physical health, for example - reduce pain, fatigue, stress in people and boost the immune system and help to recover more quickly from cold and flu (12).

Mindfulness based cognitive therapy (MBST) is a kind of therapy that uses both MBSR (mindfulness based stress reduction) and CBT (cognitive-behavioral therapy) which is used to cure the people suffering from depression. It is generally used to reducing stress, anxiety and depression etc (13).

### 6.1. Yoga for stress

Yoga helps improve how our brain works, and it does this in a different way than activities like running or other aerobic exercises. Studies support the idea that our body and mind are closely connected, how we move and use our body can affect how we think and feel. For example, the way we move our muscles and hold our posture can change how much we think and even what kind of thoughts we have (14).

**Table 1.** Studies conducted on various populations and effect on inflammation markers

| Population/ Condition | Intervention type | Stress/ Inflammation markers measured | Key findings | Ref |
|---|---|---|---|---|
| IBS & IBD patients | Relaxation Response MBI | ESR, CRP, gene expression | Improved quality of life, reduced symptoms and anxiety, gene expression changes linked to inflammation | (15) |
| Mixed (chronic stress) | Mindfulness, CBT, Yoga | IL-6, TNF-α, cortisol, immune cell activity | Chronic stress increases pro-inflammatory markers; mind-body interventions reduce stress and normalize immune function | (16) |
| Mixed (inflammatory conditions) | Mind–Body Interventions | WHO-5 Well-being Index, inflammatory biomarkers | MBI improves well-being and may reduce inflammation | (17) |

## 6.2. Body posture and emotion

How we move and hold our body can change depending on how we feel. For example, when someone feels ashamed, sad, or bored, their upper body might slump or "collapse." This could be one reason why sitting is often linked to feeling more negative emotions. Also, our muscles react during emotional experiences even if we're not actively responding to something we see or hear. All of this supports the idea that our emotions and body posture are closely connected (18).

## 7. Conclusion

Prolonged stress contributes to inflammation by causing a prolonged release of cortisol, which over time can interfere with immunological control and lead to the onset of disease. A major connection between mental discomfort and physical sickness, stress-induced inflammation impacts all bodily systems, including the gut and brain. Further demonstrating how psychological stress can impact digestive health, the gut-brain axis highlights the intricate relationship between mental and physical health. The significance of stress management for immunological balance and general health is highlighted by an understanding of these pathways.

## References


1. Chu B, Marwaha K, Sanvictores T, Awosika AO, Ayers D. Physiology, stress reaction. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 May 7. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541120/
2. Lewine HE. Understanding the stress response. Howard Health Publishing. 2024 Apr 3.
3. Weinberg JL. The impact of stress on inflammation: coping strategies for a healthier life. Ropa Health [Internet]. 2025 Jan 14. Available from: https://www.rupahealth.com/post/the-impact-of-stress-on-inflammation-coping-strategies-for-a-healthier-life
4. Menger MM, Histing T, Laschke MW, Ehnert S, Viergutz T, Fontana J. Cortisol stress response after musculoskeletal surgery: a narrative review. EFORT Open Rev. 2025 Apr 1;10(4):186–92.
5. Amasi-Hartoonian N, Sforzini L, Cattaneo A, Pariante CM. Cause or consequence? Understanding the role of cortisol in the increased inflammation observed in depression. Curr Opin Endocr Metab Res. 2022 Jun 1;24:100356.
6. Liu YZ, Wang YX, Jiang CL. Inflammation: the common pathway of stress-related diseases. Front Hum Neurosci. 2017 Jun 20;11:316.
7. Schipani D. How stress and inflammation are linked. Everyday Health. 2023 Jun 12 [cited 2025 May 21]. Available from: https://www.everydayhealth.com/wellness/united-states-of-stress/link-between-stress-inflammation/
8. Paul. Stress and inflammatory response: a review of neurogenic inflammation. SciDirect. 2002 Dec;622–53.
9. Carabotti M, Scirocco A, Maselli A, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous system. Natl Libr Med. 2015;28(2):203–9.
10. Varanoske AN, McClung HL, Sepowitz JJ, Halagarda CJ, Farina EK, Berryman C. Stress and gut-brain axis: cognitive performance, mood state, biomarkers of blood-brain barrier and intestinal permeability following severe physical and psychological stress. Brain Behav Immun. 2022;101:383–93.
11. Mindful Staff. The science of mindfulness. Mindful Healthy Mind Healthy Life. 2022 [cited 2025 May 21]. Available from: https://www.mindful.org/the-science-of-mindfulness/
12. Niazi AK, Niazi SK. Mindfulness-based stress reduction: a non-pharmacological approach for chronic illnesses. N Am J Med Sci. 2011 Jan;3(1):20-3.
13. American Psychological Association. Mindfulness meditation: Psychologists have found that mindfulness meditation changes our brain and biology in positive ways, improving mental and physical health. 2019 Oct 30.
14. Saeed SA, Cunningham K, Bloch RM. Depression and Anxiety Disorders: Benefits of Exercise, Yoga, and Meditation. Am Fam Physician. 2019 May 15;99(10):620-627.
15. Buric I, Farias M, Jong J, Mee C, Brazil IA. What is the molecular signature of mind–body interventions? A systematic review of gene expression changes induced by meditation and related practices. Front Immunol. 2017 Jun 16;8:259671.
16. Niharika L, Sharma M, Babu VS, Chahare VW. The mind-body connection in stress and immunity: a systematic review. Eur J Cardiovasc Med. 2024 Nov 23;14:303–6.
17. Nguyen TT, Jensen CG, Khoury L, Deleuran B, Blom ES, Breinholt T, et al. Effectiveness of mind–body intervention for inflammatory conditions: results from a 26-week randomized, non-blinded, parallel-group trial. J Clin Med. 2021 Jul 14;10(14):3107.
18. Francis AL, Beemer RC. How does yoga reduce stress? Embodied cognition and emotion highlight the influence of the musculoskeletal system. Complement Ther Med. 2019 Apr;43:170-175.

# From itch to inflammation: Understanding eczema in the context of immune response

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## Abstract

Atopic dermatitis (AD), commonly known as eczema, is a chronic and non-curable inflammatory skin disorder characterized by intense itching, redness, dryness, and rashes. It typically manifests during infancy or early childhood and can persist into adulthood. AD is closely linked to immune system dysregulation, elevated levels of immunoglobulin E (IgE), and a weakened skin barrier, making affected individuals more susceptible to skin infections and increasing the likelihood of developing asthma and allergies later in life—a progression known as the "Allergic March". Conventional treatment primarily involves moisturizers and topical corticosteroids; however, these are often associated with adverse effects. New therapeutic options such as topical calcineurin inhibitors and biologic agents targeting specific immune pathways have been introduced in recent years. Additionally, advancements in drug delivery systems have emerged to enhance the safety and effectiveness of treatment. This review aims to provide a comprehensive overview of the etiology, conventional and modern treatment approaches, and recent innovations in managing AD.

**Keywords**: Pathogenesis, Eczema, Emerging Nanotechnology

## 1. Introduction

Eczema, also known as atopic dermatitis (AD), is a common chronic immune-inflammatory disease characterized by itching, redness, xerosis, and eczematous lesions. About 80% of AD cases typically initiate during infancy or childhood, while the remaining cases emerge in adulthood. The acute stage of AD commences with a Th-2 cell-driven inflammatory response and elevated immunoglobulin E (IgE) levels, eosinophils, mast cells, and lymphocyte infiltration, reflecting immune system hyperactivation, which leads to erythema with ill-defined borders and intense pruritus. Chronic inflammation and immune dysregulation increase susceptibility to infections, particularly by Staphylococcus aureus (S. aureus), and AD is often the first step in the "Allergic March". Children suffering from AD may have a risk of developing asthma, allergic rhinitis, food allergies, and rheumatoid arthritis. This review aims to illuminate the underlying pathophysiological mechanism of AD and explore strategies for its management (1,2).

## 2. Pathogenesis

Eczema is a chronic inflammatory cutaneous condition with involvement of genetic, immunological, and environmental components. A prominent characteristic is dysfunction of the skin barrier, basically caused by mutations in the filaggrin (FLG) gene, which compromises the epidermis, enhances water loss, and facilitates entry of allergens and microbes.

Immune dysregulation is at the forefront of AD, characterized by a Th2-type response. Cytokines such as IL-4, IL-5, and IL-13 drive IgE production, eosinophil activation, and downregulation of barrier proteins. IL-31 has a strong association with itch, and IL-22 with thickening of the skin and disruption of the barrier. TSLP, an epithelial cytokine, drives Th2 inflammation, while Th1 (IFN-γ) and Th17 (IL-17) pathways are more prominent in chronic or severe forms.

Hormonal and neuroimmune mediators are Corticotropin-releasing hormone, histamine, prostaglandins, and leukotrienes, which increase inflammation and itch. Decreased antimicrobial peptides (AMPs) compromise skin barrier defense with Staphylococcus aureus colonization that further exacerbates inflammation by toxins and superantigens.

This dynamic interplay among cytokines, hormones, immune cells, and microbes sustains the inflammation-barrier dysfunction cycle and emphasizes the necessity for selective, multi-pathway therapies in AD (3–6). Figure 1 illustrates the pathogenesis of AD.

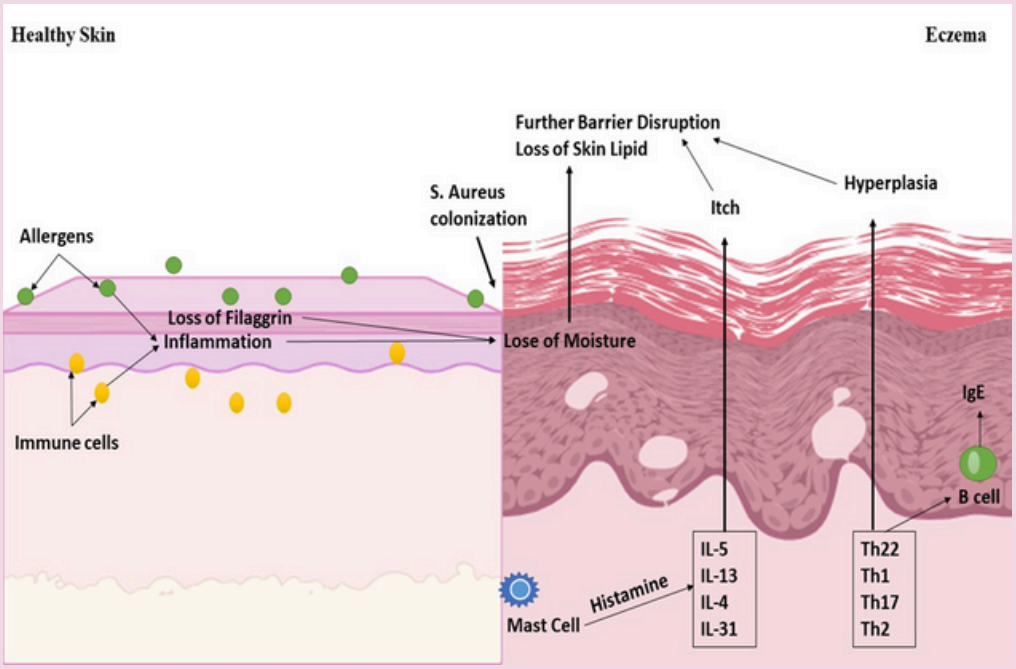


**Figure 1**. Pathogenesis of Eczema

## 3. Management

AD is a chronic inflammatory skin disease characterized by disrupted skin barrier, immune dysregulation, and increased sensitivity to environmental allergens. Conventional treatment relies on topical therapies that target barrier repair, inflammation, and itching. These treatments are, however, constrained by limitations in drug permeation, duration of action, side effects, and long-term efficacy, especially in severe or resistant disease (7). Emerging advances in drug delivery and nanotechnology offer new avenues for therapeutic enhancement, minimize side effects, and increase patient compliance. Table 1 discusses multiple intervention possibilities.

### 3.1. Traditional topical treatment

Emollients and moisturizers are still the pillars of AD management because they also hydrate the stratum corneum, decrease transepidermal water loss (TEWL), and maintain barrier integrity. Nonetheless, their inherent anti-inflammatory capacity is weak, particularly in moderate to severe disease. Topical corticosteroids (TCS) are the cornerstone of acute flares. TCS are graded according to potency and selected based on age, lesion location, and disease severity. Efficacious but potentially problematic with prolonged use is the worry of skin atrophy and hypothalamic-pituitary-adrenal axis suppression, which tends to result in "steroid phobia" and nonadherence (8,9).

Steroid-free topical calcineurin inhibitors like tacrolimus and pimecrolimus are alternatives for sensitive skin. They suppress T-cell proliferation and pro-inflammatory cytokines without thinning the skin. Although they have a black-box warning for carcinogenicity, real-world safety is excellent; however, they are costly and cause local irritation and, therefore, are restricted in use.

New topical medications have emerged that counteract the limitations of TCIs and TCSs. PDE-4 inhibitors crisaborole, reduce pro-inflammatory cytokines through increased levels of cyclic AMP. JAK inhibitors delgocitinib and tofacitinib inhibit over 60 cytokines in atopic dermatitis (AD) via the JAK-STAT pathway. These small molecules are effective against inflammation, serving patients refractory to first-line treatments. AhR agonists like tapinarof represent a new non-steroidal method of managing inflammation and enhancing barrier function.

Biologic agents such as dupilumab, tralokinumab, lebrikizumab, and nemolizumab have revolutionized the treatment of moderate-to-severe AD. Dupilumab suppresses IL-4 and IL-13, enhancing skin barrier and Th2 inflammation, and others suppress cytokines such as IL-13 and IL-31 to reduce pruritus. But these biologics are expensive and are reserved for resistant cases only (10–12).

**Table 1.** Management of AD

| Category | Intervention | Description/Examples | Comments |
|---|---|---|---|
| 1. Skin Barrier Repair | Emollients/Moisturizers | Petrolatum, ceramide-based creams, colloidal oatmeal, urea-containing products | Use liberally and regularly; essential for daily maintenance |
| 2. Topical Anti-inflammatory Therapy | Corticosteroids (TCS) | Hydrocortisone (mild), betamethasone, clobetasol (potent) | First-line for acute flares; potency chosen based on severity and site |
| | Calcineurin Inhibitors (TCIs) | Tacrolimus, Pimecrolimus | Steroid-sparing; suitable for face, eyelids, intertriginous areas |
| | PDE4 Inhibitors (Newer) | Crisaborole | Mild to moderate eczema; reduces inflammation with minimal side effects |
| 3. Systemic Therapy | Immunosuppressants | Cyclosporine, Methotrexate, Azathioprine | For moderate-to-severe cases unresponsive to topicals; require monitoring |
| | Oral Corticosteroids | Prednisone | Short-term use only; for severe flares |
| 4. Biologic Therapy | IL-4/IL-13 Inhibitors | Dupilumab | First approved biologic; highly effective with long-term disease control |
| | IL-13 Specific Inhibitors | Tralokinumab, Lebrikizumab (under development) | New targeted agents under clinical trials |
| 5. Small Molecule Inhibitors | JAK Inhibitors | Upadacitinib, Abrocitinib, Baricitinib | Oral agents; rapid action; monitor for systemic side effects |
| 6. Antimicrobial/ Adjunctive Care | Topical/Oral Antibiotics | Mupirocin (topical), Cephalexin (oral) | For secondary bacterial infections due to scratching or barrier breakdown |
| | Antihistamines | Hydroxyzine, Cetirizine | Limited role; may aid sleep and reduce nighttime itching |
| 7. Lifestyle & Supportive Measures | Allergen/Irritant Avoidance | Avoid harsh soaps, fragrances, wool, allergens | Individualized based on triggers |
| | Wet Wrap Therapy | Soaking skin and wrapping with damp and dry layers | Used during severe flares to enhance absorption of topical agents |
| | Education & Counseling | Skincare training, psychological support | Improves adherence, reduces anxiety, especially in pediatric patients |
| 8. Emerging Therapies | Microbiome-based Treatments | Topical probiotics, bacterial transplantation | Experimental; aim to restore skin microbial balance |
| | Nanocarrier-based Drug Delivery | Liposomes, NLCs, ethosomes | Improve drug penetration and reduce systemic exposure |

## 3.2. Emerging nanotechnology and novel drug delivery systems

To counteract the limitations of traditional treatment, drug delivery systems based on nanotechnology are currently leading the therapeutic revolution in AD. Such systems are engineered to enhance dermal penetration of drugs, extend drug retention at the point of inflammation, enable reduced dosing, and minimize systemic exposure. Diverse nanotechnologies for eczema management are outlined in Table 2.

### 3.2.1. Polymeric nanoparticles

Polymeric nanoparticles—especially those compounded with chitosan, PLGA, and Eudragit—have shown improved therapeutic performance in preclinical AD models. Corticosteroids (e.g., hydrocortisone) and natural antioxidants (e.g., hydroxytyrosol)-co-loaded systems substantially lowered TEWL, erythema, and cytokine levels in mice. Surface modifications with hyaluronic acid enhance epidermal adhesion and targeting. These systems provide sustained drug release, lower dosing frequencies, and improved tolerability by the skin over conventional creams (13).

### 3.2.2. Lipid-based nanocarriers

Lipid-based delivery systems like solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, ethosomes, and nanoemulsions possess high biocompatibility and resemble the skin's lipid matrix. Ethosomal gel formulations of tacrolimus and cyclosporine A exhibited enhanced drug penetration and deposition in deeper skin layers than commercial products. Further, nanoemulsions with skin-identical lipids, phytosphingosine, and linoleic acid not only provide effective drug delivery but also restore barrier function (14).

### 3.2.3. Gene-silencing nanocarriers (siRNA)

Cutting-edge strategies involve the delivery of small interfering RNA (siRNA) against transcription factors such as NF-κB or cytokines such as IL-13. Liposomal and polymeric vehicles have been effective in delivering these gene silencers in preclinical AD models, lowering mast cell infiltration, inflammatory signaling, and serum IgE. These methods have the potential for long-term disease modulation instead of the suppression of symptoms (15).

### 3.2.4. Inorganic nanoparticles

Inorganic nanocarriers (e.g., silver, zinc oxide, and silica nanoparticles) have exhibited anti-inflammatory and antimicrobial activity. Nevertheless, their therapeutic application is hampered by immunogenicity concerns and the risk of worsening AD symptoms. It has been shown that particle size and dose play a decisive role in both efficacy and safety, and strong design and toxicity testing requirements are needed (16).

### 3.2.5. Nanoparticle hybrids and intelligent delivery platforms

Hydrogel systems integrate hydrogels' moisturizing and calming effects with the sustained, targeted delivery of nanoparticles. Thermo- and pH-sensitive hydrogels provide controlled release of corticosteroids, herbal medications, and dual therapies to enhance bioavailability, skin retention, and irritation reduction—perfect for chronic AD control (17).

Intelligent delivery platforms extend this strategy by integrating nanoparticle-loaded hydrogels into wearable fabrics such as wet-wraps. Such systems ensure stimulus-responsive, on-demand release of drugs against inflamed or infected skin, ensuring precision therapy for acute and refractory AD(18).

**Table 2.** Nanotechnology-based delivery system for AD

| Nanotechnology/Delivery System | Key Components | Mechanism/Features | Application in AD | Advantages |
|---|---|---|---|---|
| **Lipid-Based Nanocarriers** | Solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs) | Encapsulate lipophilic drugs; enhance skin penetration | Delivery of corticosteroids, herbal actives | Enhanced skin permeation, reduced irritation, improved stability |
| **Polymeric Nanoparticles** | PLGA, chitosan, Eudragit | Controlled drug release; biodegradable matrices | Anti-inflammatory and immunomodulatory agents | Sustained release, targeted delivery, reduced systemic effects |
| **Nanoemulsions** | Oil-in-water or water-in-oil systems | High surface area; enhanced solubility of actives | Herbal extracts, essential oils, corticosteroids | Improved drug solubility, non-greasy feel, better skin absorption |
| **Liposomes and Niosomes** | Phospholipids (liposomes), non-ionic surfactants (niosomes) | Vesicular carriers; biocompatible | Delivery of calcineurin inhibitors, antioxidants | Skin targeting, minimized systemic absorption, enhanced drug stability |
| **Hydrogel-Nanoparticle Hybrids** | Thermo-/pH-responsive hydrogels with embedded nanoparticles | Dual-function: hydration + sustained release | Maintenance therapy, dual-drug delivery | Improved adherence, reduced irritation, prolonged contact time |
| **Microneedle Arrays** | Biodegradable or polymeric microneedles | Bypass stratum corneum, direct intradermal delivery | Biologics, peptides | Painless delivery, enhanced penetration, reduced dosing frequency |
| **Smart Textiles (Wearable Platforms)** | Wet-wraps infused with nanoparticle-loaded hydrogels | Stimulus-responsive drug release | Infected or inflamed AD lesions | On-demand release, tailored therapy, increased patient compliance |

## 4. Future perspectives

Although the mainstay of AD treatment remains traditional topical therapies, their drawbacks have led to the development of more advanced drug delivery systems. Nanocarrier-based systems offer several advantages, including greater drug solubility, targeted distribution, long-lasting therapeutic effects, and increased patient compliance, especially in complex situations, including sensitive skin areas or steroid fear. A paradigm shift in the treatment of AD is being brought about by new developments in gene silencing, intelligent delivery methods, and polymeric, lipid-based, and hybrid hydrogel systems. To bring these developments from the bench to the bedside, translational research can focus on clinical proof of concept, large-scale production, and regulatory convergence in the future.

## 5. Conclusion

The drive to apply knowledge of AD in the creation of new medication has led to fruitful research and more treatment possibilities. Adopting a multidisciplinary approach improves disease management and quality of life. Developments over recent years have enabled better treatment outcomes to be achieved, especially in advanced AD. Nanotechnology drug delivery has the potential to enhance treatment in patients, opening the door to a new generation of safer, more compliant drugs.

## References


1. What is atopic dermatitis? | Global Atopic Dermatitis Atlas [Internet]. [cited 2024 Dec 9]. Available from: https://www.atopicdermatitisatlas.org/en/atopic-dermatitis/what-is-atopic-dermatitis
2. Raimondo A, Lembo S. Atopic dermatitis: Epidemiology and clinical phenotypes. Dermatol Pract Concept. 2021 Oct 1;11(4).
3. Pareek A, Kumari L, Pareek A, Chaudhary S, Ratan Y, Janmeda P, et al. Unraveling Atopic Dermatitis: Insights into Pathophysiology, Therapeutic Advances, and Future Perspectives. Vol. 13, Cells. Multidisciplinary Digital Publishing Institute (MDPI); 2024.
4. Seneviratne J. Pathogenesis of atopic dermatitis: Current concepts. Journal of Skin and Sexually Transmitted Diseases. 2021 Apr 16;3:113–7.
5. Mandlik DS, Mandlik SK. Atopic dermatitis: new insight into the etiology, pathogenesis, diagnosis and novel treatment strategies. Vol. 43, Immunopharmacology and Immunotoxicology. Taylor and Francis Ltd.; 2021. p. 105–25.
6. Li H, Zhang Z, Zhang H, Guo Y, Yao Z. Update on the Pathogenesis and Therapy of Atopic Dermatitis. Vol. 61, Clinical Reviews in Allergy and Immunology. Springer; 2021. p. 324–38.
7. Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. J Am Acad Dermatol. 2024 Feb 1;90(2):e43–56.
8. Kwatra G, Mukhopadhyay S. Topical corticosteroids: Pharmacology. In: A Treatise on Topical Corticosteroids in Dermatology: Use, Misuse and Abuse. Springer Singapore; 2017. p. 11–22.
9. Yasir M, Goyal A, Sonthalia S. Corticosteroid Adverse Effects. StatPearls [Internet]. 2023 Jul 3 [cited 2024 Dec 22]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK531462/
10. Amiri D, Willy Schwarz C, Gether L, Skov L. Safety and Efficacy of Topical Calcineurin Inhibitors in the Treatment of Facial and Genital Psoriasis: A Systematic Review. Vol. 103, Acta Dermato-Venereologica. Medical Journals/Acta D-V; 2023.
11. Cláudia Paiva-Santos A, Gama M, Peixoto D, Sousa-Oliveira I, Ferreira-Faria I, Zeinali M, et al. Nanocarrier-based dermopharmaceutical formulations for the topical management of atopic dermatitis. Int J Pharm. 2022 Apr 25;618:121656.
12. Fujii M. The Pathogenic and Therapeutic Implications of Ceramide Abnormalities in Atopic Dermatitis. Cells. 2021;10(9):2386.
13. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. Vol. 75, Colloids and Surfaces B: Biointerfaces. 2010. p. 1–18.
14. Sguizzato M, Esposito E, Cortesi R. Lipid-Based Nanosystems as a Tool to Overcome Skin Barrier. Int J Mol Sci. 2021;22(15):8319.
15. Tseng YC, Mozumdar S, Huang L. Lipid-based systemic delivery of siRNA. Vol. 61, Advanced Drug Delivery Reviews. 2009. p. 721–31.
16. Labouta HI, Schneider M. Interaction of inorganic nanoparticles with the skin barrier: Current status and critical review. Vol. 9, Nanomedicine: Nanotechnology, Biology, and Medicine. 2013. p. 39–54.
17. Mall J, Naseem N, Haider MdF, Rahman MA, Khan S, Siddiqui SN. Nanostructured lipid carriers as a drug delivery system: A comprehensive review with therapeutic applications. Intelligent Pharmacy [Internet]. 2024 Sep 23 [cited 2025 Apr 1]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S2949866X24001023
18. Ramos Campos EV, Proença PLDF, Doretto-Silva L, Andrade-Oliveira V, Fraceto LF, de Araujo DR. Trends in nanoformulations for atopic dermatitis treatment. Expert Opin Drug Deliv. 2020;17(11):1615–30.

# DAMPs : The trigger molecules of persistent inflammation

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## Abstract

Damage-associated molecular Patterns (DAMPs) are endogenous molecules released on the onset of tissue injury, which activate various innate signalling cascades through pattern recognition receptors (PRRs). DAMPs are released due to stress, external stimuli, and cell death. They have been reported to play a crucial role in various disease conditions such as autoimmune disorders, cancer, chronic kidney disease, diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD). Crucial DAMPs, such as HMGB1, HSP90, S100 proteins, and ATP, tend to exert their inflammatory activity primarily through cell surface receptors, including TLR4, RAGE, CD36, P2X7, and P2Y2. The DAMPs often activate NF-κB, MAPK, and NLRP3 inflammasome formation, further increasing the inflammation via positive feedback. In the past decades, various inhibitors of DAMPs and interacting receptors have been developed, which have to be evaluated for their safety and efficacy. Further, the various signalling mechanism of the DAMPs contributing to its inflammatory function needs to be elucidated. However, DAMPs inevitably remain as a potent mediator of persistent inflammation that needs to be addressed for developing therapeutics to overcome the catastrophic effects of DAMP molecules.

**Keywords:** DAMPs, PRRs, inflammation, NLRP3

## 1. Introduction

Inflammation is a key process that initially serves as the first line of defence against external stimuli such as pathogens and damaged cells. While acute inflammation is essential for normal recovery and healing, chronic inflammation often leads to a plethora of diseases, including autoimmune disorders, cancer, chronic kidney disease, diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD) (1,2). In the absence of infection, the inflammatory response is called sterile inflammation, indicating that endogenous molecules play a role in triggering the inflammatory response. Inflammation is a fundamental component of the innate immune response, initiated when pattern recognition receptors (PRRs) detect invading pathogens or endogenous molecules released during tissue injury (3).

Upon tissue injury, endogenous molecules known as damage-associated molecular patterns (DAMPs), released from the cells, serve as the triggering molecules of inflammation by activating the innate immune system. This mechanism promotes the chemotactic recruitment of immune effector cells, such as neutrophils, phagocytes, and macrophages, to the site of cellular damage for the clearance of necrotic debris. Furthermore, DAMPs can disseminate to distal tissues or organs, where they propagate systemic inflammatory responses and mediate inter-organ communication through an inflammatory signalling network (4). DAMPS originates from various sources and includes components of the extracellular matrix, such as biglycan and tenascin-C; intracellular constituents like high-mobility group box 1 (HMGB1), S100 family

proteins, and heat shock proteins (HSPs); and plasma proteins, including fibrinogen, Gc-globulin, and serum amyloid A (SAA). PRRs such as Toll-like receptors (TLRs), RAGE, and scavenger receptors recognize various DAMPs and activate various signalling pathways, leading to the progression of persistent inflammation and related diseases (3). Thus, DAMPs are important triggers and mediators of inflammation.

## 2. Release of DAMPs

Various types of DAMPs tend to follow similar release patterns from injured or dying cells. They are primarily released during different forms of regulated cell death, including apoptosis, ferroptosis, cuproptosis, pyroptosis, necroptosis, and NETosis, as shown in Figure 1.

### 2.1. Apoptosis

Apoptosis is a form of programmed cell death that occurs without compromising the integrity of the plasma membrane, which includes distinct morphological changes like cell shrinkage, membrane blebbing, chromatin condensation, and fragmentation of DNA. During apoptosis, several molecules such as HMGB1, histones, extracellular RNAs (exRNAs), cell-free DNA (cfDNA), and ATP have been reported to be released into the extracellular environment (5).

### 2.2. Necroptosis

Necrosis, triggered by severe physical or chemical stress, leads to cell swelling and membrane rupture, often due to ATP depletion and oxidative damage. This passive cell death results in the release of DAMPs such as HMGB1, ATP, histones, HSPs, exRNAs, cfDNA, and possibly eCIRP. Reperfusion can further exacerbate damage through oxidative stress (5).

### 2.3. Pyroptosis

Pyroptosis is a caspase-dependent inflammatory cell death triggered by inflammasomes like NLRP3, activating caspase-1, or by caspase-4/5/11. Activated caspases cleave gasdermin D (GSDMD), forming membrane pores that release intracellular contents. Pyroptosis mainly releases IL-1β through GSDMD pores, while other DAMPs like HMGB1, ATP, and cfDNA are also released, often through cell lysis. Notably, HMGB1 release requires specific post-translational modifications before pyroptosis occurs (5).

### 2.4. Ferroptosis

A programmed cell death with characteristics such as mitochondrial membrane loss, chromatin condensation, cell swelling, and rupture of the plasma membrane, dependent on iron and lipid peroxidation. Ferroptosis has been shown to release HMGB1, ATP, HSPs, and cell-free DNA and calreticulin (5,6).

### 2.5. Cuproptosis

Similar to ferroptosis, Cuproptosis is a form of cell death regulated by the copper ion, characterized by its accumulation and proteotoxic stress and has been implicated in inflammatory diseases, such as atherosclerosis, inflammatory bowel disease, tumors, and neurodegenerative diseases (5).

### 2.6 NETosis

NETosis is a unique process by which neutrophils, a type of white blood cell, defend the body by casting out web-like structures known as neutrophil extracellular traps (NETs). These sticky nets, made of loosened DNA and antimicrobial proteins, help capture and destroy invading microbes. While this response is vital for fighting infections, it can sometimes go too far, triggering excessive inflammation and damaging healthy tissues, especially in autoimmune and inflammatory diseases. Histones, extracellular DNA, HMGB1, S100A8/A9, LL-37, and Myeloperoxidase (MPO) are released by NETosis, which aggravates various inflammatory diseases (7).

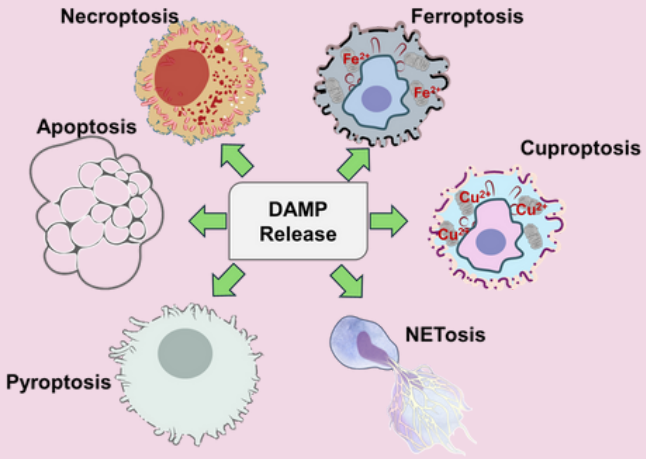


**Figure 1.** Various forms of regulated cell death contribute to the release of DAMPs.

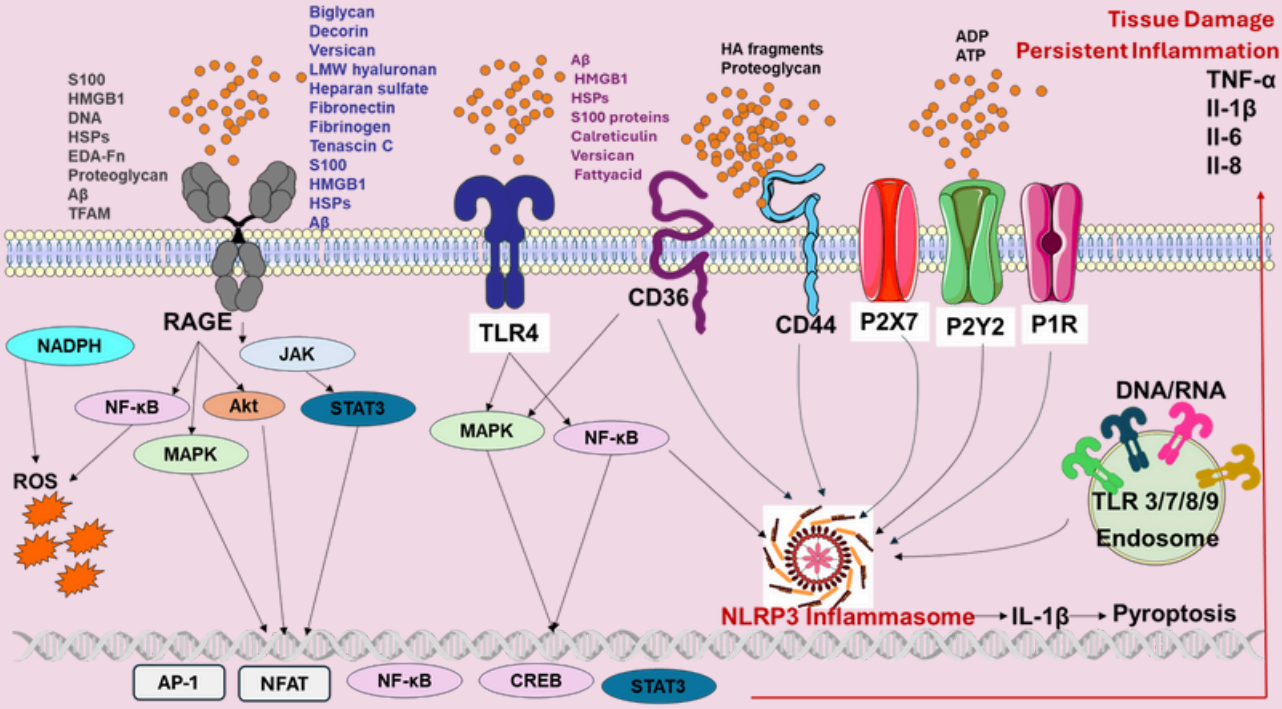


**Figure 2.** DAMPs and their interacting receptors with downstream effectors responsible for persistent inflammation. Aβ – Amyloid beta; Akt – Protein Kinase B; AP-1 – Activator Protein 1; ATP – Adenosine Triphosphate; CREB – cAMP Response Element-Binding protein; DNA – Deoxyribonucleic acid; EPA-Ffa – Eicosapentaenoic Acid–Free Fatty Acids; Fibronectin – Extracellular matrix glycoprotein; HMGB1 – High-Mobility Group Box 1; HSPs – Heat Shock Proteins; JAK – Janus Kinase; LMW hyaluronan – Low Molecular Weight Hyaluronan; MAPK – Mitogen-Activated Protein Kinase; NADPH – Nicotinamide Adenine Dinucleotide Phosphate (reduced form); NF-κB – Nuclear Factor kappa-light-chain-enhancer of activated B cells; NFAT – Nuclear Factor of Activated T-cells; NLRP3 – NOD-, LRR- and Pyrin domain-containing protein 3; P1R – Purinergic P1 Receptor; P2X7 – Purinergic Receptor P2X, Ligand-Gated Ion Channel 7; P2Y7 – Purinergic P2Y Receptor (possibly P2Y2/P2Y6); S100 – S100 calcium-binding proteins (e.g., S100A8/A9); STAT3 – Signal Transducer and Activator of Transcription 3; TFAM – Transcription Factor A, Mitochondrial; TLR 3/4/7/8/9 – Toll-Like Receptors 3, 4, 7, 8, and 9.

## 3. Role of DAMPs in inflammation and associated diseases

DAMPs like HMGB1, S100 proteins, and HSPs signal through PRRs such as TLRs, FPRs, C-type lectins, and RAGE receptors, which PAMPs also use. These activate key inflammatory pathways (e.g., NF-κB, MAPKs, inflammasomes), leading to cytokine release (IL-1β, IL-6, TNF, IFNγ) and immune cell recruitment. Chronic inflammation, especially via IL-1, IL-6, and LT-β, along with ectopic lymphoid structures near damaged tissue, may drive cancer development. DAMPS tend to initiate immunosenescence by inducing chronic inflammation or facilitating immune dysfunction, leading to tumor formation (8). The serum levels of HSP90, HMGB1, and S100A9 have been identified as potential biomarkers of cancer metastasis in cancer patients (9). HMGB1 expression is regarded as associated with hallmarks of cancer and interacting with RAGE activates oval cells and inflammation-associated liver cancer. However, it also activates NF-κB and MAPK-dependent pathways, along with cytokine release (10).

In the case of autoimmune disease, such as rheumatoid arthritis, the critical role of DAMPs has been well documented. Various studies have shown the upregulated levels of DAMPs such as HMGB1, HSP90, and S100A8, S100A9, S100A8/A9, and S100A12 in the serum, synovial fluid, and synovial tissues of RA patients. Furthermore, the proteins tend to interact predominantly with RAGE and TLR4 receptors and trigger various immunological cascades, aggravating the pathogenesis of the diseases, as shown in Figure 2. Neutralization of HMGB1 expression in the arthritic animal models has protected them from cartilage destruction (3).

In osteoarthritis, the hyaluronan, which acts as DAMP, is an ECM glycoprotein that confers its protective effect. However, when cleaved into its lower molecular weight, it exhibits proinflammatory effects via triggering cartilage destruction, production of proinflammatory cytokines, and matrix-degrading enzymes upon interaction with TLRs. Various studies have shown that the low molecular weight hyaluronan has aggravated the pathogenesis of OA (11,12). The DAMPs and their interacting receptors, along with their associated diseases, are provided in Table 1. Thus, the DAMPs play a critical role in the sustenance of inflammation in diseased conditions.

**Table 1.** List of DAMPs with their putative receptors and associated inflammatory diseases (3,16)

| Location | DAMP | Receptor(s) | Associated Diseases |
|---|---|---|---|
| Nucleus | Histones | TLR2, TLR4, NLRP3 | Kidney injury, sepsis, APAC |
| | Genomic DNA | TLR9 | SLE, AGS, liver injury, etc. |
| | HMGB1 | TLR2, TLR4, RAGE, TREM1, TLR9, cGAS, Casp11, AIM2 | Sepsis, stroke, spinal cord injury, and viral infection |
| | IL-1α | IL-1R | Inflammatory diseases |
| | IL-33 | ST2 | Inflammatory and autoimmune diseases |
| | ATP | P2X7, P2Y2, NLRP3 | RA, pain, infection, CAPS |
| | Uric acid/ sUA | NLRP3, P2X7 | Renal fibrosis, gout |
| | F-actin | DNGR-1 | Infection, sepsis |
| | Cyclophilin A | CD147 | RA, lung inflammation, liver injury |

| | | | |
|---|---|---|---|
| Cytosol | Heat Shock Proteins (HSPs) | TLR2, TLR4, CD91 | RA, tumors, vascular diseases |
| | Ferritin | TLR2, TLR4, RAGE | Inflammatory conditions |
| | S100 proteins | TLR2, TLR4, RAGE, EGFR, CD36, GPCR | Psoriasis, arthritis, tumors |
| | Aβ | *TLR2, CD36, RAGE, NLRP1, NLRP3* | Alzheimer's disease |
| Mitochondria | mtDNA | TLR9, RAGE | SLE, liver injury, infection |
| | TFAM | RAGE | Inflammation |
| | Formyl peptides | FPR1 | Intracerebral hemorrhage, injury |
| | mROS | NLRP3 | Oxidative stress-related diseases |
| ER | Calreticulin | CD91 | Tumors |
| Granules | Cathelicidin (LL-37) | P2X7, FPR2 | Infection |
| | Defensins | TLR4 | Infection, inflammation |
| | EDN | TLR2 | Inflammation |
| | Granulysin | TLR4 | Infection, immune modulation |
| Plasma Membrane | Syndecans | TLR4 | Inflammation |
| | Glypicans | | Inflammation |
| ECM | Biglycan | TLR2, TLR4, NLRP3 | Sepsis, fibrosis, RA |
| | Hyaluronan (LMW) | | RA, obesity, IBD, OA |
| | Heparan sulfate | TLR2, RAGE, TLR5 TLR4 | Inflammation, OA |
| | Fibronectin (EDA) | | RA, fibrosis, tumors |
| | Tenascin C | | RA, colitis, OA |

| | | | |
|---|---|---|---|
| Nucleic Acids | Various DNA types | TLR9, AIM2, cGAS, RAGE, IFI16, CLEC2D, NLRP3, ZBP1 | SLE, cancer, AGS, ALS, etc. |
| | RNA types | TLR7, TLR8, TLR3, RIG-I, MDA5, ZBP1 | SLE, infection, tumor, AGS |
| Others | Misfolded proteins | IRE1, PERK, PKR, ATF6 | T2D, cancer, inflammation |
| | Lipid metabolites | NLRP3, TLR4, TRPA1, CD14 | AS, inflammation, tumor |
| | Fatty acids | TLRs, NLRP3, CD36, GPR43 | Obesity, T2D, NAFLD |
| | Citrate, succinate | HIF-1α, NLRP3 | Infection, inflammation |
| | cGAMP | STING | Viral infection, cancer |

AGS – Aicardi-Goutières Syndrome, AIM2 – Absent in Melanoma 2, ALS – Amyotrophic Lateral Sclerosis, APAC – Acute Pancreatitis and Acute Cholangitis, AS – Ankylosing Spondylitis, ATF6 – Activating Transcription Factor 6, CAPS – Cryopyrin-Associated Periodic Syndromes, CD14 – Cluster of Differentiation 14, CD36 – Cluster of Differentiation 36, CD91 – Cluster of Differentiation 91, CD147 – Cluster of Differentiation 147, cGAS – Cyclic GMP-AMP Synthase, CLEC2D – C-Type Lectin Domain Containing 2D, DNGR-1 – Dendritic Cell Natural Killer Lectin Group Receptor-1, EGFR – Epidermal Growth Factor Receptor, FPR1 – Formyl Peptide Receptor 1, FPR2 – Formyl Peptide Receptor 2, GPCR – G-Protein-Coupled Receptor, GPR43 – G-Protein-Coupled Receptor 43, HIF-1α – Hypoxia-Inducible Factor 1-alpha, IBD – Inflammatory Bowel Disease, IFI16 – Interferon Gamma Inducible Protein 16, IL-1R – Interleukin-1 Receptor, IRE1 – Inositol-Requiring Enzyme 1, MDA5 – Melanoma Differentiation-Associated Protein 5, NAFLD – Non-Alcoholic Fatty Liver Disease, NLRP1 – NOD-, LRR- and Pyrin Domain-Containing Protein 1, NLRP3 – NOD-, LRR- and Pyrin Domain-Containing Protein 3, OA – Osteoarthritis, P2X7 – Purinergic Receptor P2X, Ligand-Gated Ion Channel, 7, P2Y2 – Purinergic Receptor P2Y, G-Protein Coupled, 2, PERK – Protein Kinase RNA-Like Endoplasmic Reticulum Kinase, PKR – Protein Kinase R, RA – Rheumatoid Arthritis, RAGE – Receptor for Advanced Glycation End Products, RIG-I – Retinoic Acid-Inducible Gene I, SLE – Systemic Lupus Erythematosus, ST2 – Suppression of Tumorigenicity 2, STING – Stimulator of Interferon Genes, T2D – Type 2 Diabetes, TLR – Toll-Like Receptor, TREM1 – Triggering Receptor Expressed on Myeloid Cells 1, TRPA1 – Transient Receptor Potential Ankyrin 1, ZBP1 – Z-DNA Binding Protein 1

## 4. Currently available DAMP, Receptors, and downstream effectors inhibitors.

Various molecules and biologics have been identified that target DAMPs, their receptors, and downstream signaling pathways. Several of these agents have been approved for clinical use, while others are currently under preclinical or clinical evaluation. A comprehensive summary is presented in Table 2 (DAMP inhibitors) and Table 3 (receptor antagonists).

**Table 2.** DAMPs Inhibitors

| DAMP | Inhibitor(s) | Mechanism | Ref |
|---|---|---|---|
| HMGB1 | Glycyrrhizin, Ethypyruvate, FPS-ZM1 | Binds to HMGB1 or blocks its interaction with receptors | (17–19) |
| S100A9 | Paquinimod, Tasquinimod | Binds to S100A9, preventing receptor interaction | (20) |
| Mitochondrial DNA (mtDNA) | MitoTEMPO | Reduces mtROS | (21) |
| ATP | Apyrase, P2X7 receptor blockers (e.g., A438079, KN-62) | Degrades extracellular ATP or blocks P2X7 | (22) |
| HSPs (e.g., HSP70, HSP90) | Geldanamycin, 17-AAG (Tanespimycin) | Inhibits HSP function | (23) |

**Table 3.** DAMPs Receptors Antagonists

| Receptor | Inhibitor(s) | Mechanism | Ref |
|---|---|---|---|
| TLR4 | TAK-242 (Resatorvid), Eritoran | Blocks TLR4–MD2 interaction | (24) |
| RAGE | FPS-ZM1, Azeliragon (TTP488), sRAGE (soluble decoy) | Blocks ligand binding or acts as a decoy | (25–27) |
| TLR2 | OPN-301, CU-CPT22 | TLR2 antagonists | (28,29) |
| CD36 | Sulfosuccinimidyl oleate (SSO), AP5055 | Blocks fatty acid/DAMP binding | (30,31) |
| P2X7 | A438079, AZD9056 | Inhibits ATP-mediated inflammasome activation | (32) |
| NLRP3 inflammasome | MCC950, OLT1177, CY-09, Dapansutrile | Blocks inflammasome assembly | (33,34) |

## 5. Future perspectives

In recent times, the critical role of DAMPs has been explored in various diseases. Multiple studies have shown and established DAMPs as a potent biomarker of inflammation and therapeutic targets in various diseases. Thus, there is a wide arena for further exploration to identify the therapeutic DAMPs and develop therapeutics for the treatment of inflammatory diseases.

## 6. Conclusion

Conclusively, it can be said that the DAMPs are persistent mediators of inflammation, aggravating the pathogenesis of various diseases, but not limited to cancer, SLE, Rheumatoid arthritis, and osteoarthritis. Thus, the development of potent and safe DAMP inhibitors is crucial now to mitigate the catastrophic effects of DAMPs in inflammatory diseases.

## References


1. Chavda VP, Feehan J, Apostolopoulos V. Inflammation: The Cause of All Diseases. Vol. 13, Cells. 2024.
2. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25(12):1822–32.
3. Roh JS, Sohn DH. Damage-Associated Molecular Patterns in Inflammatory Diseases. Immune Netw. 2018 Aug;18(4).
4. Shim YR, Jeong WI. Recent advances of sterile inflammation and inter-organ cross-talk in alcoholic liver disease. Exp Mol Med. 2020;52(5):772–80.
5. Murao A, Aziz M, Wang H, Brenner M, Wang P. Release mechanisms of major DAMPs. Apoptosis. 2021;26(3):152–62.
6. Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. Cell Res. 2021;31(2):107–25.
7. Qi L, Ruke C, Ziyan Z, Zhou S, Haibo W. Mechanisms and immune crosstalk of neutrophil extracellular traps in response to infection. mBio. 2025 Apr 16;16(5):e00189-25.
8. Chen F, Tang H, Cai X, Lin J, Kang R, Tang D, et al. DAMPs in immunosenescence and cancer. Semin Cancer Biol. 2024;106–107:123–42.
9. Songjang W, Nensat C, Jitpewngarm W, Jiraviriyakul A. Potential Serum HMGB1, HSP90, and S100A9 as Metastasis Predictive Biomarkers for Cancer Patients and Relevant Cytokines: A Pilot Study. Int J Mol Sci. 2024;25(24).
10. Wang S, Zhang Y. HMGB1 in inflammation and cancer. J Hematol Oncol. 2020;13(1):116.
11. Bartels YL, van Lent PLEM, van der Kraan PM, Blom AB, Bonger KM, van den Bosch MHJ. Inhibition of TLR4 signalling to dampen joint inflammation in osteoarthritis. Rheumatology. 2024 Mar 1;63(3):608–18.
12. Lambert C, Zappia J, Sanchez C, Florin A, Dubuc JE, Henrotin Y. The Damage-Associated Molecular Patterns (DAMPs) as Potential Targets to Treat Osteoarthritis: Perspectives From a Review of the Literature. Front Med (Lausanne). 2021;Volume 7-2020.
13. Cicchinelli S, Pignataro G, Gemma S, Piccioni A, Picozzi D, Ojetti V, et al. PAMPs and DAMPs in Sepsis: A Review of Their Molecular Features and Potential Clinical Implications. Int J Mol Sci. 2024;25(2).
14. Ma M, Jiang W, Zhou R. DAMPs and DAMP-sensing receptors in inflammation and diseases. Immunity. 2024 Apr 9;57(4):752–71.
15. Huang Y, Jiang W, Zhou R. DAMP sensing and sterile inflammation: intracellular, intercellular and inter-organ pathways. Nat Rev Immunol. 2024;24(10):703–19.
16. Kang N, Liu X, Haneef K, Liu W. Old and new damage-associated molecular patterns (DAMPs) in autoimmune diseases. Rheumatology & Autoimmunity. 2022 Dec 1;2(4):185–97.

17. Oh H, Choi A, Seo N, Lim JS, You JS, Chung YE. Protective effect of glycyrrhizin, a direct HMGB1 inhibitor, on post-contrast acute kidney injury. Sci Rep. 2021;11(1):15625.
18. Zhang T, Guan XW, Gribben JG, Liu FT, Jia L. Blockade of HMGB1 signaling pathway by ethyl pyruvate inhibits tumor growth in diffuse large B-cell lymphoma. Cell Death Dis. 2019;10(5):330.
19. Qiao X, Li W, Zheng Z, Liu C, Zhao L, He Y, et al. Inhibition of the HMGB1/RAGE axis protects against cisplatin-induced ototoxicity via suppression of inflammation and oxidative stress. Int J Biol Sci. 2024;20(2):784–800.
20. Khayer N, Jalessi M, Farhadi M, Azad Z. S100a9 might act as a modulator of the Toll-like receptor 4 transduction pathway in chronic rhinosinusitis with nasal polyps. Sci Rep. 2024;14(1):9722.
21. Wen JJ, Williams TP, Cummins CB, Colvill KM, Radhakrishnan GL, Radhakrishnan RS. Effect of Mitochondrial Antioxidant (Mito-TEMPO) on Burn-Induced Cardiac Dysfunction. J Am Coll Surg. 2021;232(4).
22. Drill M, Jones NC, Hunn M, O'Brien TJ, Monif M. Antagonism of the ATP-gated P2X7 receptor: a potential therapeutic strategy for cancer. Purinergic Signal. 2021;17(2):215–27.
23. Lee EJ. Cancer Chemoprevention Effects of Geldanamycin and 17-AAG in Human Oral Squamous Cell Carcinoma. The Korean Journal of Clinical Laboratory Science. 2018;50(4):462–9.
24. Samarpita S, Kim JY, Rasool MK, Kim KS. Investigation of toll-like receptor (TLR) 4 inhibitor TAK-242 as a new potential anti-rheumatoid arthritis drug. Arthritis Res Ther. 2020;22(1):16.
25. Audard J, Godet T, Blondonnet R, Joffredo JB, Paquette B, Belville C, et al. Inhibition of the Receptor for Advanced Glycation End-Products in Acute Respiratory Distress Syndrome: A Randomised Laboratory Trial in Piglets. Sci Rep. 2019;9(1):9227.
26. Liu Y, Shen W, Chen Q, Cao Q, Di W, Lan R, et al. Inhibition of RAGE by FPS-ZM1 alleviates renal injury in spontaneously hypertensive rats. Eur J Pharmacol. 2020;882:173228.
27. Magna M, Hwang GH, McIntosh A, Drews-Elger K, Takabatake M, Ikeda A, et al. RAGE inhibitor TTP488 (Azeliragon) suppresses metastasis in triple-negative breast cancer. NPJ Breast Cancer. 2023;9(1):59.
28. Ahmad B, Choi S. Unraveling the Tomaralimab Epitope on the Toll-like Receptor 2 via Molecular Dynamics and Deep Learning. ACS Omega. 2022 Aug 16;7(32):28226–37.
29. Cheng K, Wang X, Zhang S, Yin H. Discovery of Small-Molecule Inhibitors of the TLR1/TLR2 Complex. Angewandte Chemie International Edition. 2012 Dec 3;51(49):12246–9.
30. Rekhi UR, Catunda RQ, Alexiou M, Sharma M, Fong A, Febbraio M. Impact of a CD36 inhibitor on Porphyromonas gingivalis mediated atherosclerosis. Arch Oral Biol. 2021;126:105129.
31. Kuda O, Pietka TA, Demianova Z, Kudova E, Cvacka J, Kopecky J, Abumrad NA. Sulfo-N-succinimidyl oleate (SSO) inhibits fatty acid uptake and signaling for intracellular calcium via binding CD36 lysine 164: SSO also inhibits oxidized low density lipoprotein uptake by macrophages. J Biol Chem. 2013 May 31;288(22):15547-55.
32. Zhang W jun, Luo C, Huang C, Pu F qin, Zhu J feng, Zhu Z ming. PI3K/Akt/GSK-3β signal pathway is involved in P2X7 receptor-induced proliferation and EMT of colorectal cancer cells. Eur J Pharmacol. 2021;899:174041.
33. Teske KA, Corona C, Wilkinson J, Mamott D, Good DA, Zambrano D, et al. Interrogating direct NLRP3 engagement and functional inflammasome inhibition using cellular assays. Cell Chem Biol. 2024;31(2):349-360.e6.
34. Klück V, Jansen TLTA, Janssen M, Comarniceanu A, Efdé M, Tengesdal IW, et al. Dapansutrile, an oral selective NLRP3 inflammasome inhibitor, for treatment of gout flares: an open-label, dose-adaptive, proof-of-concept, phase 2a trial. Lancet Rheumatol. 2020 May 1;2(5):e270–80.

# Targeting interleukins: An approach for management of inflammatory skin diseases



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**Abstract**
Inflammatory skin diseases (ISDs) are a group of skin diseases that are a result of an immunological reaction or autoimmunity. They are characterized by the production of cytokines like interleukins (ILs). Such disorders include acne, psoriasis, vitiligo etc. Studies have concluded that the significant role of various ILs in the majority of ISDs makes it a highly potent target for treatment. This article outlines various available therapies, presents challenges in targeting ILs, novel targeting approaches and upcoming possibilities for effective management of ISDs.

**Keywords**: Interleukins, inflammation, skin diseases

## 1. Introduction

### 1.1. Inflammatory skin diseases

ISDs are characterized by the production of proinflammatory cytokines, resulting in activation of innate and adaptive immunity. These are categorized as autoimmune and autoinflammatory diseases. Autoimmune disease like lupus erythematosus, Sjögren's syndrome, and vitiligo involves the roles of B and T cells in errant responses to autoantigen and autoantibodies. Whereas autoinflammatory skin diseases result in tissue damage due to activation of innate immune cells like neutrophils, natural killer cells, and mast cells. Few diseases involve both components, autoinflammatory and autoimmune, such as psoriasis, lichen planus, and allergic contact dermatitis (1,2).

### 1.2. Interleukins & their role in inflammatory skin disorders

ILs are a class of cytokines that are produced by various cells of the body, like leukocytes. Alteration in expression of ILs can cause proliferation, differentiation and activation to modulate during immune responses and inflammation (3,4). They play a significant role in the pathogenesis of ISDs like psoriasis and lupus erythematosus. Psoriasis is a chronic relapsing autoimmune disorder characterized by silvery scales, dryness and inflamed skin. IL-1α and IL-1β have been known to be a part of early pathogenesis in psoriasis. The expression level of protein of IL-36γ are higher in psoriasis as compared to other ISDs like atopic dermatitis (AD), eczema, etc. The missense mutation in a gene coding for IL-36 Ra results in decreased production of IL-36, this deficiency causes the generation of pustular psoriasis (5,6). IL-17 produced by neutrophils, is one of the most studied pro-inflammatory cytokines that has been associated with several pathways in the pathogenesis of skin diseases mediated by immune responses, including vitiligo, psoriasis, lichen planus and acne. Presence of neutrophils in skin biopsy samples of ISDs like psoriasis and pyoderma gangrenosum (PG) confirms the role of IL-17 and neutrophil activity in such disorders. Further, IL-6 and IL-8 are neutrophil-activating cytokines induced by IL-17, thus aggravating the severity of the disease. IL-23 levels are found to be elevated in PG and AD. Also, in vivo studies on the mouse model suggest that upregulation of

IL-25 (IL-17E) in AD causes the release of endothelin-1, resulting in pruritus development. Nonetheless, IL-17 can also serve as a marker of the disease severity in conditions like erosive lichen planus and systemic lupus erythematosus (7,8).

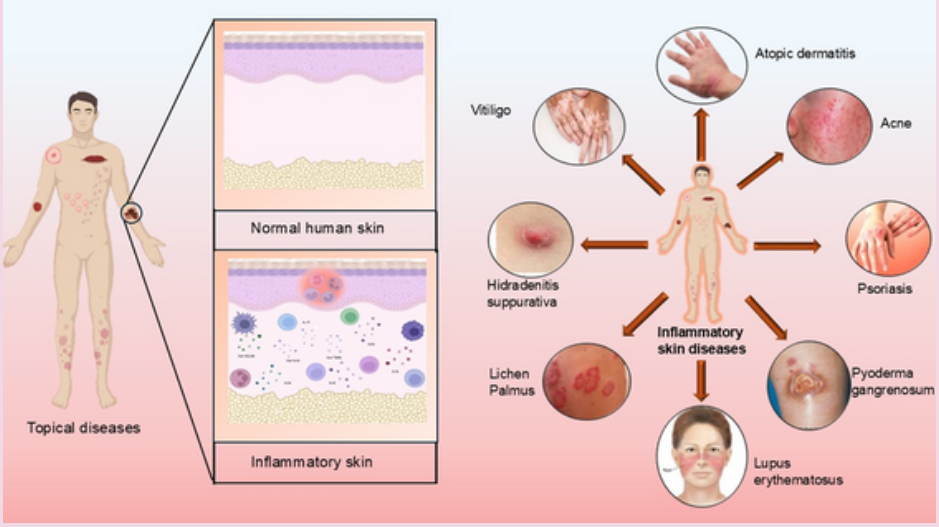


**Figure 1**. Types of IL- IL-associated IS

## 2. Available treatment for targeting interleukins

Over the years, research and clinical trials have concluded that ILs are a promising therapeutic target for effective management of ISDs. The major section of therapies targeting ILs consists of monoclonal antibodies (mAbs). Treatment options other than anti-ILs therapy include corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) and pulsed laser therapies. Though all these therapies have a significant effect on reducing the disease severity, but present side effects like telangiectasia, teratogenicity, bone marrow suppression etc. (9). Several IL inhibitors are available in the market. Approved mAbs for AD include dupilumab (inhibitor of IL-4Ra) and tralokinumab (inhibitor of IL-13). Tozorakimab, fezakinumab, and eblasakimab are a few agents explored under clinical trials for AD. Similarly, mAbs for the treatment of psoriasis include ustekinumab, secukinumab, brodalumab and so on (10). Majorly, agents acting on IL-23/IL-17 axis are widely explored and an effective treatment option for psoriasis; secukinumab, ixekizumab, briakinumab and risankizumab are examples of approved agents, to name a few (11). Further IL-1 (IL-1α and IL-1β) inhibiting agents such as anakinra, canakinumab and rilonacept are also dominant in the market with wider application in skin conditions including inflammation like Schnitzler syndrome, hidradenitis suppurativa and Sweet's syndrome. Gevokizumab is a novel IL-1 inhibitory agent that is in the clinical trial stage for the treatment of acne (12).

## 3. Challenges in interleukins targeted drug delivery

Despite the therapeutic potential of IL-targeted drug delivery in ISDs, it faces several challenges such as skin barrier penetration, off-target effects, and drug stability.

### 3.1. Physical barrier and skin environment

Inflammation causes edema and altered tissue structure of the skin. Further inflammatory skin environments are chemically hostile, characterized by elevated protease activity, oxidative stress, acidic pH, and increased immune cell infiltration which can rapidly degrade biologics in diseases like AD. These pathological changes hinder the topical delivery of the ILs-targeted agents which are usually hydrophilic large molecules (9). The inflammatory process itself can also lead to changes in the expression and availability of target molecules, affecting the effectiveness of the inhibitors (13).

For example, Secukinumab, an IL-17A inhibitor used in psoriasis, must be administered subcutaneously because it cannot penetrate thickened SC. However, lower drug loading and patient acceptability are challenges in approaches explored to deliver secukinumab topically (14). Another example is Ixekizumab which has protein structure that makes it susceptible to enzymatic degradation by protease in the body, contributing to their metabolic clearance and relatively shorter half-lives compared to other biologics (7).

### 3.2. Challenges in systemic drug delivery

Systemic administration can lead to widespread immunosuppression, increasing the risk of infections and other systemic side effects. Dupilumab, an IL-4 and IL-13 inhibitor used in the treatment of AD, must be administered via the subcutaneous route. It has high systemic side effects such as conjunctivitis, oral herpes, and cold sores on the mouth/lips (15).

### 3.3. Formulation related challenges

Proper folding is critical for antibody function, and aggregation is the most frequent issue in mAbs, impacting both potency and safety of treatments. To address this, several strategies are employed, including glycosylation, modifying protein charge, and rationally designing antibodies to eliminate aggregation-prone regions. Moreover topical vehicles like gels or creams may affect structural integrity and activity (16).

## 4. Novel targeting approaches

Systemic delivery of IL-targeted therapeutic agents like mAbs may lack specificity and cause systemic toxicity. Novel targeted drug delivery approaches that focus on IL modulation can enhance the treatment precision and minimize systemic side effects (Table 1).

**Table 1**. Novel targeting approaches focusing on IL modulation

| S. No. | Targeting Approach | Drug | Formulation | Remarks | Ref |
|---|---|---|---|---|---|
| 1 | Amphiphilic lipid nanocarrier | Erlotinib and IL36 siRNA | Topical delivery of IL36 siRNA with erlotinib in psoriasis by using novel amphiphilic lipid augments | The delivery of erlotinib and IL36 siRNA was increased by developing the cationic lipid nanocarrier, which disrupts the stratum corneum layer of the skin. | (17) |
| 2 | Thermoresponsive Polymeric Dexamethasone Prodrug | Dexamethasone | N- (2-hydroxypropyl) methacrylamide (HPMA) copolymer based thermoresponsive dexamethasone prodrug (ProGel-Dex) | The ProGel-DEX has shown improved efficacy and safety in treating psoriasis as compared to topical dexamethasone treatment | (18) |
| 3 | Nanoemulsion | Pioglitazone | nanoemulsion of pioglitazone (PGZ) as a topical cream | This formulation significantly reduced inflammatory cytokines (IL-6, IL-1β, TNF-α) and improved stratum corneum structure. Histopathology revealed decreased dermal thickness and inflammatory cell infiltration in atopic dermatitis. | (19) |
| 4 | Nanocapsules | Cycosporin-A | PLGA nanocarriers were prepared by solvent displacement method for atopic dermatitis | Cyclosporin A showed enhanced penetration into deeper skin layers and reduced pro-inflammatory cytokine levels. IL-6 and IL-8 levels decreased by ~50%, highlighting strong anti-inflammatory activity. | (20) |

| | | | | | |
|---|---|---|---|---|---|
| 5 | novel self-diffusible polymeric nanoparticle loaded in silk fibrin hydrogel | curcumin | Curcumin was encapsulated in self-assembled polymeric nanoparticles formed from RRR-α-tocopheryl succinate-grafted ε-polylysine (VES-g-ε-PLL) conjugates. | The positively charged nanoparticles enhanced skin penetration and, when incorporated into a silk fibroin hydrogel, diffused into deeper layers. In vivo studies confirmed significant reductions in TNF-α, NF-κB, and IL-6 levels. | (21) |
| 6 | Micellpelex | siRNA | Micellpelex consisted of tri block micelles (poly (ethylene glycol)-b-poly (L-lysine)-b-poly (L leucine) (PEG-PLL-PLLeu) | The prepared micelles demonstrated high transfection efficiency, no cytotoxicity, effective DNA condensation, and lysosomal escape, making them efficient nonviral gene delivery vectors. They successfully knocked down Rel expression, reducing IL-23 and IL-17 levels. | (22) |
| 7. | Chitosan-based NPs | hydrocortisone (HC) and hydroxytyrosol (HT) | Chitosan nanoparticles were prepared by the ionic cross-linking method | Co-loaded nanoparticles of hydrocortisone and hydroxytyrosol demonstrated enhanced skin accumulation,reduced systemic permeation, and improved therapeutic outcomes in atopic dermatitis. This delivery system offers a promising approach for effective and safer topical treatment. | (23) |
| 8. | Dual targeting fusion protein (DTF) | Anti- IL-17A scFv/ sTNFR1-Fc | DTF is generated with an anti-IL-17 A single chain variable fragment, a soluble TNF receptor 1, and a 32-amino-acid linker which was used to join the two parts. | The prepared fusion protein was found to be more potent thanetanercept in ameliorating psoriasis. It reduces the expression of keratin in psoriasis like skin in mice. | (24) |
| 9. | Polymeric nanoparticles | Isotretinoin | Isotretinoin-delonix polymeri nanoparticles by nanoprecipitation method | The polymeric nanoparticles shows 3 fold higher accumulation of drug in hair follicles compared to plain drug solution, acts on IL-6 expression and reduced the photo irritation | (25) |

### 4.1. Vesicular system

Vesicular delivery systems, including liposomes, niosomes, transferosomes and ethosomes are emerging as effective platforms for delivering ILs inhibitors. These nanocarriers can encapsulate both hydrophilic and lipophilic drugs, protecting sensitive biologics like mAbs or cytokine inhibitors from degradation. Their lipid-based composition allows for enhanced interaction with the skin barrier, improving the penetration through the SC and facilitating targeted delivery to inflamed tissues. In diseases such as psoriasis and AD, vesicular systems can localize the action of ILs inhibitors at the site of inflammation, thereby minimizing the systemic exposure and associated side effects (26).

#### 4.1.1. Lipid nanoparticles

Among various lipid-based carrier systems, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are considered highly effective for dermal drug delivery. Their small particle size and high lipid content allow them to adhere closely to the skin, forming a uniform, occlusive film over the SC. This film enhances skin hydration and improves drug retention at the application site. Additionally, incorporating the drug within the lipid matrix enhances its chemical stability by protecting it from degradation and minimizing leaching. These systems also offer favorable aesthetic characteristics like their opaque appearance, smooth texture, and fluid consistency. This results in a light, non-greasy skin feel, making them more comfortable and appealing for patients, which is especially important for long-term use in chronic ISDs (27).

#### 4.1.2. Microneedles (MNs)

MNs offer a promising strategy for delivering biologics in ISDs by overcoming the barrier posed by the SC. They create microchannels that allow large biomolecules, such as IL inhibitors, to penetrate directly into the epidermis and dermis, where inflammation is active. Additionally, MNs can be designed using biodegradable materials that protect biologics from degradation in the hostile inflamed environment. Their minimally invasive, painless nature makes them patient-friendly, encouraging better adherence (28).

#### 4.1.3. Polymeric nanoparticles

Polymeric nanoparticles are highly promising carriers due to their customizable properties and biocompatibility. Their size, shape, surface charge, and composition can be precisely engineered to deliver fragile mAbs which allows for enhanced stability, prolonged release, and targeted accumulation at inflamed sites. Their biodegradability further reduces long-term toxicity risks. Additionally, control over polymer chemistry and supramolecular assembly enables the design of stimuli-responsive systems that can release biologics in response to skin-specific triggers like pH or enzymes. These features make polymeric nanoparticles a robust platform for localized, sustained, and safe delivery of biologics in chronic ISDs (29).

### 4.2. Hydrogel

A hydrogel is a 3-D network of hydrophilic polymers that can absorb and retain a large amount of water. The long-term systemic administration of IL-targeting biologics poses a greater risk of adverse effects compared to topical treatments. The biologics entrapped hydrogels facilitate the delivery of the drug directly to the affected skin areas in a controlled manner. The added advantage of hydrogel is that it allows the maintenance of the structural integrity of biological and large molecules (30).

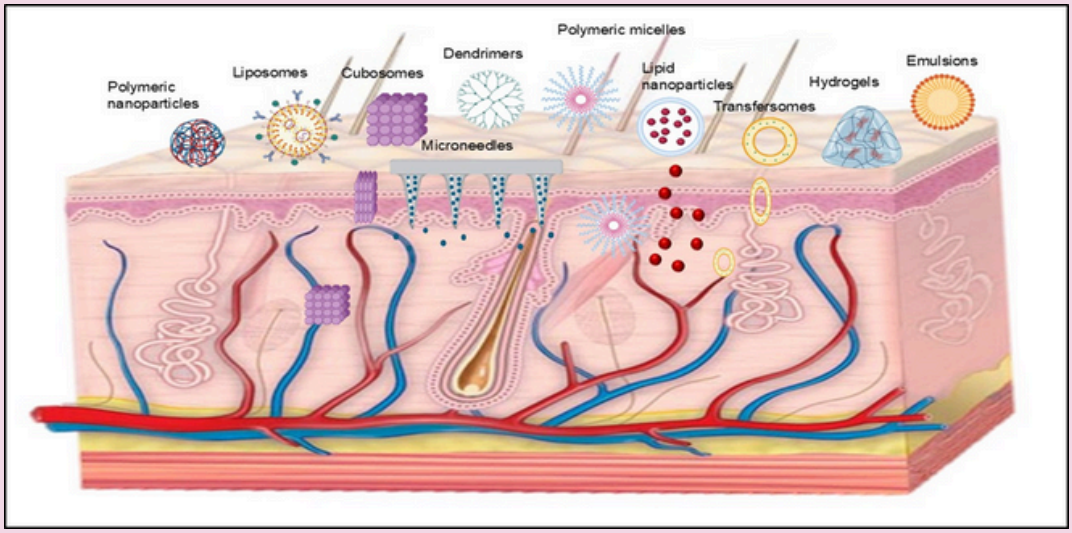


**Figure 2**. Drug Delivery approaches for IL targeted therapy in ISDs

## 5. Future prospects

Current treatment modalities use single agent for treatment of ISDs. But the complexity of immune system, which includes several signalling pathways demands for targeting multiple ILs. Targeting multiple ILs would provide synergistic effects. One such example is Sanofi's tetravalent bispecific tandem immunoglobulin that inhibits both IL-4 and IL-13. Such agents open window for new opportunities to explore dual effect that is both systemic and local effects. However, use of fixed combination drugs may be complex to study the effect of single drug on treatment (30).

## 6. Conclusion

ILs are crucial part of pathogenesis of ISDs, making then promising target for therapeutic intervention. Current treatment strategies have certain barriers like stability issue and systemic side effects, also targeted delivery is challenging. These issues can be resolved by employing discussed novel drug delivery. However, research and advancements in the therapeutic agents and their delivery systems are encouraged to improve IL-targeted therapy and quality of life of patients with ISDs.

## References

1. Mesas-Fernández A, Bodner E, Hilke FJ, Meier K, Ghoreschi K, Solimani F. Interleukin-21 in autoimmune and inflammatory skin diseases. Eur J Immunol. 2023;53(4):1–12.
2. Sheida Naderi-Azad, medical student, University of Toronto Faculty of Medicine, Toronto, ON C. DermaNet. Inflammasomes and inflammatory skin diseases. Available from: https://dermnetnz.org/topics/inflammasomes-and-inflammatory-skin-diseases
3. Weiss E, Mamelak AJ, La Morgia S, Wang B, Feliciani C, Tulli A, et al. The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases. J Am Acad Dermatol. 2004;50(5):657–75.
4. Angel A. Justiz Vaillant; Ahmad Qurie. Interleukin [Internet]. StatPearls. StatPearls Publishing LLC; Available from: https://www.ncbi.nlm.nih.gov/books/NBK499840/
5. Buhl A lena, Wenzel J. Interleukin-36 in Infectious and Inflammatory Skin Diseases. 2019;10(May):1–11.
6. D LC, Fiocco Z, Satoh TK, Peris K, French LE, Calabrese L. Therapeutic potential of targeting interleukin-1 family cytokines in chronic inflammatory skin diseases *. 2022;10(Table 2):925–41.
7. Speeckaert R, Lambert J, Grine L, Van Gele M, De Schepper S, van Geel N. The many faces of interleukin-17 in inflammatory skin diseases. Br J Dermatol. 2016;175(5):892–901.
8. Beelen AJ Van, Teunissen MBM, Kapsenberg ML, Jong EC De. Interleukin-17 in inflammatory skin disorders. 2007;(II):374–81.
9. Guo JW, Jee SH. Strategies to develop a suitable formulation for inflammatory skin disease treatment. Int J Mol Sci. 2021;22(11).
10. Bieber T. Disease modification in inflammatory skin disorders: opportunities and challenges. Nat Rev Drug Discov. 2023;22(8):662–80.
11. Tsai YC, Tsai TF. Anti-interleukin and interleukin therapies for psoriasis: current evidence and clinical usefulness. Ther Adv Musculoskelet Dis. 2017;9(11):277–94.
12. Fenini G, Contassot E, French LE. Potential of IL-1, IL-18 and inflammasome inhibition for the treatment of inflammatory skin diseases. Front Pharmacol. 2017;8(MAY):1–20.
13. Raina N, Rani R, Thakur VK, Gupta M. New Insights in Topical Drug Delivery for Skin Disorders: From a Nanotechnological Perspective. ACS omega. 2023 Jun;8(22):19145–67.
14. Type I, Gazala I. The development of a liposomal form Secukinumab – an IL 17 pathway inhibitor in the treatment of psoriasis. 2025;
15. Hemrajani C, Negi P, Parashar A, Gupta G, Jha NK, Singh SK, et al. Overcoming drug delivery barriers and challenges in topical therapy of atopic dermatitis: A nanotechnological perspective. Biomed Pharmacother. 2022;147:112633.
16. Stevens N, Cowin A. Overcoming the challenges of topical antibody administration for improving healing outcomes: a review of recent laboratory and clinical approaches. Wound Pract Res. 2017;25:188.

17. Boakye CHA, Patel K, Doddapaneni R, Bagde A, Marepally S, Singh M. Novel amphiphilic lipid augments the co-delivery of erlotinib and IL36 siRNA into the skin for psoriasis treatment. J Control release Off J Control Release Soc. 2017 Jan;246:120–32.
18. Jiang H, Fu X, Zhao G, Du X, Georgesen C, Thiele GM, et al. Intradermal Injection of a Thermoresponsive Polymeric Dexamethasone Prodrug (ProGel-Dex) Ameliorate Dermatitis in an Imiquimod (IMQ)-Induced Psoriasis-like Mouse Model. Mol Pharm. 2024;21(10):4995–5004.
19. Espinoza LC, Silva-Abreu M, Calpena AC, Rodríguez-Lagunas MJ, Fábrega MJ, Garduño-Ramírez ML, et al. Nanoemulsion strategy of pioglitazone for the treatment of skin inflammatory diseases. Nanomedicine. 2019 Jul;19:115–25.
20. Badihi A, Frušić-Zlotkin M, Soroka Y, Benhamron S, Tzur T, Nassar T, et al. Topical nano-encapsulated cyclosporine formulation for atopic dermatitis treatment. Nanomedicine. 2020 Feb;24:102140.
21. Mao KL, Fan ZL, Yuan JD, Chen PP, Yang JJ, Xu J, et al. Skin-penetrating polymeric nanoparticles incorporated in silk fibroin hydrogel for topical delivery of curcumin to improve its therapeutic effect on psoriasis mouse model. Colloids Surf B Biointerfaces. 2017 Dec;160:704–14.
22. Fan T, Wang S, Yu L, Yi H, Liu R, Geng W, et al. Treating psoriasis by targeting its susceptibility gene Rel. Clin Immunol. 2016 Apr;165:47–54.
23. Hussain Z, Katas H, Mohd Amin MCI, Kumolosasi E, Buang F, Sahudin S. Self-assembled polymeric nanoparticles for percutaneous co-delivery of hydrocortisone/hydroxytyrosol: an ex vivo and in vivo study using an NC/Nga mouse model. Int J Pharm. 2013 Feb;444(1–2):109–19.
24. Liu Z, Liu H, Xu P, Yin Q, Wang Y, Opoku YK, et al. Ameliorative effects of a fusion protein dual targeting interleukin 17A and tumor necrosis factor α on imiquimod-induced psoriasis in mice. Biomed Pharmacother [Internet]. 2018;108:1425–34. Available from: https://www.sciencedirect.com/science/article/pii/S0753332218352211
25. Ogunjimi AT, Chahud F, Lopez RF V. Isotretinoin-Delonix polymeric nanoparticles: Potentials for skin follicular targeting in acne treatment. Int J Pharm [Internet]. 2021;610:121217. Available from: https://www.sciencedirect.com/science/article/pii/S0378517321010231
26. Gupta M, Udita A, and Vyas SP. Nanocarrier-based topical drug delivery for the treatment of skin diseases. Expert Opin Drug Deliv. 2012 Jul;9(7):783–804.
27. Arora R, Sameer S. K, Varun K, and Jain S. Solid lipid nanoparticles and nanostructured lipid carrier-based nanotherapeutics in treatment of psoriasis: a comparative study. Expert Opin Drug Deliv. 2017 Feb;14(2):165–77.
28. Han Y, Qin X, Lin W, Wang C, Yin X, Wu J, et al. Microneedle-Based Approaches for Skin Disease Treatment. Nano-Micro Lett. 2025;17(1):132.
29. Elsabahy M, Wooley KL. Design of polymeric nanoparticles for biomedical delivery applications. Chem Soc Rev. 2012;41(7):2545–61.
30. Cao H, Wang M, Ding J, Lin Y. Hydrogels: a promising therapeutic platform for inflammatory skin diseases treatment. J Mater Chem B. 2024;12(33):8007–32.

Name: _____



# Contributing Factors to Inflammation

N Q B R U V T L E R F N P P E A V S Y Z
S T T D A F E Y V H Z D V K P F X T H C
S A S V S J M S P E J E V W F S L Z X N
K W W K B X E H B H G K R Q W B Z J P O
F S C V R L C K T A X O B E A B N B L I
Y A D I E T O T V Y I J V P S U R K Y T
P S J Y M U L L T H A M P Z H N E B X C
I X O N T K H E K S T Y P G J V U K L A
P U X I K I Z X T Y A E S U Y Y F W Z E
G G W M U Y S R X G J T P G F E I W E R
L N L S Y S E E U K N K Q S K A M H P E
T B O V B S Y Q B M Y I N F E C T I O N
R A T D S M N R W O S H K F V A F T X U
N H Z E Q K X S U G J A Z O V N H N D M
K C G R E N Y H R J J L L V M B R O Z M
K M Y A M H O R M O N E S P O S J F O I
B A U V C D K E I J A I D M O G L X C O
E F K W N O V B E Y W S N A H E R R I T
Z M Z T R X Y N J A S F B A Z B N J Z U
E L Y T S E F I L Y R A T N E D E S X A

AGE
AUTOIMMUNE REACTION
DIET
HORMONES
INFECTION
INJURY
NEOPLASM
OBESITY
SEDENTARYLIFESTYLE
SMOKING
STRESS

**Answers on Page 100**

# Inflammation and aging: Unraveling cellular signals and innovative therapies

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**Abstract**

As we grow older, our body starts to experience persistent, low grade inflammation- referred to as inflammaging. Unlike the acute responses which promotes healing, this chronic inflammation acts as a wildfire which leads to initiation and progression of various age-related disorders including cardiovascular disease, metabolic and neurological disorders. Inflammaging arises as a result of combination of complex overlapping processes- cellular senescence, gradual weakening of the immune system (immunosenescence) and build up of cellular stress and damage. These process together create a self-reinforcing cycle that along with driving aging at cellular level also contributes in overall physical and mental decline. The article explores how inflammaging impacts different organs and tissues in the body. Additionally, it highlights the promising therapeutic strategies such as senolytic drugs, anti-inflammatory compounds, life-style modification, which aims at restoring healthy body and support resilient aging.

**Keywords**: Aging, cellular senescence, inflammation, immunosenescence, therapeutic strategies

## 1. Introduction

Aging refers to a complex biological process shaped by various factors including genetic suspectibility, lifestyle, metabolic alterations and enviromental contact. These factors gradually accumulates worsening the body system over the years and lead to functional decline of the tissues and organs. Among the many changes that occur due to aging, inflammaging has come out as a key contributor to age-related functional decline (1,2). Inflammaging refers to a state of persistent low-level chronic inflammation which acts as a menace for the body. This chronic response is fueled by variouss overlapping process, one among which is cellular senescence. In this phenomenon the cells permanently lose their ability to divide

because of DNA damage, telomerase shortening or oxidative stress- all of these acts as a stressor. The senescent cells then release a mix of bioactive compounds including cytokines, proteases, growth factors and chemokines collectively known as Senescence-associated secretory phenotype (SASP), which spreadout the inflammation and hinders the tissue repair process.

Another process contributing to inflammaging is immunosenescence, which refers to the gradual decline or weakning of immune response with aging. As individual grows older, the adaptive immune response weakens, losing its potential to fight pathogens or respond actively to vaccines, while the innate immune response becomes erratic, often hyperactive contributing to chronic inflammation. This imbalance is responsible for worsening the balanced state of body, increasing vulnerability to chronic diseases and infections (3).

These overlapping processes which includes cellular senescence, immunosenescence and molecular damage fuel a vicious cycle of inflammation, that accelarates aging, contributing to the intiation of age-related disorders including cardiovascular disorders, diabetes, cancer, neurodegeneration and sarcopenia (figure 1).

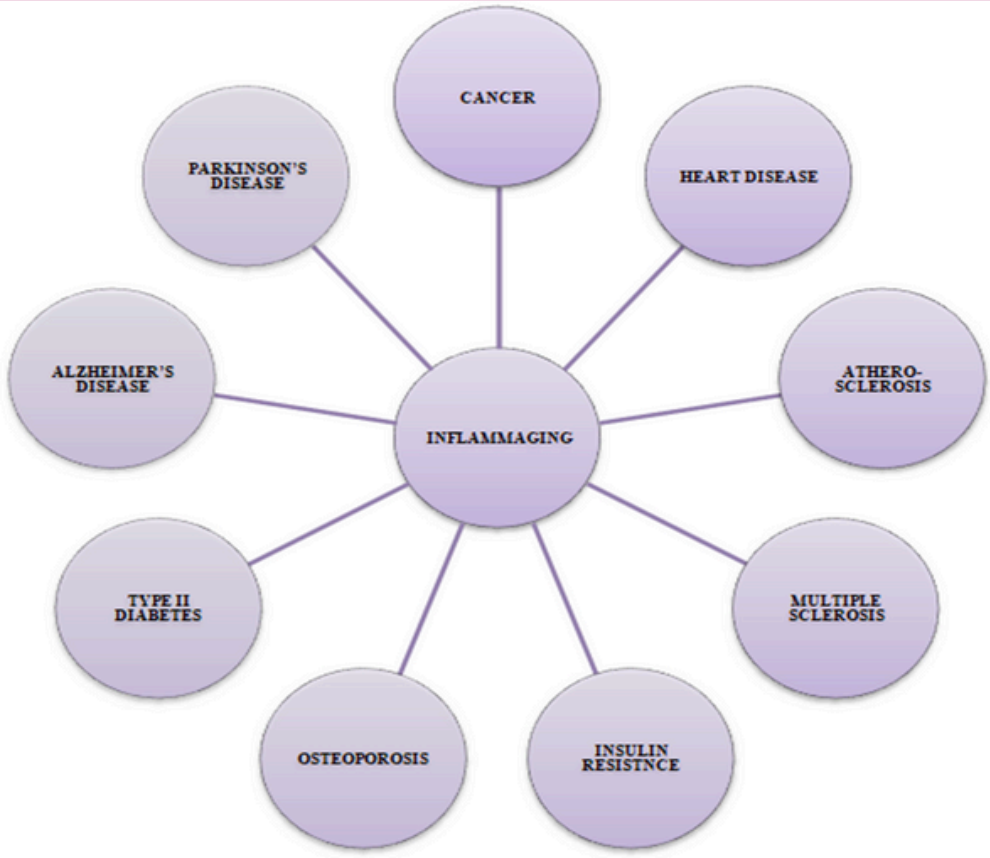


**Figure 1**. Spectrum of age-related diseases linked to chronic inflammation

Inflammaging has become a key focus area, with widespread growing interest in healthy aging. Researchers are exploring novel therapeutics such as senolytics, immuno-modulators in order to slow down or reduce the aging process, opening doors for resilient aging and improving quality of life of people.

## 2. Inflammaging at the cellular level

### 2.1. Senescence-associated secretory phenotype (SASP)

Cellular senescence refers to a state where the cells permanently lose their ability to divide, but remain active in terms of signalling and metabolism. Instead of becoming dormant, these cells begin to release wide range of biologically active substances collectively termed as SASP (Senescence-associated secretory phenotype). These bioactive compounds include pro-inflammatory cytokines like

(IL-1, IL-6, TNF-α), growth factors, chemokines and enzymes such as matrix metalloproteinases (MMPs), that are responsible for degrading matrix enzymes. SASP displays positive role by helping in wound healing and preventing cancer by halting damaged cells growth. But when the senescent cells keep on accumulating over time, the continuous release of SASP factors lead to chronic inflammation, disrupting normal tissue structure. These signals further spread to healthy cells inducing them to also undergo senescence. This further creates a dominant effect worsening situation by weakening the tissue functionality intensifying inflammation. This chain plays a key role in inflammaging, therefore understanding and exploring ways to suppress harmful effects of SASP and target the senescent cells is now the major focus area in order to promote healthy aging (4).

### 2.2. Hematopoietic stem cell (HSC) dysfunction

As one grows older, Hematopoietic stem cells (HSCs), the cells tasked with maintaining body's blood and immune cells beings to lose their efficiency. They lose their ability to self renew and forms more myeloid cells- cells of the innate immune system, at the expense of the lymphoid cells, which are important for adaptive immunity, with a resulting distorted immune response. This age-induced alteration is attributed to elevated amounts of pro-inflammatory signals including Interleukin (IL-1) and granulate colony stimulating factor (G-CSF). Second, the maintenance of the integrity of the milieu surrounding HSC's within bone marrow via signalling pathway CXCL12/CXCR4 fails with advancing age. Also, increased ROS and enhanced genomic instability, which deteriorates the ability of HSC's further are generated through aging. The overall impact of these alternations is a weakened immune system with an inflammatory bias. Inflammaging is a low grade chronic inflammation that is characteristic of aging and contributes significantly to the pathogenesis of age-related disease (5).

### 2.3. Immune cell aging

Various elements of the immune system face functional decline with growing age, with further leads to immunoscence. They are as follows:

- **2.3.1. Neutrophils:** Although their numbers remain relatively stable, aged neutrophils show reduced chemotaxis, phagocytic activity, and oxidative burst, impairing their ability to eliminate pathogens (6).
- **2.3.2. Monocytes/macrophages:** With aging, their characteristics shift toward a more pro-inflammatory state marked by elevated SASP secretion, while reduced autophagic activity results in the buildup of cellular debris and exacerbates inflammation (7).
- **2.3.3. Natural killer (NK) cells:** These cells experience a reduction in cytotoxic granule release and diminished cytokine production, weakening the response to tumors and viral infections (8).
- **2.3.4. B and T Lymphocytes:** Advancing age leads to a decline in lymphocyte diversity, diminished proliferative capacity, and weakened responsiveness to antigens. Moreover, there is a tendency toward pro-inflammatory memory cell phenotypes, which sustains chronic systemic inflammation (9).

## 3. Inflammaging at the organ level

### 3.1. Lymphoid organs

- **3.1.1. Bone marrow:** With age, both hematopoietic stem cells and mesenchymal stem cells (MSCs) exhibit senescence, reducing regenerative capacity and favoring myeloid-biased hematopoiesis.
- **3.1.2. Thymus:** Undergoes age-associated involution, leading to decreased production of naive T cells and impaired adaptive immunity.
- **3.1.3. Spleen and lymph nodes:** Structural changes such as fibrosis and disrupted architecture result in reduced lymphocyte trafficking and diminished antigen presentation, contributing to immune inefficiency (10).

### 3.2. Sterile organs

Inflammaging extends beyond the immune system and affects "sterile" organs—those not typically exposed to external pathogens:

**3.2.1. Brain:** Microglia and astrocytes become activated and senescent, releasing SASP factors that contribute to neuroinflammation, a key feature of neurodegenerative diseases such as Alzheimer's.

**3.2.2. Heart::** Senescent cardiac fibroblasts and macrophage polarization toward an M1 phenotype promote fibrosis and impair contractility.

**3.2.3. Kidneys:** Age-related mitochondrial dysfunction, oxidative stress, and immune activation increase susceptibility to acute kidney injury and chronic kidney disease.

**3.2.4. Liver:** Senescent hepatocytes and activated hepatic stellate cells drive fibrogenesis, compromising liver function and promoting systemic inflammation.

**3.2.5. Skin and lungs:** Barrier integrity declines due to senescence and inflammation, with increased infiltration of immune cells and SASP-driven damage accelerating epidermal thinning, wrinkling, and pulmonary inflammation.

## 4. Mechanisms and triggers of inflammaging

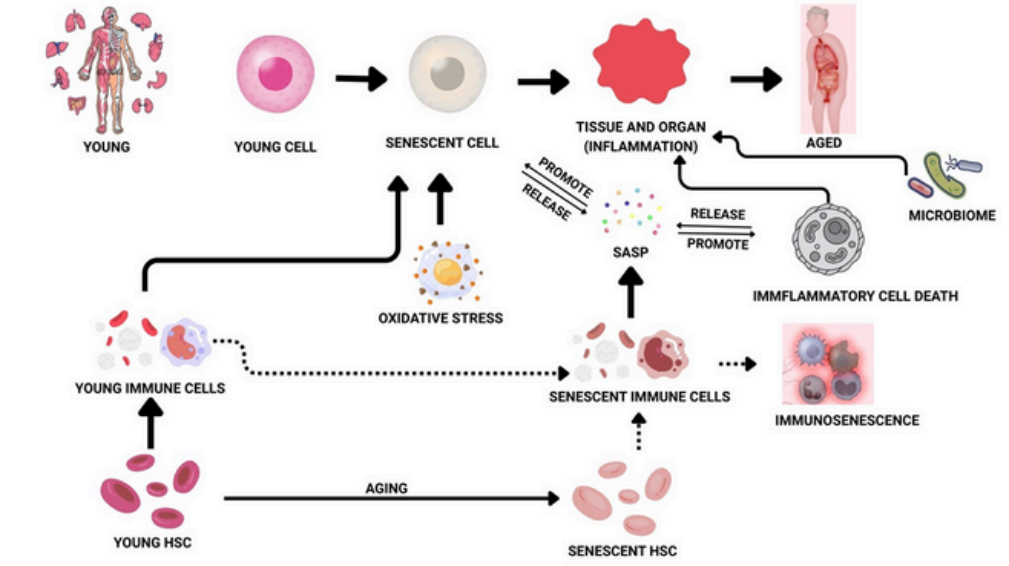


**Figure 2**. Inflammation at molecular, cellular, and organ levels, its triggers and mechanism of action

### 4.1. Oxidative stress and DNA damage

Prolonged oxidative stress results in the gradual accumulation of DNA damage, mitochondrial impairment, and activation of DNA damage response (DDR) mechanisms. A key pathway in this process involves NF-κB, a transcription factor that regulates the expression of numerous pro-inflammatory SASP elements. Continuous DDR activity helps maintain a persistent inflammatory milieu and sustains SASP expression, thereby reinforcing the cycle of Inflammaging (12).

### 4.2. Microbiome dysbiosis

Aging brings about notable shifts in the gut microbiome, characterized by decreased microbial diversity and a rise in pro-inflammatory bacterial populations. This imbalance, referred to as dysbiosis, compromises the gut barrier, enabling bacterial components like lipopolysaccharides to enter the bloodstream and initiate systemic inflammation. Additionally, age-related changes in the microbiota reduce the production of immune-regulating metabolites such as short-chain fatty acids (SCFAs), further impairing immune homeostasis (13).

### 4.3.Inflammatory cell death

Several forms of programmed cell death contribute to inflammaging (2):

**4.3.1. Necroptosis:** A form of lytic cell death that releases DAMPs and activates immune responses.

4.3.2. **Pyroptosis:** A form of programmed inflammatory cell death characterized by the activation of caspase-1 and gasdermin-D, leading to cell membrane pore formation and the release of pro-inflammatory cytokines such as IL-1β and IL-18.

4.3.3. **Ferroptosis:** Iron-dependent oxidative cell death, closely linked to lipid peroxidation.

4.3.4. **NETosis:** In neutrophils, the release of neutrophil extracellular traps (NETs) can promote chronic inflammation and tissue injury.

## 5. Therapeutic strategies targeting inflammaging

### 5.1. Senolytics and senomorphics

Senolytics are drugs that selectively induce apoptosis in senescent cells. Examples include dasatinib, quercetin, and navitoclax, which have shown promising results in animal models by improving physical function and reducing inflammation (14,15). Senomorphics modulate the SASP without killing the cells. Agents like rapamycin and metformin suppress mTOR signaling and SASP production, providing anti-inflammatory benefits (14,15).

### 5.2. Anti-inflammatory agents

NSAIDs inhibit cyclooxygenase enzymes but may cause gastrointestinal and cardiovascular side effects with long-term use. Cytokine inhibitors such as IL-1 (anakinra) and IL-6 (tocilizumab) blockers, show potential in modulating chronic inflammation but require careful monitoring (16).

### 5.3. Immunomodulation and stem cell therapies

Hematopoietic Stem cell transplantation (HSCT) has been investigated as a strategy for rejuvenating the aging immune system (17). Mesenchymal stem cells (MSCs) exhibit strong anti-inflammatory and immunomodulatory capabilities, demonstrating promise in preclinical studies for repairing tissue damage and enhancing immune responses (17).

### 5.4. Microbiome interventions

Restoring microbiome homeostasis can significantly reduce systemic inflammation. Strategies include (18)**:**

- Probiotics and prebiotics to enhance beneficial bacteria.
- Fecal microbiota transplantation (FMT) to reintroduce a healthy microbiome.
- Dietary fibers to boost SCFA production, reducing gut inflammation.

### 5.5. Lifestyle modifications

Aging and inflammation are greatly influenced by lifestyle choices (18):

- **Mediterranean diet:** Rich in anti-inflammatory compounds such as omega-3 fatty acids, polyphenols, and fiber.
- **Caloric restriction:** Extends lifespan in various species and reduces inflammatory markers.
- **Exercise:** Enhances anti-inflammatory cytokine production and improves immune surveillance.
- **Sleep hygiene and stress management:** Critical for maintaining circadian rhythm and hormonal balance, reducing systemic inflammation.

## 6. Conclusion

Inflammaging, that is referred to as low-grade chronic inflammation is recognized as the key hallmark of aging. It is closely linked with complex processes i.e. cellular senescence, immunosenescence and gradual organ deterioration. This chronic inflammation plays a central role in initiation and progression of various age-related disorders including cardiovascular, neurodegeneration and metabolic disorders. Understanding and research into the molecular drivers of inflammaging provides insights into potential therapeutic target for therapy. Promising interventions such as senolytics, gut-microbiome based therapies have helped regulate immune response, reducing systemic inflammation. These treatments when combined with life-style modifications such as having healthy diet, performing regular physical

exercise and taking adequate sleep has shown significant effective results. The target is not just expansion of lifespan but also healthspan- i.e. the years being lived in good health By delving deep into inflammaging, the Quality of life can be improved.

## References


1. Liu Z, Liang Q, Ren Y, Guo C, Ge X, Wang L, et al. Immunosenescence: molecular mechanisms and diseases. Signal Transduct Target Ther. 2023;8:200.
2. Santoro A, Bientinesi E, Monti D. Immunosenescence and inflammaging in the aging process: age-related diseases or longevity? Ageing Res Rev. 2021;71:101422.
3. Sayed N, Huang Y, Nguyen K, Krejciova-Rajaniemi Z, Grawe AP, Gao T, et al. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. Nat Aging. 2021;1:598–615.
4. Liggett LA, Sankaran VG. Unraveling hematopoiesis through the lens of genomics. Cell. 2020;182:1384–400.
5. Mansell E, Lin DS, Loughran SJ, Milsom MD, Trowbridge JJ. New insight into the causes, consequences, and correction of hematopoietic stem cell aging. Exp Hematol. 2023;125–126:1–5.
6. Bui TA, Jickling GC, Winship IR. Neutrophil dynamics and inflammaging in acute ischemic stroke: a transcriptomic review. Front Aging Neurosci. 2022;14.
7. Quin C, Breznik JA, Kennedy AE, DeJong EN, Andary CM, Ermolina S, et al. Monocyte-driven inflamm-aging reduces intestinal barrier function in females. Immun Ageing. 2024;21:65.
8. Brauning A, Rae M, Zhu G, Fulton E, Admasu TD, Stolzing A, et al. Aging of the immune system: focus on natural killer cells phenotype and functions. Cells. 2022;11:1017.
9. Shchukina I, Bohacova P, Artyomov MN. T cell control of inflammaging. Semin Immunol. 2023;70:101818.
10. Yousefzadeh MJ, Flores RR, Zhu Y, Schmiechen ZC, Brooks RW, Trussoni CE, et al. An aged immune system drives senescence and ageing of solid organs. Nature. 2021;594:100–5.
11. Giunta S, Wei Y, Xu K, Xia S. Cold-inflammaging: when a state of homeostatic-imbalance associated with aging precedes the low-grade pro-inflammatory-state (inflammaging): meaning, evolution, inflammaging phenotypes. Clin Exp Pharmacol Physiol. 2022;49:925–34.
12. Tepebaşı MY, İlhan İ, Temel EN, Sancer O, Öztürk Ö. Investigation of inflammation, oxidative stress, and DNA damage in COVID-19 patients. Cell Stress Chaperones. 2023;28:191–9.
13. Mostafavi Abdolmaleky H, Zhou J-R. Gut microbiota dysbiosis, oxidative stress, inflammation, and epigenetic alterations in metabolic diseases. Antioxidants. 2024;13:985.
14. Luís C, Maduro AT, Pereira P, Mendes JJ, Soares R, Ramalho R. Nutritional senolytics and senomorphics: implications to immune cells metabolism and aging – from theory to practice. Front Nutr. 2022;9.
15. Rad AN, Grillari J. Current senolytics: mode of action, efficacy and limitations, and their future. Mech Ageing Dev. 2024;217:111888.
16. Li X, Li C, Zhang W, Wang Y, Qian P, Huang H. Inflammation and aging: signaling pathways and intervention therapies. Signal Transduct Target Ther. 2023;8:239.
17. Cohn RL, Gasek NS, Kuchel GA, Xu M. The heterogeneity of cellular senescence: insights at the single-cell level. Trends Cell Biol. 2023;33:9–17.
18. Sharma R, Diwan B, Sharma A, Witkowski JM. Emerging cellular senescence-centric understanding of immunological aging and its potential modulation through dietary bioactive components. Biogerontology. 2022;23:699–729.

# Inflammation unleashed: What sparks it, how it affects you, and ways to take control

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**Abstract**
Inflammation is the body's natural reaction to injury, infection, or harmful substances. It involves activating the immune system and releasing substances that help fight off invaders and repair the tissue. While acute inflammation helps clear infection and start the healing process, problems arise when it becomes uncontrolled or long-lasting. Chronic inflammation can lead to many serious diseases, like heart disease, arthritis, type 2 diabetes, neurodegenerative disorders, and even cancer. This article delves into how inflammation works at the molecular and cellular levels, exploring the host defense mechanism, signaling pathways, etc. It also focuses on common internal and external triggers, the effect of ongoing inflammation on the body, and ways to manage it, such as medication, diet, and lifestyle changes. Understanding the good and bad sides of inflammation is vital for guiding medical practices and health policies to maintain balance in the body and prevent disease.

**Keywords**: Inflammation, triggers of inflammation, signaling pathway

## 1. Introduction

Inflammation is a response activated by damage to living tissue. Inflammation is a natural response by the body to injury or stimuli. It is an essential response to eliminate injurious agents and the body can start to heal. The response may start from a change in blood flow, an increase in permeability of blood vessels, and migration of fluids, and proteins from the circulation site to damage tissue. The inflammatory response if persists for a few days called acute while continues for a longer period called chronic inflammation (1-4).

## 2. Theory of inflammation

### 2.1. Immune system activation

The body starts a chemical signalling cascade in response to tissue damage, which triggers reactions meant to repair damaged tissues. Leukocyte chemotaxis from the general circulation to injury sites is triggered by these signals. The cytokines produced by these activated leukocytes cause inflammatory reactions (5).

### 2.2. Inflammatory mediators

After injury or damage to the cell, release tiny molecules called inflammatory mediators. The immune response, which results in inflammation and tissue repair, is triggered and regulated by them (6).

## 3. Causes of inflammation

**3.1. Infections:** When the body confronts bacteria, viruses, and fungi, our body's immune system starts an inflammatory response to fight against infection (7).
**3.2. Injuries:** Physical trauma, cuts, burns, and other injuries can lead to inflammation to repair damaged tissue (7).
**3.3. Chronic stress:** Emotional and physical stress can lead to the secretion of hormones which starts inflammation (8).
**3.4. Poor diet:** The impact of inflammatory foods (processed foods, sugar, Trans fats) are the main cause of inflammation (8,9).
**3.5. Environmental toxins:** Pollution, smoking, and chemicals contribute to inflammation (8,9).
**3.6. Autoimmune diseases:** Conditions like rheumatoid arthritis, lupus, and Crohn's disease involve the immune system attacking the body itself (8,9).

## 4. Strategies to mitigate inflammation

**4.1. Regular exercise:** Exercise mainly helps to manage weight and cytokine levels. Cytokines in large amounts may lead to inflammation.
**4.2. Manage stress:** Chronic stress may lead to high levels of cortisol, which is responsible for inflammation. Meditation, Yoga, and deep breathing may lead to relaxation.
**4.3. Medication:** Anti-inflammatory drugs may help to treat inflammation (10,13).

## 5. Impact of Inflammation on health

Inflammation may involve chronic disease conditions like cancer, heart disease, Diabetes, autoimmune disease. Several symptoms, such as physical discomfort, exhaustion, sadness, and gastrointestinal problems, might be signs of chronic inflammation (14,15).

## 6. Management strategies for tackling inflammation

Managing inflammation effectively involves several strategies, including lifestyle adjustments, pharmacological treatments, and stress management, all of which play a crucial role (16).

### 6.1. Lifestyle adjustments

### 6.1.1. Dietary interventions

Nutrition plays a vital role in managing inflammation (17), with several diets and food types showing promising results in reducing inflammatory markers, some diet modifications are discussed below.

### 6.1.2. Mediterranean diet

This diet is characterized by high levels of omega-3 fatty acids, polyphenols, and dietary fiber, commonly found in foods like olive oil, fatty fish, nuts, whole grains, fruits, and vegetables. Omega-3 fatty acids are known to regulate inflammatory pathways, while polyphenols exert antioxidant effects. Studies have shown that adherence to the Mediterranean diet can lower C-reactive protein (CRP), a key inflammation marker, by as much as 30% (18-20).

- **Anti-inflammatory foods:** Specific foods possess compounds with anti-inflammatory properties. For instance:
- **Turmeric (curcumin):** A potent compound found in turmeric, curcumin has shown significant efficacy in reducing pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in clinical trials, as confirmed by a 2022 review in Nutrients (21,22).
- **Green tea (EGCG):** Epigallocatechin gallate (EGCG), a powerful antioxidant in green tea, can suppress inflammation by modulating cellular signalling (23).
- **Dark leafy greens and berries:** Rich in polyphenols and other nutrients, these foods are known to curb oxidative stress and inflammation (24).
- **Physical activity:** Engaging in regular exercise is another robust strategy to tackle inflammation (25).
- **Moderate-intensity exercise:** Activities such as brisk walking, cycling, or swimming have been shown to lower systemic inflammation (26). By improving circulation and modulating immune responses, exercise reduces levels of CRP and other inflammatory markers (27).

### 6.2. Pharmacological management

Pharmacological management also plays an important role in controlling the inflammation, especially in chronic stages.

### 6.2.1. NSAIDs (Non-steroidal anti-inflammatory drugs)

Drugs like ibuprofen and aspirin act by inhibiting cyclooxygenase (COX) enzymes, thereby preventing the production of prostaglandins—substances that play a critical role in promoting inflammation (28).

### 6.2.2. Biologic agents

Advanced therapies targeting specific cytokines have revolutionized treatment for autoimmune diseases. Examples include:

- **TNF inhibitors** (e.g., infliximab): This block tumor necrosis factor-alpha, a cytokine heavily involved in inflammatory pathways (29).
- **IL-6 blockers** (e.g., tocilizumab): These suppress interleukin-6 activity, reducing inflammation effectively (30).

### 6.2.3. Statins

Primarily used to lower cholesterol, statins have an additional benefit of reducing inflammation. They lower CRP levels by 13–35% regardless of lipid profile changes (31). Chronic stress is a major contributor to systemic inflammation, often mediated by the overactivation of the sympathetic nervous system (32). Mindfulness practices, such as meditation, yoga, and breathing exercises, provide effective solutions (33).

- **Mindfulness programs:** These interventions work by reducing sympathetic activity and altering the expression of genes associated with inflammation. For example, an NIH-funded study showed an 18% reduction in inflammatory markers, including IL-6, after participants engaged in an 8-week mindfulness program (34,35).
- **Yoga:** Beyond physical benefits, yoga emphasizes relaxation and mental focus, contributing to a balanced immune response (36).

## 7. Recent innovations for tackling inflammation

**7.1. Microbiome modulation:** Imbalances in gut microbiota (gut dysbiosis) are strongly linked to chronic inflammation. Interventions like probiotics and prebiotics aim to restore gut health, thereby reducing systemic inflammation (37).

**7.2. Senolytics:** Cellular senescence—the process in which cells stop dividing and secrete pro-inflammatory factors—contributes to aging-related inflammation. Senolytics, a novel class of drugs, selectively eliminate these senescent cells (38).

## 8. Conclusion

Continuing inflammation results in tissue damage and chronic disorders, controlling inflammation is essential for general health and well-being. The negative consequences of severe or protracted inflammation can be lessened with early management and a comprehensive approach to care.

## References


1.Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860–7.
2.Kumar V, Abbas AK, Aster JC. Robbins and Cotran Pathologic Basis of Disease. 9th ed. Elsevier; 2014.
3.Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol. 2005;6(12):1191–7.
4.Fitzgerald GA. Inflammation, the endothelium, and the cardiovascular system. J Clin Invest. 2003;111(4):431–5.
5.Bertoletti A, Maini MK. Immune response in inflammation. Curr Opin Immunol. 2013;25(4):499–503.
6.Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol. 2011;31(5):986–1000.
7.Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1β generation. Clin Exp Immunol. 2007;147(2):227–35.
8.Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428–35.
9.Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9(6):7204–18.
10. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochem Soc Trans. 2017;45(5):1105–15.

11. Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868–74.
12. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–7.
13. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014;105(2):141–50.
14. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25(12):1822–32.
15. Dattolo A, Torres M, Frias-Toral E, et al. Beyond the skin: endocrine, psychological and nutritional aspects in women with hidradenitis suppurativa. J Transl Med. 2025;23(1):167.
16. Wunderle C, Stumpf F, Schuetz P. Inflammation and response to nutrition interventions. J Parenter Enteral Nutr. 2024;48(1):27–36.
17. Naik RG, Purcell SA, Gold SL, et al. From evidence to practice: a narrative framework for integrating the Mediterranean diet into inflammatory bowel disease management. Nutrients. 2025;17(3):470.
18. Naik RG, Purcell SA, Gold SL, Christiansen V, D'Aloisio LD, Raman M, Haskey N. From Evidence to Practice: A Narrative Framework for Integrating the Mediterranean Diet into Inflammatory Bowel Disease Management. Nutrients. 2025 Jan 28;17(3):470.
19. Tseng PT, Zeng BY, Zeng BS, Yeh PY, Stubbs B, Kuo JS, Sun CK, Cheng YS, Chen YW, Chen TY, Wu YC. The efficacy and acceptability of anti-inflammatory omega-3 polyunsaturated fatty acid supplements in sepsis management: a network meta-analysis of randomized controlled trials. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2024 Mar 1;202:102633.
20. Tauil RB, Golono PT, de Lima EP, de Alvares Goulart R, Guiguer EL, Bechara MD, Nicolau CC, Junior JL, Fiorini AM, Méndez-Sánchez N, Abenavoli L. Metabolic-Associated Fatty Liver Disease: The Influence of Oxidative Stress, Inflammation, Mitochondrial Dysfunctions, and the Role of Polyphenols. Pharmaceuticals. 2024 Oct 10;17(10):1354.
21. Cozmin M, Lungu II, Gutu C, Stefanache A, Duceac LD, Șoltuzu BD, Damir D, Calin G, Bogdan Goroftei ER, Grierosu C, Boev M. Turmeric: From spice to cure. A review of the anti-cancer, radioprotective, and anti-inflammatory effects of turmeric-sourced compounds. Frontiers in Nutrition. 2024 May 22;11:1399888.
12. Jain D, Singh K, Gupta P, Gupta JK, Sahu PK, Dwivedi S, Sharma MC, Kumar S. Exploring Synergistic Benefits and Clinical Efficacy of Turmeric in Management of Inflammatory and Chronic Diseases: A Traditional Chinese Medicine Based Review. Pharmacological Research – Modern Chinese Medicine. 2025 Jan 3:100572.
23. Capasso L, De Masi L, Sirignano C, Maresca V, Basile A, Nebbioso A, Rigano D, Bontempo P. Epigallocatechin Gallate (EGCG): Pharmacological Properties, Biological Activities and Therapeutic Potential. Molecules. 2025 Feb 1;30(3):654.
24. Yu X, Pu H, Voss M. Overview of anti-inflammatory diets and their promising effects on non-communicable diseases. British Journal of Nutrition. 2024 Oct 14:1-21.
25. Dures E, Farisoğulları B, Santos EJ, Molto A, Feldthusen C, Harris C, Elling-Audersch C, Connolly D, Elefante E, Estévez-López F, Bini I. 2023 EULAR recommendations for the management of fatigue in people with inflammatory rheumatic and musculoskeletal diseases. Annals of the Rheumatic Diseases. 2024 Oct 1;83(10):1260-1267.
26. Munir M, Rejeki PS, Pranoto A, Sari DR, Izzatunnisa N, Putra RA, Halim S. Response of Pro-Inflammatory Cytokines After A Single Bout of Moderate-Intensity Endurance Exercise in Obese. Sport Mont. 2024 Feb 1;22(1):123-127.
27. Guo Y, Qian H, Xin X, Liu Q. Effects of different exercise modalities on inflammatory markers in the obese and overweight populations: unraveling the mystery of exercise and inflammation. Frontiers in Physiology. 2024 Jun 12;15:1405094.
28. Wirth T, Lafforgue P, Pham T. NSAID: Current limits to prescription. Joint Bone Spine. 2024 Jul 1;91(4):105685.
29. Nielsen OH, Hammerhøj A, Ainsworth MA, Gubatan J, D'Haens G. Immunogenicity of Therapeutic Antibodies Used for Inflammatory Bowel Disease: Treatment and Clinical Considerations. Drugs. 2024 Nov 13:1-9.
30. Parisi S, Ditto MC, Ghellere F, Panaro S, Piccione F, Borrelli R, Fusaro E. Update on tocilizumab in rheumatoid arthritis: a narrative review. Frontiers in Immunology. 2025 Feb 24;16:1470488.
31. Feinstein MJ. Statins, inflammation, and tissue context in REPRIEVE. JAMA Cardiology. 2024 Apr 1;9(4):334-335.
32. Seaton N, Hudson J, Harding S, Norton S, Mondelli V, Jones AS, Moss-Morris R. Do interventions for mood improve inflammatory biomarkers in inflammatory bowel disease?: a systematic review and meta-analysis. EBioMedicine. 2024 Feb 1;100.
33. Moreno JJ. Modulation of inflammatory response and pain by mind-body therapies such as meditation. Brain, Behavior and Immunity – Integrative. 2024 Jan 1;5:100036.
34. Dusek J, McKee MD, Kallenberg G, Storrow A, Hughes R, Coyne C, Nielsen A, Karasz A, Vago D, Surdam J. ICIMH 2022 Abstracts.
35. Wells RE, Seng EK, Edwards RR, Victorson DE, Pierce CR, Rosenberg L, Napadow V, Schuman-Olivier Z. Mindfulness in migraine: A narrative review. Expert Review of Neurotherapeutics. 2020 Mar 3;20(3):207-225.
36. Estevao C. The role of yoga in inflammatory markers. Brain, Behavior, & Immunity – Health. 2022 Mar 1;20:100421.
37. Wang G, Fan Y, Zhang G, Cai S, Ma Y, Yang L, Wang Y, Yu H, Qiao S, Zeng X. Microbiota-derived indoles alleviate intestinal inflammation and modulate microbiome by microbial cross-feeding. Microbiome. 2024 Mar 19;12(1):59.
38. Sangfuang N, McCoubrey LE, Awad A, Marzorati M, Ghyselinck J, Verstrepen L, De Munck J, De Medts J, Gaisford S, Basit AW. Effects of senotherapeutics on gut microbiome dysbiosis and intestinal inflammation in Crohn's disease: A pilot study. Translational Research. 2025 Apr 1;278:36-47.

# Antistress skincare: Role of antioxidants, adaptogens, and neurocosmetics

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**Abstract**

Skin, a key sensory organ, gets affected by internal as well as external stress. Stress triggers cortisol release centrally as well as locally in the skin, which is then responsible for several types of skin disorders, including acne, pigmentation, premature ageing, sensitivity, etc. To overcome this stress, the most ideal approach would be to identify the cause of stress and address the same. Several cosmetic preparations are used to manage such skin disorders. Complementary approaches such as healthy lifestyle choices, well-balanced diet, meditation, etc, are also very useful. This article dives into three classes of compounds, namely antioxidants, adaptogens, and the newly emerging class of neurocosmetics, when used topically, will help address these skin conditions effectively.

**Keywords**: Skin, stress, homeostasis, antioxidants, adaptogens, neurocosmetics

## 1. Introduction

Skin is a multifunctional sensory organ that helps manage our relationship with the external environment and is directly connected to the central nervous system. Epidermis, the outer layer of skin, has ectodermal origin and has dense innervation except for the stratum corneum. This innervation helps skin to examine both internal (mental, emotional) as well as external (environmental changes, heat, light) stimuli and respond appropriately via mediators known as neurotransmitters. The receptors for neurotransmitters and the enzymes to degrade them are also present in the cutaneous and immune cells. This connection of the nervous, immune, cutaneous, and endocrine (NICE) network helps maintain skin homeostasis, i.e tendency of skin to resist change despite changes in its environment (1-3,12).

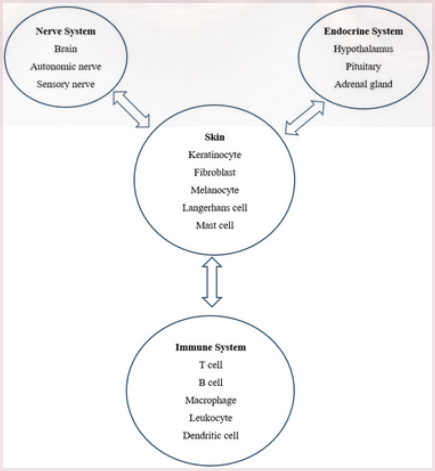


**Figure 1.** Diagrammatical demonstration of how the skin(cutaneous), nervous, immune, and endocrine systems interact with each other and regulate several skin functions like the immune function, skin barrier function, melanin production via regulators like neurotransmitters, hormones, and interleukins (Reproduced from (4))

Stress is any condition that triggers anxiety and constantly negatively challenges the state of homeostasis. Stress can be internal (mental, emotional, psychological) or external (harsh environmental factors heat, UV light, pollution). Stress, if short lived, may not impact skin, but if not; it constantly assaults human body and can affect several body systems including skin. Skin responds to stress in the form of acne (due to increased sebum secretion), redness (due to increased skin inflammation), rashes (due to weakened skin barrier, shortened lifetime of skin cells), fine lines and wrinkles (due to premature skin ageing, lack of sleep, collagen breakdown), and hyperpigmentation (due to prolonged exposure to UV light and pollution).

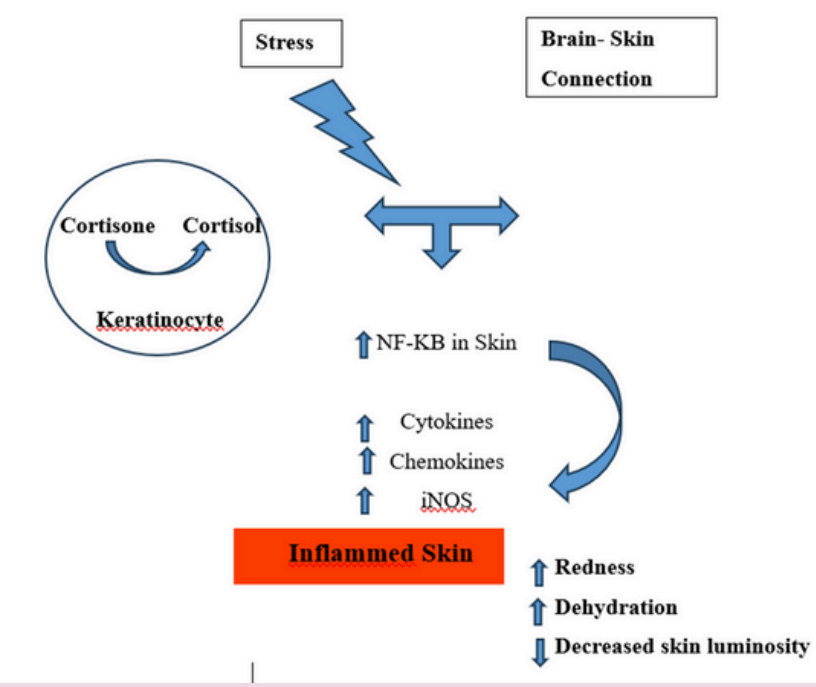


**Figure 2.** Representation of the stress pathway (Reproduced from (1))

Skin cannot differentiate between the origin of the stressors and responds to all kinds of stress. Any kind of stress increases cortisol levels in the body as well as in epidermal skin layers, leading to inflammation, thus triggering and aggravating skin disorders. Oxidative stress is most prevalent under internal and external long-term stressful conditions. Reactive species generated in skin due to oxidative stress also impact the skin microbiome population, which ultimately results in skin dysbiosis (5). Skin symptoms created by stress can also be addressed by using appropriate skincare cosmetic formulations that contain ceramides to strengthen the skin barrier, niacinamide, kojic acid to address skin pigmentation, hyaluronic acid for skin hydration, D-panthenol and cica extracts to soothe skin, and salicylic acid to address acne. These skin care formulations can further be infused with stress-alleviating actives like antioxidants, adaptogens, and neurocosmetics to provide a multitargeted approach to achieve skin homeostasis. Along with the concoction of actives, stress can be minimized through correct dietary habits, good sleep, healthy lifestyles and life choices, meditation, exercises, yoga, etc. This topic will cover more details on the role and types of antioxidants, adaptogens, and neurocosmetics that can be utilised in “antistress skin care”.

## 2.Antioxidants

Skin is affected by oxidative stress, excess generation of reactive species triggers skin inflammation and results in several skin disorders. Reactive oxygen species are also generated internally in our bodies due to mitochondrial metabolism. However, the body’s innate antioxidant defense mechanism in the form of several antioxidant enzymes, eg, catalase, glutathione peroxidase, help maintain skin homeostasis. Antioxidants themselves oxidise and prevent free radical generation thereby reducing skin inflammation and preventing as well as reversing skin disorders. The use of natural plant-based antioxidants is on rise. Plant extracts contain several molecules which have antioxidant potential mainly polyphenols (flavonoids, stilbenes, terpenes). Polyphenols are found in natural sources like tea leaves, grapes, pomegranate, blue berries etc. Their phenolic group influences protein phosphorylation and thus inhibits

lipid peroxidation. Flavonoids are also known for their antioxidant potential which helps scavenge free radicals eg. pycnogenol from pine bark and epicatechin -3-gallate (EGCG) found in green tea. Resveratrol, a stilbene derivative found in grapes, berries is not only a powerful antioxidant but is also known to upregulate endogenous antioxidant pathway via NrF2 pathway activation. Some examples of potential natural terpene antioxidants are limonene, 1,8-Cineole. Similarly, mineral antioxidants such as selenium, copper, zinc also have a role to play in skin cosmetics as they are the co-factors of enzymatic antioxidants. Other antioxidants include L-Ascorbic acid (Vitamin C) that helps reduce production of ROS created by exposure to sunlight, dust, pollution, particulate matter, smoke etc. As L-Ascorbic acid is unstable in dissolved aqueous condition, several stable esters are also widely used like magnesium ascorbyl phosphate, ascorbic acid 2-glucoside, sodium ascorbyl phosphate, O-ethyl ascorbic acid. L-ascorbic acid and its derivatives have been widely used to tackle skin conditions like pigmentation, skin sagging due to overexposure to sun and pollution. Also, tocopherol(Vitamin E) and its derivative tocopherol acetate is widely used as oil soluble strong antioxidant which works synergistically with Vitamin C. Thus, several antioxidants have been used in skincare to address skin inflammation. However, their limitations include low stability, poor bioavailability, sensitivity to light and heat and their potential to induce allergic reactions (5,6).

## 3. Adaptogens

Adaptogens are powerful plant-based molecules which help improve blood circulation, balance out skin stress and thus help improve overall skin health. They are mainly obtained from traditionally known herbs, roots and extracts well documented in Ayurvedic and Chinese texts known for their antioxidant and anti-inflammatory action. They negate skin inflammation caused due to heightened cortisol and adrenaline levels and thus help calm skin, rebuild skin barrier, improve skin health and hydration. Some known and widely used adaptogens are (7)

**3.1. Ashwagandha (*Withania somnifera*):** Key active molecules in ashwagandha extract are withanolides and alkaloids. It helps preserve hyaluronic acid levels in skin.

**3.2. Amla *(Phyllanthus emblica*):** Rich in vitamin C, polyphenol (ellagic acid) and helps calm skin inflammation and also preserve skin collagen.

**3.3. Turmeric *(Curcuma longa)*:** Key polyphenol present in turmeric is curcumin which is known antioxidant, anti-inflammatory and well as antimicrobial agent

**3.4. Gotukola *(Centella asiatica)*:** Gotukola is rich source of triterpene saponins and improves skin firmness and enhances dermal repair

Other adaptogens well documented in Chinese medicines are mushrooms (Reishi, Chaga) & *Panax ginseng* (red, white).

For best efficacy of adaptogens in skin care, following should be considered:

a) Use of standardised extracts for ensuring potency

b) Use at active levels

c) Store in dark places as these are light sensitive

d) Recommend regular use for best results

## 4. Neurocosmetics

Neurocosmetics are products which are intended to work only at topical neurological level and not elsewhere. As skin and brain have same ectodermal origin, both trigger release of cytokines, chemokines, neurotransmittors and neurohormones when under stress and homeostasis is impacted. It is known that the conversion of inactive cortisone to cortisol triggers skin inflammation leading to several skin disorders (1,8,9) Recently several neurocosmetics have been designed to balance cortisol levels and thus help combat skin stress. Neurocosmetics activate or inhibit skin's neuroreceptors or modulate neurotransmitters to improve cell to cell communication (10). Some examples of marketed neurocosmetics include:

### 4.1. Agascalm™ by Provital

*Agastache mexicana* flower /leaf/ stem extract is proven to inhibit release of cytokines by 104% in *in vitro* study and also inhibits movement of NF-κB transcription factor to nucleus by upto 70% *in vitro*

thus indicating its potential to reduce skin inflammation and redness with regular use (11).

### 4.2. Sepicalm™ S WP by Seppic

*Nymphaea alba* flower extract combined with amino acids and minerals is proven to reduce skin inflammation by reducing inflammatory mediators (IL-6 and IL-8) and improving production of β-endorphins. It also helps soothe irritated and also boost skin radiance (1).

### 4.3. Mariliance™ by GIVAUDAN

“Neuro-soothing” extract derived from *Rhodosorus marinus*, a red microalga has been proven to downregulates TRPV1 expression, inhibit the release of neuroinflammatory mediators (IL-1α and NGF). This active can be used effectively in products targeting sensitive skin, in post depilatory care, after sun care, post peeling treatments and in aftershave lotions for reducing skin sensitivity and providing feeling of comfort to sensitive skin (1).

### 4.4. Pinolumin™ by Mibelle Biochemistry

Concentrated extract of Swiss stone pine wood is a rich source of stilbenoid pinosylyin, a neurorelaxing molecule. This is proven to reduce generation of inflammatory markers during oxidative stress and thus address local redness and inflammation (1).

### 4.5. Neurophroline™ by Givaudan Active Beauty

The extract of wild indigo (*Tephrosia purpurea*) is proven to reduce skin's cortisol levels and boost β-endorphins levels. Neurophroline has been clinically proven to reduce skin and improved skin luminosity (1).

### 4.6. Algaktiv® Zen by Greenaltech

This microalgal active blend has been proven to bind to glucocorticoid receptors and clinically proven to improve skin youth and radiance (13).

### 4.7. Zenakine™ by Croda Beauty

This biotechnology based active stimulates production of feel-good messengers in skin, alleviates cortisol stress. Proven skin benefits been fewer lines, smoother skin (14).

Neurocosmetics is a new emerging class of actives which, when utilised in cosmetics, hold promise to further improve its cosmetic pleasantness. Key caution- currently claims around mechanisms of action of neurocosmetics pose concerns from regulatory aspects. Formulators need to ensure that levels used need to ensure only topical, local action.

## 5. Conclusions

This article discusses the role of skin and the importance of its healthy state to maintain homeostasis. It further deep dives into types of stress and their impact on skin. The article further discusses various antioxidants, adaptogens, and neurocosmetics, which hold promise to alleviate skin concerns when used along with current conventional skin care actives. The key advantage of including these compounds in skincare cosmetics is that they will help address the root cause of stress (within the cosmetic domain, i.e, epidermis) and thus will further support the specific skincare actives to achieve the state of homeostasis faster.

## References

1.Rizzi V, Gubitosa J, Fini P, Cosma P. Neurocosmetics in Skincare—The Fascinating World of Skin–Brain Connection: A Review to Explore Ingredients, Commercial Products for Skin Aging, and Cosmetic Regulation. Cosmetics. 2021 Sep;8(3):66.
2.Jiao Q, Zhi L, You B, Wang G, Wu N, Jia Y. Skin homeostasis: Mechanism and influencing factors. Journal of Cosmetic Dermatology. 2024;23(5):1518–26.
3.Cibrian D, de la Fuente H, Sánchez-Madrid F. Metabolic Pathways That Control Skin Homeostasis and Inflammation. Trends Mol Med. 2020 Nov;26(11):975–86.

4.Hosoi J. Stress and the skin. Int J Cosmet Sci. 2006 Aug;28(4):243–6.
5.Chen J, Liu Y, Zhao Z, Qiu J. Oxidative stress in the skin: Impact and related protection. Int J Cosmet Sci. 2021 Oct;43(5):495–509.
6.Hoang HT, Moon JY, Lee YC. Natural Antioxidants from Plant Extracts in Skincare Cosmetics: Recent Applications, Challenges and Perspectives. Cosmetics. 2021 Dec;8(4):106.
7.Gadberry R. Skin Inc. 2025 [cited 2025 May 19]. Adaptogens: Nature's Destressors. Available from: https://www.skininc.com/science/ingredients/article/22928157/adaptogens-natures-destressors
8.Chen Y, Lyga J. Brain-Skin Connection: Stress, Inflammation and Skin Aging. Inflamm Allergy Drug Targets. 2014 Jun;13(3):177–90.
9.Terao M, Katayama I. Local cortisol/corticosterone activation in skin physiology and pathology. J Dermatol Sci. 2016 Oct;84(1):11–6.
10.Dobos KA. Beauty and the brain: How the nervous system shapes neurocosmetic innovations. 2024;19.
11Agascalm™ | CareActives | Cosmetic ingredients by Provital [Internet]. [cited 2025 May 19]. Available from: https://www.weareprovital.com/en/careactives/agascalm
12.Vidal Yucha SE, Tamamoto KA, Kaplan DL. The importance of the neuro-immuno-cutaneous system on human skin equivalent design. Cell Prolif. 2019 Nov;52(6):e12677.
13.Algaktiv® Zen by Greenaltech [Internet] Discover our exclusive and innovative plant-based actives.. Available from: Greenaltech Launches Algaktiv Zen to Reduce Stress | Cosmetics & Toiletries [cited 2016 Feb 24].
14.Zenakine™ by Crodabeauty [Internet] Zenakine™ | Croda Beauty. Available from: Croda Beauty Launches Zenakine, Taking Sleep x Emotion x Skin Health Connection to a New Level | Cosmetics & Toiletries [cited 2025 April 8].

# Understanding and managing inflammation: A holistic approach to health

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## Abstract

Inflammation is a fundamental biological response to injury or infection, aiming to eliminate the cause, clear debris, and initiate repair. Characterized by redness, heat, swelling, and pain, it involves the recognition of harmful stimuli, release of mediators, immune cell migration, and resolution. Chronic inflammation, however, can damage tissues. Management involves lifestyle modifications like an anti-inflammatory diet, exercise, stress management, and adequate sleep, often complemented by medications (NSAIDs, corticosteroids, DMARDs). Natural remedies like turmeric, ginger, and omega-3 fatty acids may also help. A holistic, personalized approach involving healthcare professionals is crucial for effective inflammation management and overall well-being.

**Keywords:** Inflammation, nonsteroidal anti-inflammatory drugs (NSAIDs), natural remedies

## 1. Introduction

Inflammation, a fundamental biological defense, arises in response to tissue injury, infection, or irritation. This intricate process involves the immune system, vascular changes, and diverse molecular signals. The main aim of inflammation is to remove the agent causing the initial cellular damage due to pathogens like bacteria or viruses, damaged cells, or irritants, to remove debris from the initial damage, and to initiate tissue repair (1).

Historically, the classic signs of inflammation, first described by the Roman encyclopedist Celsus, are: (2)

- **Redness (Rubor):** An increase in blood flow to the injured tissue leads to the visible redness called rubor
- **Heat (Calor):** The elevated blood flow contributes to the warmth felt at the inflamed area.
- **Swelling (Tumor):** Fluid leaks from the blood vessels into the surrounding tissues.
- **Pain (Dolor):** The release of certain chemicals stimulates nerve endings, causing pain.

## 2. Inflammation cascade

A holistic approach is crucial in managing inflammation because it recognizes that inflammation isn't just a localized issue but is deeply interconnected with various aspects of your overall health and lifestyle. Addressing inflammation effectively requires looking beyond just treating symptoms with medication and considering the whole person. Inflammation is characterized by a cascade of biological events involving:

2.1. **Recognition of harmful stimuli:** This could be pathogens, damaged cells, or irritants. Specialized receptors on immune cells recognize these threats (3,4).
2.2. **Release of inflammatory mediators:** Cells release substances like histamine, cytokines, and chemokines. These molecules cause blood vessels to widen, become leakier, and draw immune cells to the location of the injury (5).
2.3. **Migration of immune cells:** Neutrophils and macrophages, types of white blood cells, travel to the inflamed area to eliminate the cause of the harm and remove cellular waste (6).
2.4. **Resolution of inflammation:** Ideally, the inflammatory response subsides once the threat is eliminated, and the tissue begins to heal. The resolution phase involves the creation of anti-inflammatory signals and the elimination of immune cells from the site (7).

Chronic inflammation occurs when this process fails to resolve, leading to persistent inflammation that can damage healthy tissues.

## 3. Management strategies

Management of inflammation can involve various approaches, depending on whether it's acute or chronic and its underlying cause. For both acute and chronic inflammation, certain lifestyle changes can play a significant role (Table 1).

**Table 1.** Lifestyle modification and management (8-11)

| Lifestyle modification | Management |
|---|---|
| **Anti-inflammatory diet** | Choosing a diet that emphasizes fruits, vegetables, whole grains, legumes, and healthy fats, notably omega-3 fatty acids from sources like fatty fish, flaxseeds, and walnuts, can be beneficial in mitigating inflammation. Limiting processed foods, refined sugars, unhealthy fats, and red meat is also beneficial |
| **Regular exercise** | Regular exercise generally reduces chronic, low-grade inflammation in the long term |
| **Weight management** | Obesity is associated with increased inflammation, so maintaining a healthy weight is crucial. |
| **Stress management** | Utilizing techniques like mindfulness, yoga, or meditation to mitigate the inflammatory effects of chronic stress. |
| **Smoking cessation** | Smoking is a key factor in causing inflammation in the body |
| **Adequate sleep** | Prioritizing quality sleep to support the body's natural anti-inflammatory processes. |
| **Hydration** | Ensuring sufficient water intake for optimal bodily functions |
| **Gut health** | Recognizing the crucial role of the gut microbiome in inflammation and supporting it through diet and potentially probiotics |
| **Mind-body practices** | Examining the possible benefits of acupuncture, massage, or chiropractic care in managing inflammation and pain. |
| **Environmental considerations** | Minimizing exposure to environmental toxins that can contribute to inflammation. |

## 3.1. Anti-inflammatory diet

Limiting processed foods, refined sugars, unhealthy fats, and red meat is also beneficial.

**3.1.1. Increase omega-3 fatty acids:** abundant in fatty fish (like salmon, mackerel, and sardines), flaxseeds, chia seeds, and walnuts, possess significant anti-inflammatory properties. They contribute to a healthier balance of fatty acids in the body, thereby reducing the production of molecules that promote inflammation (12).

**3.1.2. Fruits and vegetables:** A generous intake of fruits and vegetables provides a wealth of antioxidants, vitamins, and polyphenols that fight oxidative stress and inflammation. Focus on incorporating a variety of colorful fruits like berries, cherries, and oranges, as well as vegetables such as leafy greens, broccoli, and bell peppers.

**3.1.3. Whole grains:** Option for whole grains such as oats, brown rice, and quinoa instead of refined grains like white bread and pasta. Whole grains are rich in fiber, which can aid in stabilizing blood sugar levels and decreasing inflammation (13).

**3.1.4. Healthy fats:** Use olive oil and avocado oil as primary cooking fats. They contain oleic acid, which has anti-inflammatory properties (14).

**3.1.5. Lean protein sources:** fish, poultry, beans, and lentils over red and processed meats, which can promote inflammation (15).

**3.1.6. Anti-inflammatory spices:** Incorporate spices like turmeric (containing curcumin), ginger, and cinnamon into your cooking. It has been observed that these have effects that counteract inflammation (16).

**3.1.7. Limit pro-inflammatory foods:** Reduce or eliminate processed foods, sugary drinks, refined carbohydrates, fried foods, and excessive amounts of saturated and trans fats.

## 3.2. Regular exercise

Moderate physical activity can help reduce inflammation over time. Regular exercise generally reduces chronic, low-grade inflammation in the long term. While a single intense workout can temporarily increase inflammatory markers, consistent moderate activity has the opposite effect such as:

**3.2.1. Improving insulin sensitivity:** Reducing inflammatory pathways linked to insulin resistance.

**3.2.2. Promoting a healthy weight:** Decreasing pro-inflammatory visceral fat.

**3.2.3. Releasing anti-inflammatory cytokines (myokines):** These substances counteract inflammatory processes.

**3.2.4. Improving immune regulation:** Helping the immune system function more effectively.

## 4. Medications

When lifestyle modifications aren't sufficient to manage inflammation, various medications are available. The choice of medication depends on the type, severity, and location of the inflammation, as well as the individual's overall health. An overview of common medication classes used in inflammation management is mentioned in Table 2.

**Table 2.** Medications used in inflammation management (17-21)

| Medications | Types | Common uses | Potential side effects |
|---|---|---|---|
| **Nonsteroidal Anti-inflammatory Drugs(NSAIDs)** | **Over the counter (OTC):** Aspirin (Bayer, Ecotrin), Naproxen (Aleve), Ibuprofen (Advil, Motrin) **Prescription**: Diclofenac (Voltaren, Cataflam),Meloxicam (Mobic), Celecoxib (Celebrex) - a COX-2 selective inhibitor, Indomethacin (Indocin), Ketorolac (Toradol) | Arthritis (osteoarthritis, rheumatoid arthritis), Muscle aches and sprains, Back pain, Menstrual cramps, Headaches, Fever | • Gastrointestinal issues (stomach pain, heartburn, ulcers, bleeding)<br>• Long-term use, or use in individuals with existing heart problems, may elevate the risk of heart attack or stroke<br>• Kidney problems<br>• Increased bleeding risk<br>• Fluid retention and swelling. |

| | | | |
|---|---|---|---|
| **Corticosteroids** | **Oral**: Prednisone, Dexamethasone, Methylprednisolone<br>**Injectable**: Triamcinolone, Betamethasone<br>**Topical**: Hydrocortisone cream<br>**Inhaled:** Budesonide, Fluticasone (used primarily for respiratory conditions like asthma)<br>**Nasal sprays**: Fluticasone, Budesonide (used for allergic rhinitis)<br>**Eye drops:** Prednisolone acetate (used for eye inflammation) | Autoimmune diseases (e.g., lupus, rheumatoid arthritis), Skin conditions (e.g., eczema, psoriasis), Joint and muscle inflammation, Asthma and allergies, Organ transplant rejection prevention, Inflammatory bowel disease (IBD) | • Weight gain<br>• Increased risk of infections<br>• Increased appetite<br>• High blood pressure<br>• Increase blood sugar levels<br>• Osteoporosis (thinning of bones)<br>• Skin thinning and bruising<br>• Mood changes<br>• Cataracts and glaucoma<br>• Sleep disturbances |
| **Disease-modifying antirheumatic drugs (DMARDs)** | **Conventional synthetic DMARDs (csDMARDs):** Sulfasalazine, Hydroxychloroquine, Leflunomide, Methotrexate<br>**Targeted synthetic DMARDs (tsDMARDs):** JAK inhibitors (e.g.,Tofacitinib, Baricitinib, Upadacitinib)<br>**Biologic DMARDs (bDMARDs):** TNF inhibitors (e.g.,Infliximab, Adalimumab, Etanercept), Interleukin inhibitors (e.g., Tocilizumab, Secukinumab), B-cell depleters (e.g.,Rituximab), T-cell costimulation inhibitors (e.g., Abatacept) | Ankylosing spondylitis, Rheumatoid arthritis, Inflammatory bowel disease (certain types), Psoriatic arthritis, Lupus | • Increased risk of infections<br>• Liver problems<br>• Blood disorders<br>• Skin reactions<br>• Gastrointestinal issues |
| **Other medications** | • **Antihistamines:** To reduce inflammation associated with allergic reactions.<br>• **Mast cell stabilizers:** Also used for allergy-related inflammation.<br>• **Colchicine:** Used to treat gout flares, an inflammatory condition caused by uric acid crystal buildup.<br>• **Specific biologics:** For conditions like Crohn's disease and ulcerative colitis that target specific inflammatory pathways. | | |

## 5. Natural Remedies and Supplements

Some natural substances have anti-inflammatory properties, but it's essential to discuss their use with a healthcare professional. Certain herbs have demonstrated anti-inflammatory effects.

**5.1. Turmeric (Curcumin):** Turmeric, containing the active compound curcumin, is a powerful anti-inflammatory and antioxidant agent. Black pepper can enhance its absorption. Beyond the basics, curcumin's anti-inflammatory effects are attributed to its ability to interact with numerous molecular targets involved in inflammation (22).

**5.2. Ginger:** It contains gingerol, a compound known for its anti-inflammatory and antioxidant effects. Beyond gingerols, ginger contains other beneficial compounds like shogaols, paradols, and zingerone, which also contribute to its medicinal properties. Shogaols, which tend to be more concentrated in dried ginger, can also demonstrate strong anti-inflammatory and antioxidant effects (23).

**5.3. Green Tea:** Green tea is rich in EGCG, an antioxidant that also has anti-inflammatory properties. Epigallocatechin gallate (EGCG) is the most prevalent and potent catechin found in green tea, but other catechins such as epicatechin (EC), epigallocatechin (EGC), and epicatechin gallate (ECG) also contribute to its beneficial effects on health (24).

**5.4. Boswellia (Indian Frankincense):** May inhibit pro-inflammatory cytokines. Boswellia has been a staple in Ayurvedic medicine for centuries, used to treat arthritis, asthma, skin conditions, and inflammatory bowel disease (25).

**5.5. Cat's claw:** Indigenous people of the Amazon rainforest have used cat's claw for centuries for a wide array of health issues, including inflammation for conditions like arthritis and other inflammatory disorders (26).

**5.6. Devil's claw:** Contains iridoid glycosides, notably harpagoside, which are believed to be the source of its anti-inflammatory and pain-relieving properties. Its mechanism of action may involve blocking the production of pro-inflammatory cytokines and prostaglandins. Primarily used for osteoarthritis, back pain, and general pain relief (27).

**5.7. Holy basil:** Contains compounds such as eugenol, rosmarinic acid, and caryophyllene, which have shown both antioxidant and anti-inflammatory effects. Additionally, it's classified as an adaptogen, meaning it may help the body manage stress, potentially leading to an indirect reduction in inflammation. Research indicates possible benefits for arthritis and other inflammatory conditions (28).

**5.8. Rosemary:** Is rich in rosmarinic acid and carnosic acid, potent antioxidants that can also inhibit inflammatory enzymes like COX-2 and reduce the production of pro-inflammatory cytokines. Traditionally used for pain relief and cognitive function. Rosemary extract is being studied for its potential in various inflammatory conditions (29).

## 6. Conclusion

In conclusion, addressing inflammation effectively involves a comprehensive strategy tailored to the individual. Managing inflammation often involves making lifestyle changes such as adjusting one's diet to include more anti-inflammatory foods, engaging in regular exercise, practicing stress management techniques, and prioritizing sufficient sleep. When needed, these lifestyle adjustments are supported by suitable medical treatments, which can include over-the-counter pain medications and anti-inflammatory drugs, as well as prescription medications that target specific inflammatory processes. Crucially, understanding the specific type of inflammation, identifying its underlying cause, and considering individual health factors are paramount in developing a personalized management plan. Therefore, consulting with healthcare professionals is essential for accurate diagnosis, determining the root cause of the inflammation, and receiving expert guidance on the most suitable and safe management strategies. A collaborative approach between the individual and their healthcare team ensures the most effective and sustainable outcomes in managing inflammation and promoting overall well-being.

## References


1.Oronsky B, Caroen S, Reid T. What exactly is inflammation (and what is it not?). IJMS. 2022;23(23):14905.
2.Finlay AY, Griffiths TW, Belmo S, Chowdhury MM. Why we should abandon the misused descriptor 'erythema'. Br. J. Dermatol. 2021;185(6):1240.
3.Gusev E, Zhuravleva Y. Inflammation: A new look at an old problem. Int.J.Mol.Sci. 2022 ;23(9):4596..
4.Wijesekara T, Luo J, Xu B. Critical review on anti-inflammation effects of saponins and their molecular mechanisms. Phytother Res. 2024;38(4):2007-22.
5.Alkhatib AJ. The Role of Adult Stem Cells in Tissue Healing and Therapeutic Applications. PSM Microbiology. 2024;9(3):42-61.
6.Smolgovsky S, Theall B, Wagner N, Alcaide P. Fibroblasts and immune cells: at the crossroad of organ inflammation and fibrosis. Am. J. Physiol. Heart Circ. Physiol. 2024;326(2):H303-16
7.Oronsky B, Caroen S, Reid T. What exactly is inflammation (and what is it not?)Int.J.Mol.Sci.2022;23(23):14905.
8.Nasb M, Li F, Dayoub L, Wu T, Wei M, Chen N. Bridging the gap: Integrating exercise mimicry into chronic disease management through suppressing chronic inflammation. J Adv Res. 2024;70:307.
9.Conte HA, Janket SJ, Diamandis EP. Lifestyle modification is appropriate as primary prevention.JAMA Cardiol. 2022;7(2):231-2.
10.Ghodeshwar GK, Dube A, Khobragade D, Dube AH. Impact of lifestyle modifications on cardiovascular health: a narrative review. Cureus. 2023;15(7).
11.Metsios GS, Moe RH, Kitas GD. Exercise and inflammationBest Pract. Res. Clin. Rheumatol. 2020;34(2):101504
12.Ajabnoor SM, Thorpe G, Abdelhamid A, Hooper L. Long-term effects of increasing omega-3, omega-6 and total polyunsaturated fats on inflammatory bowel disease and markers of inflammation: a systematic review and meta-analysis of randomized controlled trials. Eur J Nutr. 2021;60:2293-316.

13.Swann OG, Breslin M, Kilpatrick M, O'Sullivan TA, Mori TA, Beilin LJ, Oddy WH. Dietary fibre intake and its association with inflammatory markers in adolescents. Br J Nutr. 2021;125(3):329-36.
14.Stumpf F, Keller B, Gressies C, Schuetz P. Inflammation and nutrition: friend or foe?. Nutrients. 2023;15(5):1159.
15.Al Bander Z, Nitert MD, Mousa A, Naderpoor N. The gut microbiota and inflammation: an overview. Int. J. Environ. Res. Public Health. 2020;17(20):7618.
16.Majd M, Saunders EF, Engeland CG. Inflammation and the dimensions of depression: a review. Front. Neuroendocrinol. 2020 ;56:100800.
17.Sohail R, Mathew M, Patel KK, Reddy SA, Haider Z, Naria M, Habib A, Abdin ZU, Chaudhry WR, Akbar A, Patel KK. Effects of non-steroidal anti-inflammatory drugs (NSAIDs) and gastroprotective NSAIDs on the gastrointestinal tract: a narrative review. Cureus. 2023;15(4).
18.L Kiss A. Inflammation in focus: the beginning and the end. POR. 2022;27:1610136.
19.Al-kaf AG, Al-yahawi AA. The Pharmacotherapy of Corticosteroids. 2025. DOI: 10.5772/intechopen.1008693
20.Zhang Q, McDermott GC, Juge PA, Chang SH, Vanni KM, Qian G, Bade KJ, Mueller KT, Kowalski EN, Saavedra AA, Sparks JA. Disease-modifying antirheumatic drugs and risk of incident interstitial lung disease among patients with rheumatoid arthritis: A systematic review and meta-analysis. Semin Arthritis Rheum 2024 (p. 152561). WB Saunders.
21.Houglum JE, Harrelson GL, Seefeldt TM. Drugs for treating inflammation. InPrinciples of Pharmacology for Athletic Trainers 2024 (pp. 96-123). Routledge.
22.Razavi BM, Ghasemzadeh Rahbardar M, Hosseinzadeh H. A review of therapeutic potentials of turmeric (Curcuma longa) and its active constituent, curcumin, on inflammatory disorders, pain, and their related patents. Phytother. Res. 2021 Dec;35(12):6489-513.
23..Ballester P, Cerdá B, Arcusa R, Marhuenda J, Yamedjeu K, Zafrilla P. Effect of ginger on inflammatory diseases. Molecules. 2022;27(21):7223.
24.Jalali Kondori B, Esmaili Gouvarchin Ghaleh H, Hosseini SM. Effect of green tea extract on exercise-induced inflammatory markers. J. Mil. Med. 2022 ;23(1):69-74.
25.Rawat P, Kumar S, Malik JK, Serrata B. Herbal Remedy to Reduce Inflammation.RJMP.2023:02(1)8-14
26.Arado GM, Amatto PD, Marins M, Rizzi ES, França SD, Coppede JD, Carmona F, Pereira AM. Anti-inflammatory and/or immunomodulatory activities of Uncaria tomentosa (cat's claw) extracts: A systematic review and meta-analysis of in vivo studies. Front. Pharmacol. 2024;15:1378408.
27.Gxaba N, Manganyi MC. The fight against infection and pain: Devil's claw (Harpagophytum procumbens) a rich source of anti-inflammatory activity: 2011–2022. Molecules. 2022;27(11):3637.
28.Dakshayani L, Merchant N, Smitha S, Surendra G, Reddy TG, Mamatha D, Deepthi G, Ramana DV, Chandrasekhar T, Reddy MC. Holy basil: A potential herbal source for therapeutic applications. Curr. trends. biotechnol. pharm 2021 Feb 12;15(1):87-100.
29.Elbouny H, Amssayef A, Benjamaa R, Ajebli M, Ouahzizi B, Bammou M, Sellam K, Alem C. Thyme, oregano, and rosemary: herbs and food supplements for the management of metabolic associated fatty liver disease. Nutrire. 2025;50(1):6.

# Cellular and molecular mechanisms of inflammation: A modern perspective


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## Abstract
Inflammation is a fundamental immunological response triggered by tissue damage, poisoning, or infection. Although unchecked or persistent inflammation can develop into chronic inflammation, which may lead to various serious diseases such as diabetes, cardiovascular disease, autoimmune disorders, and neurodegenerative conditions, acute inflammation serves as a protective mechanism essential for healing and re-establishing homeostasis. Complex signalling pathways are involved in the inflammatory process, including the activation of downstream signalling molecules like MAPKs and NF-kB, as well as cytokines (such as IL-1β, IL-6, and TNF-α) and their receptors. Immune cell recruitment and activation result from these coordinated interactions. Numerous factors contribute to chronic inflammation, such as immunological reactions, infections, poor diet, stress, obesity, and environmental pollutants. While inflammation is vital for survival, its dysregulation necessitates the use of specific management strategies. These include pharmaceutical treatments (e.g., biologics, NSAIDs), anti-inflammatory diets, stress reduction, exercise, and emerging treatments like Semaglutide, Dupixent, and NLRP3 inflammasome inhibitors.

**Keywords:** Cytokines, immune response, inflammation, NF-kB signalling

## 1. Introduction
The body has several defense mechanisms, one of which is inflammation. It is an immunologic reaction of the body to harmful stimuli. The process of inflammation may be triggered by poisons, toxic chemicals, tissue damage, or various infections (bacteria, viruses). TNF-α, interleukin-1β (IL-1β), interleukin-6, and other inflammatory cytokines are released when leukocytes are activated by such harmful stimuli, which set off a series of signalling events. TLR4, GM-CSFR, TNFR-1, TNFR-2, IL-6R, and other receptors are activated and coupled with these cytokines. The activation of receptors causes the phosphorylation of numerous signalling molecules, including nuclear factor kappa-B (NF-kB), Janus kinase, and mitogen-activated protein kinase (MAPK), which in turn activate transcription factors. This coordinated activation of signalling molecules not only recruits inflammatory cells from the blood but also regulates the levels of inflammatory mediators in resident tissue cells. The body uses acute inflammation as a defensive mechanism to eliminate harmful stimuli and initiate the healing process, thereby restoring the body's homeostasis (1).

However, failure to control acute inflammation may lead to chronic inflammation, which can serve as a

foundation for several serious chronic diseases, including cancer, multiple sclerosis, lateral disease, autoimmune diseases, diabetes, cardiovascular diseases, Parkinson's disease, Alzheimer's disease, and fibrillation.Although aetiology varies, the inflammatory mediators, as well as those involved in control and signalling, are typically the same. To register and transmit signals through the plasma membrane into the cell interior, receptors must be located on the cell membrane and internalized. The components of the signalling cascade, including transcription factors and various kinases, must gather in a location known as “signalling organelles/endosomes”, where they become activated. Activated transcription factors must migrate into the nucleus to regulate inflammatory genes, resulting in the synthesis and release of inflammatory cytokines into the environment. Inflammation can be classified as either acute or chronic. Acute inflammation is temporary and typically advantageous because it promotes the body's ability to recover from wounds like cuts and sprains. The redness, swelling, and warmth at the injury site are signs that the immune system is actively working. Chronic inflammation is a long-lasting inflammation that occurs due to the action of the immune response without any threat. This chronic inflammation continues, which affects the healthy tissues also and may lead to many infections like cancer, heart disease, Diabetes, arthritis, and also neurological disorders like Alzheimer’s disease (2).

The detection of infections or tissue injury by immune cells like neutrophils and macrophages triggers cellular inflammation. The cytokines and prostaglandins that these cells release encourage blood flow to the afflicted location and draw in additional immune cells. This leads to the characteristic signs of inflammation, which include pain, swelling, redness, heat, and loss of function. These reactions provide short-term protection, but long-term inflammation can harm healthy tissues. Persistent infections, prolonged exposure to irritants, autoimmune reactions, or lifestyle factors, including smoking, stress, poor food, and lack of exercise, can all lead to chronic inflammation. In contrast to acute inflammation, which goes away as soon as healing starts, chronic inflammation can go unnoticed for years and subtly advance a disease. Excessive inflammation is the starting point for systemic inflammation, including sepsis, which results in a protracted immunosuppressed condition. It uses functional assays and single-cell transcriptomics to show that the immunosuppression is caused by decreased type I interferon signalling and poor monocyte maturation, both of which can be restored by interferon-β therapy. According to a recent study, GZMK was created by the majority of immunological CD8+ T cells in rheumatoid arthritis patients' joints (3). Furthermore, it was discovered that people with a variety of chronic inflammatory disorders have higher levels of these GZMK-secreting immune cells in their inflammatory tissues. Additionally, the study has looked into how this pathway affects different diseases and is currently working on creating inhibitors that target GZMK in the hopes of providing patients with autoimmune and inflammatory diseases with new, focused treatments.

## 2. What causes inflammation?

Several factors can trigger inflammation in the body. These include (4):

### 2.1. Infections

Harmful microorganisms like bacteria, fungi, and viruses can enter the body, the immune system gets activated immediately to fight off inflammation. With the effect of microbes, white blood cells move to the site and affect the release of chemicals, which are responsible for swelling, redness, and pain. This is used to remove the pathogen.

### 2.2. Physical injuries

Wounds such as cuts, sprains, and bruises can cause inflammation. This is known as localized inflammation. Due to the body’s mechanism, the affected area can receive increased blood flow and immunological activity. This initiates tissue regeneration and helps to prevent infection.

### 2.3. Chemical and environmental irritants

Exposure to chemicals, tobacco smoke, and other air pollutants may cause irritation to the lungs and

other organs, prompting an inflammatory response. People who work in these environments with harmful substances may be at a higher risk of chronic inflammatory diseases.

### 2.4. Autoimmune disorders

The immune system incorrectly perceives the body's tissues as dangerous and launches attacks on them in autoimmune disorders such as lupus and rheumatoid arthritis. This can cause chronic inflammation that will affect organs, joints, and other tissues.

### 2.5. Obesity

Adipokines are a type of pro-inflammatory chemical released by fat cells, particularly those found in abdominal fat. Throughout the body, these chemicals encourage chronic, low-grade inflammation. This gives clarification on why obesity is a major risk factor for Type 2 diabetes and heart disease.

### 2.6. Stress

Emotional and psychological stress can lead to increased cortisol levels, which causes the disruption of immune function and promotes inflammation. Long-term stress can lead to ongoing inflammation, contributing to a number of medical conditions, including as depression and hypertension.

### 2.7. Poor diet

Inflammatory reactions can be brought on by a diet heavy in sugar, bad fats, and processed foods. It is also identified that the processed foods that contain more carbohydrates and trans fats can also lead to inflammation. Eating foods with high nutrients, like almonds, oily salmon, and green leafy vegetables, helps in decreasing inflammation.

## 3.How inflammation affects the body

Although inflammation is meant to protect the body, long-term inflammation can do the opposite, causing damage instead of healing (5). This has occurred due to various reasons, which include:

### 3.1. Development of chronic diseases

Chronic inflammation has been linked to neurological diseases, cancer, heart disease, and Type 2 diabetes. For example, blood vessel inflammation raises the risk of heart attacks and strokes by promoting plaque accumulation.

### 3.2. Damage to the joints and tissue

In autoimmune diseases, inflammation can attack and destroy healthy tissues. In rheumatoid arthritis, for example, the joints become inflamed and painful, eventually leading to erosion of cartilage and bone.

### 3.3. Pain and swelling

Inflammation increases blood flow and causes fluid buildup at the site of injury, leading to swelling. Chemicals like prostaglandins and histamines also irritate nerves, resulting in pain. This is why inflamed areas often feel tender and sore (6).

### 3.4. Suppressed immunity

Ironically, chronic inflammation can weaken the immune system. When the body is always on alert, it may start misfiring, causing immune fatigue or making the body more susceptible to infections and illnesses.

## 4. Managing inflammation naturally and medically

Fortunately, inflammation is manageable and even reversible with the correct techniques. Some useful strategies to deal with it are as follows (7):

### 4.1. Medications

- NSAIDs (e.g., ibuprofen, aspirin): These over-the-counter drugs help reduce inflammation and relieve pain.

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- Corticosteroids (e.g., prednisone): Often prescribed for more serious inflammation, especially in autoimmune diseases, to suppress the immune system.
- Biologic drugs: These target specific parts of the immune system and are used in cases like rheumatoid arthritis or inflammatory bowel disease.
-

### 4.2. Anti-Inflammatory diet

Adopting a diet that fights inflammation is one of the best long-term strategies. This includes:

- Fruits and vegetables rich in antioxidants (e.g., berries, spinach, broccoli)
- Healthy fats like omega-3s found in fish (salmon, sardines) and flaxseeds
- Whole grains instead of refined grains
- Spices like turmeric, ginger, and cinnamon which have natural anti-inflammatory effects

### 4.3. Exercise

Moderate physical activity helps regulate immune function and reduce the production of inflammatory chemicals. Activities like brisk walking, cycling, and yoga not only improve fitness but also reduce stress and inflammation.

### 4.4. Stress management

Mindfulness practices like meditation, journaling, and deep breathing help lower stress hormones. Chronic stress is a major contributor to inflammation, so learning to manage it is crucial for overall health.

### 4.5. Quality sleep

Lack of sleep is strongly linked to increased inflammatory markers in the body. In order to promote immunological balance and recuperation, try to get 7 to 9 hours of adequate sleep per night.

### 4.6. Supplements

The following natural substances may aid in reducing inflammation:

- Omega-3 fatty acids
- Curcumin, Vitamins D, C, and E

Always get medical advice before beginning a supplement regimen.

### 4.7. Changes in lifestyle

- Reduce alcohol intake and stop smoking. Weight should be managed to ease the strain on the inflammatory reactions.
- Whenever possible, stay away from recognized poisons like pesticides and air pollutants.

As per the anti-inflammatory therapies, new drugs targeting disorders have been developed from recent studies. Here is a summary of a few noteworthy treatments:

**Table 1.** Emerging and novel anti-inflammatory drugs (8-10**)**

| Drug | Mechanism | Efficacy |
|---|---|---|
| Dupixent (Dupilumab) | Reduces lung inflammation by focusing on the IL-4 and IL-13 pathways. | In clinical trials, it was shown to enhance lung function and reduce exacerbations by 30–34% when taken in conjunction with traditional inhalation therapy. |
| Semaglutide (Ozempic, Wegovy) | Glucagon-like peptide-1 mimics the natural hormone GLP-1's activities. | According to recent research, it may decrease biological ageing and reduce inflammation markers by 43% |

| | | |
|---|---|---|
| Duvakitug | Prevents tumour necrosis factor-like ligand 1A (TL1A) from attaching itself to death receptor 3 (DR3). | In phase 2 trials, ulcerative colitis patients experienced remission rates of 36.2% and 47.8%, while placebo patients experienced remission rates of 20.5%. |
| Velsipity (Etrasimod) | Reduces inflammation by altering sphingosine-1-phosphate receptors to stop T-cell migration. | Shown effectiveness in ulcerative colitis induction and maintenance treatments. |
| Vamorolone (Agamree) | Working in conjunction with the glucocorticoid receptor (GR) to provide immunosuppressive and anti-inflammatory effects | Demonstrated a notable improvement in linear growth and the persistence of improvements in motor outcomes. |
| Nibrozetone (RRx-001) | Reduces neuroinflammation by inhibiting the NLRP3 inflammasome. | Reduced inflammasome activation and better motor deficit were observed in animal experiments. |

## 5. Conclusion

Inflammation is an important immune pathway that increases the healing process and keeps the body safe from harmful situations. Acute inflammation is mainly associated with benign and transient conditions, but chronic inflammation may lead to other diseases, such as Cancer, Diabetes, Heart disease and Neurological disorders. Chronic inflammation is triggered by Infections, Trauma, Stress, Obesity, autoimmune disorders. and poor eating habits. NF-κB and MAPKs signalling pathways and cytokines are the essential mediators for the inflammatory processes. Anti-inflammatory diet, regular exercise, adequate sleep, and stress management are all helpful in the management of inflammation. Along with this, the medical agents like Corticosteroids, NSAIDs, and novel therapeutic agents also play an important role in the management of inflammation. Novel agents mainly target the inhibition of GZMK and also modify the action of cytokines, thereby showing anti-inflammatory activity. Understanding the mechanism and the unwanted effects of inflammation is very essential for further development of new drug entities for the treatment of inflammation and also for the maintenance of health and prevention of diseases.

## References


1. Favier AL, Nikovics K. Molecular and Cellular Mechanisms of Inflammation and Tissue Regeneration. Biomedicines. 2023 May 10;11(5):1416.
2. Dhavendra Kumar, Chapter 22 - Molecular biology of acute and chronic inflammation, Clinical Molecular Medicine,2020, Pages 389-402
3. Duan M, Sun L, He X, Wang Z, Hou Y, Zhao Y. Medicinal chemistry strategies targeting NLRP3 inflammasome pathway: A recent update from 2019 to mid-2023. Eur J Med Chem. 2023 Nov 15;260:115750.
4. Kim ME, Lee JS. Molecular Foundations of Inflammatory Diseases: Insights into Inflammation and Inflammasomes. Curr Issues Mol Biol. 2024 Jan 3;46(1):469-484.
5. Gusev E, Zhuravleva Y. Inflammation: A New Look at an Old Problem. Int J Mol Sci. 2022 Apr 21;23(9):4596.
6. Medzhitov R. The spectrum of inflammatory responses. Science. 2021 Nov 26;374(6571):1070-1075.
7. Tapia N, Hanau J, Shliozberg J, Poretsky L. Inflammation: Pathogenesis and Biological Markers. In: Avtanski D, Poretsky L. (eds) Obesity, Diabetes and Inflammation. Contemporary Endocrinology, 2023, PP1-13.
8. Gade A, Ghani H, Patel P, et al. Dupilumab. (Updated 2024 Feb 28). In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2025 Jan-.
9. Kommu S, Whitfield P. Semaglutide. (Updated 2024 Feb 11). In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2025 Jan-.
10. Reinisch W, Stepek D, Kempinski R, Danese S, Sands BE, Ratiu-Duma B, et al. OP41 Duvakitug (TEV-48574), an anti-TL1a monoclonal antibody, demonstrates efficacy and favourable safety as an induction treatment in adults with moderately to severely active ulcerative colitis: Results from a phase 2b, randomised, double-blind, placebo-controlled, dose-ranging, basket trial (RELIEVE UCCD), Journal of Crohn's and Colitis, Volume 19, Issue Supplement_1, January 2025, Pages i79–i80.

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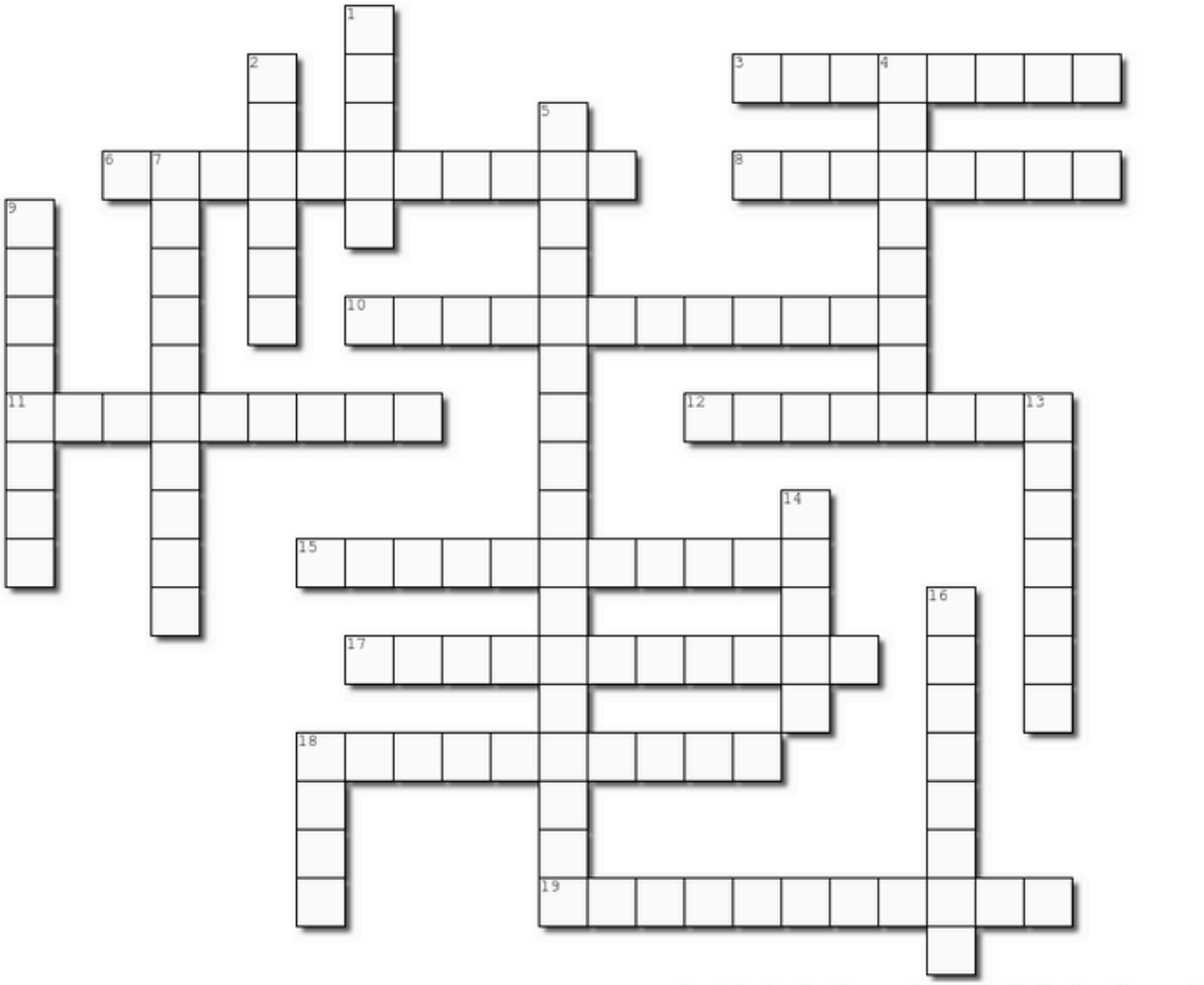
Complete the crossword puzzle below



Created using the Crossword Maker on TheTeachersCorner.net

**Across**

**3.** Type of fat releasing cytokines
**6.** First responders to inflammation, a type of white blood cell
**8.** Tissue death from inflammation
**10.** Signaling molecules in inflammation
**11.** Nuclear receptor with anti-inflammatory roles
**12.** Inflammatory cytokine from macrophages
**15.** DNA mutation process caused by inflammation
**17.** Anti-inflammatory hormone from fat
**18.** Age-related brain inflammation
**19.** Inflammation with pus

**Down**

**1.** Sign of inflammation that causes redness
**2.** Lung condition with airway inflammation
**4.** Natural hormone mimicked by corticosteroids
**5.** Chronic inflammatory bowel disease
**7.** TNF-alpha blocker biologic
**9.** Signaling pathway for inflammation
**13.** Immune-triggering molecule
**14.** Pain-relieving and anti-inflammatory drug (abbr.)
**16.** Tissue scarring from chronic inflammation
**18.** Advanced glycation end products (abbr.)

**Answers on Page 101**

# From inflammation to ovulation: Rethinking PCOS pathophysiology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**Abstract**

Polycystic-Ovary Syndrome (PCOS) is a common endocrinological disorder in women belonging to active reproductive age, marked by hyperandrogenism, recurrent anovulation, and polycystic ovarian morphology. Recent findings indicate a substantial correlation between PCOS and persistent low-grade systemic inflammation, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and several adipokines having prominent role as inflammatory biomarkers. As of 2025 WHO statistics and factsheets, approximately 6-13% of women are experiencing this disorder worldwide with a prevalence of 3.7-22.5% in India. Approximately 70% of the suffering population goes undiagnosed. The bidirectional association between inflammation and PCOS suggests that inflammation may serve as both a result and a contributor to the syndrome's clinical manifestations. Comprehending the inflammatory mechanisms of PCOS may facilitate the development of innovative therapeutic strategies aimed at inflammatory pathways to regulate and alleviate the symptoms.

**Keywords:** Polycystic-ovary syndrome, inflammatory mechanism, inflammatory biomarkers

## 1. Introduction

### 1.1. The PCOS-insulin-inflammation triangle

Chronic inflammation and insulin resistance are closely related with progression of PCOS. Insulin resistance feeds hyperinsulinemia and availability of free androgen in circulation while the inflammatory mechanisms exacerbate the insulin signalling. They collectively work together to cause reproductive and metabolic dysfunctions in the ovarian cycle.(1) Inflammation impairs insulin signalling. Pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β interfere with insulin signalling by activating stress related kinases such as JNK, IKKβ and p38 MAPK which phosphorylate the Insulin Receptor Substrate (IRS) protein on serine residues instead of tyrosine. (2) Additionally, Suppressor of Cytokine Signalling (SOCS) proteins are also induced by this inflammatory response further inhibiting insulin receptor activity. (3) Inhibition of downstream insulin signalling ultimately results into insulin resistance. These metabolic changes due to elevated free fatty acids and glucose in circulation trigger a series of complexities like oxidative stress and mitochondrial dysfunction, activated inflammatory responses in hepatic and adipose tissues and macrophage infiltration into them. The disrupted insulin signalling also hinders hepatic production of Sex Hormone Binding Globulin (SHBG) which in turn escalates free androgen availability in the blood circulation leading to vicious PCOS symptoms like hirsutism, alopecia, acne and unwanted belly fact.(4) Figure no. 1 describes the interwinding relation between inflammatory triggers, insulin resistance and progression of PCOS.

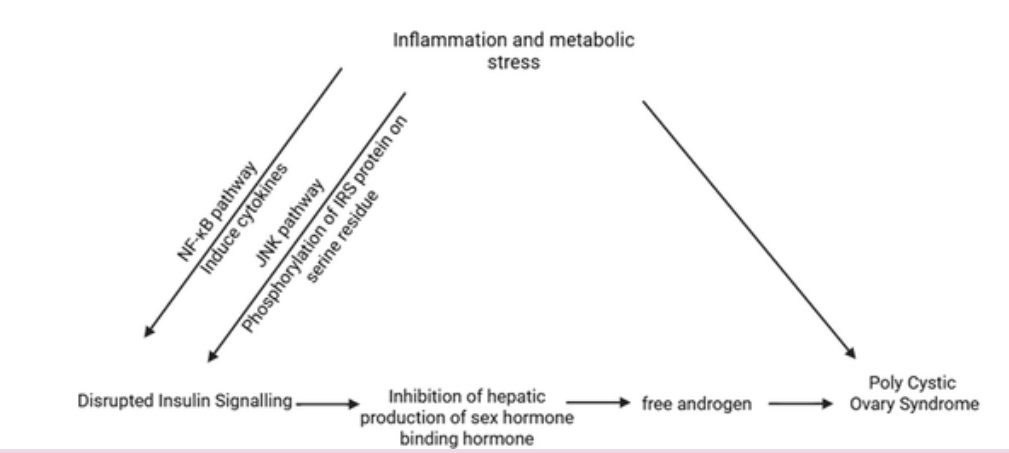


**Figure 1.** Inflammation and metabolic stress trigger activation of the NF-κB and JNK signalling pathways, resulting in cytokine production and the phosphorylation of insulin receptor substrate (IRS) proteins on serine residues respectively. The metabolic changes further interfere with standard insulin signalling process subsequently hindering the hepatic synthesis of SHBG. The decrease in SHBG elevates free androgen levels in circulation, a significant factor in the pathogenesis of PCOS.

## 2. Role of inflammatory mediators in the genesis of PCOS and associated metabolic disorders

The pathophysiological pathway of development of PCOS is complex and multifactorial, with chronic low-grade inflammation playing a key role in its progression. Women with PCOS frequently exhibit elevated levels of systemic inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and various pro-inflammatory adipokines such as leptin and resistin. This inflammatory milieu not only contributes to reproductive dysfunction but also increases the risk of prolonged metabolic complications, including type 2 diabetes mellitus and cardiovascular diseases. (5) Furthermore, local inflammation within ovarian tissue can impair follicular development and ovulatory functions, perpetuating the anovulatory state typical of PCOS. A typical role of inflammatory mediators towards ignition of poly-cysts is discussed in the Table no. 1 and Figure no. 2 below.

**Table 1.** Summarises the inflammatory mediators and their role in development of a poly cystic ovary via various mechanistic pathways (5–9)

| S. N. | Inflammatory mediators involved | Role of inflammatory mediators in development of PCOS |
|---|---|---|
| 1. | **C-Reactive Protein (CRP)** | CRP is linked with insulin resistance and endothelial dysfunction, contributing to both metabolic and cardiovascular complications of PCOS. |
| 2. | **Tumor Necrosis Factor-alpha (TNF-α)** | TNF-α interferes insulin signalling pathway by promoting insulin resistance. It stimulates androgen production by ovarian theca cells, contributing to hyperandrogenism. Also involved in the recruitment of immune cells that exacerbate local ovarian inflammation. |
| 3. | **Interleukin-6 (IL-6)** | IL-6 is elevated in PCOS and promotes hepatic production of CRP. It impairs insulin action in adipose and muscle tissues, worsening insulin resistance. IL-6 may disrupt folliculogenesis and ovulation through inflammatory damage to ovarian tissue. |

| | | |
|---|---|---|
| 4. | **Interleukin-1β (IL-1β)** | Plays a role in follicular arrest and anovulation by interfering with granulosa cell function.Contributes to ovarian inflammation and disruption of steroidogenesis. |
| 5. | **Monocyte Chemoattractant Protein-1 (MCP-1)** | MCP-1 levels are increased in PCOS, promoting macrophage infiltration into adipose and ovarian tissues. Macrophages secrete additional cytokines, thereby exacerbatin inflammation and insulin resistance. |
| 6. | **Leptin** | Leptin levels are often elevated in PCOS, especially in obese individuals. It acts as a pro-inflammatory adipokine, stimulating TNF-α and IL-6 production. Alters hypothalamic-pituitary-ovarian axis function, potentially affecting ovulation. |
| 7. | **Resistin** | Promotes insulin resistance by disrupting insulin receptor signalling pathways. It has pro-inflammatory properties that contribute to systemic inflammation in PCOS. |
| 8. | **Nuclear Factor-kappa B (NF-κB)** | A key transcription factor activated by inflammatory signals. Drives expression of cytokines and chemokines, contributing to chronic inflammation and insulin resistance in PCOS. |

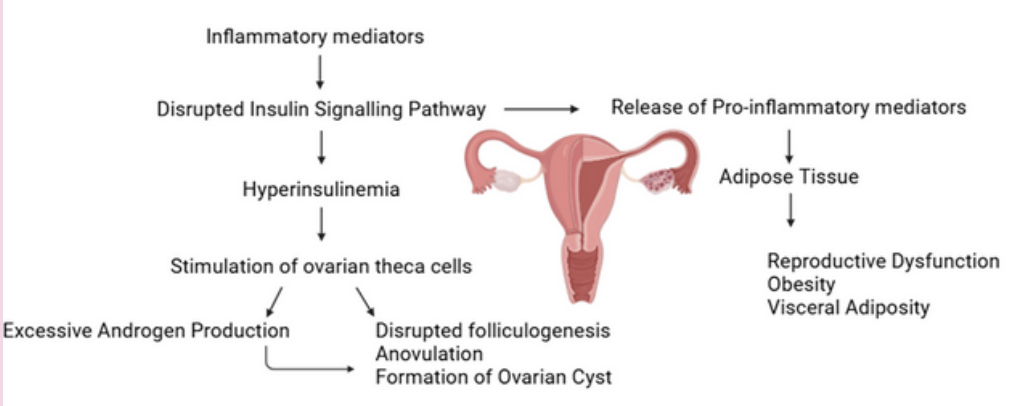


**Figure 2.** Depicts the pathophysiological pathway of PCOS development due to altered insulin signalling pathway caused by inflammatory mediators. Apart from disturbed folliculogenesis and reproductive functions, these inflammatory mediators are also responsible for inhibition of hepatic production of sex hormone binding globulin. As a result, free androgen becomes available in blood stream which is responsible for vicious symptoms of PCOS like acne outbreaks, alopecia and hirsutism (5,10,11)

## 3. Anti-inflammatory agents: New potential for fighting PCOS

Although the treatment or management of PCOS is mainly dependent upon the patient's need; anti-inflammatory agents offer novel options. Metformin, an insulin-sensitizing medication used to treat PCOS, also reduces inflammation. Metformin lowers inflammatory indicators like CRP and TNF-α, reducing systemic inflammation. Metformin lowers insulin and indirectly reduces androgen by enhancing insulin sensitivity, restoring regular ovulatory cycles. (12) Some recent trials are also focussing on salicylate derivatives and ibuprofen.(13) Meanwhile, Poly Unsaturated Fatty Acids (PUFAs) have emerged as potent servers. Omega-3-fatty acids, in particular Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) have proven to show significant anti-inflammatory properties and are increasingly recognised for their potential in management of PCOS by modulating the production of pro-inflammatory cytokines. Omega-3 supplementation improves insulin sensitivity, lowers blood triglycerides, and lowers androgen in PCOS women. Menstrual regularity and ovulatory frequency may also benefit from omega-3s (14).

## 4. Conclusion

Infertility, menstrual irregularities, hyperandrogenism, weight loss and metabolic disease management are the goals of current treatment regimen of PCOS. Underlying molecular mechanism of pathophysiology of PCOS is the recent research goal and moreover role of chronic inflammation in progression of disease is expanding. Future therapeutic strategy for PCOS may include anti-inflammatory medications.

## References


1. Xu Y, Qiao J. Association of Insulin Resistance and Elevated Androgen Levels with Polycystic Ovarian Syndrome (PCOS): A Review of Literature. Abdulhay E, editor. J Healthc Eng. 2022 Mar 21;2022:1–13.
2. Rudnicka E, Suchta K, Grymowicz M, Calik-Ksepka A, Smolarczyk K, Duszewska AM, et al. Chronic Low Grade Inflammation in Pathogenesis of PCOS. Int J Mol Sci. 2021 Apr 6;22(7):3789.
3. Rakhshanizade N, Sargazi S, Karajibani M, Majidpour M, Karajibani A, Montazerifar F, et al. Influence of Suppressor of Cytokine Signaling 1 (SOCS1) Gene Variations on Polycystic Ovary Syndrome. Indian J Clin Biochem [Internet]. 2024 Jul 10 [cited 2025 Jun 3]; Available from: https://link.springer.com/10.1007/s12291-024-01248-2
4. Sun Y, Li S, Liu H, Bai H, Hu K, Zhang R, et al. Oxidative stress promotes hyperandrogenism by reducing sex hormone-binding globulin in polycystic ovary syndrome. Fertil Steril. 2021 Dec;116(6):1641–50.
5. Rostamtabar M, Esmaeilzadeh S, Tourani M, Rahmani A, Baee M, Shirafkan F, et al. Pathophysiological roles of chronic low-grade inflammation mediators in polycystic ovary syndrome. J Cell Physiol. 2021 Feb;236(2):824–38.
6. He Z, Wang Y, Zhuan L, Li Y, Tang Z ouyin, Wu Z, et al. MIF-mediated NF-κB signaling pathway regulates the pathogenesis of polycystic ovary syndrome in rats. Cytokine. 2021 Oct;146:155632.
7. Aboeldalyl S, James C, Seyam E, Ibrahim EM, Shawki HED, Amer S. The Role of Chronic Inflammation in Polycystic Ovarian Syndrome—A Systematic Review and Meta-Analysis. Int J Mol Sci. 2021 Mar 8;22(5):2734.
8. Wu Z, Fang L, Li Y, Yan Y, Thakur A, Cheng J, et al. Association of circulating monocyte chemoattractant protein-1 levels with polycystic ovary syndrome: A meta-analysis. Am J Reprod Immunol. 2021 Aug;86(2):e13407.
9. Al-Awadi AM, Saldhana FL, Bauyrzhanova Z, Nemr R, Mahmood NA, Almawi WY. Relation of resistin gene variants to resistin plasma levels and altered susceptibility to polycystic ovary syndrome: A case control study. Am J Reprod Immunol. 2023 Jul;90(1):e13731.
10. Oróstica L, Poblete C, Romero C, Vega M. Pro-Inflammatory Markers Negatively Regulate IRS1 in Endometrial Cells and Endometrium from Women with Obesity and PCOS. Reprod Sci. 2020 Jan;27(1):290–300.
11. Kuang H, Duan Y, Li D, Xu Y, Ai W, Li W, et al. The role of serum inflammatory cytokines and berberine in the insulin signaling pathway among women with polycystic ovary syndrome. Zhang M, editor. PLOS ONE. 2020 Aug 12;15(8):e0235404.
12. Diamanti-Kandarakis E, Paterakis T, Alexandraki K, Piperi C, Aessopos A, Katsikis I, et al. Indices of low-grade chronic inflammation in polycystic ovary syndrome and the beneficial effect of metformin. Hum Reprod. 2006 Jun 1;21(6):1426–31.
13. Banaszewska B, Ozegowska K, Polska M, Pawelczyk L, Chang RJ, Duleba AJ. Ibuprofen Reduces Testosterone Level in Women With Polycystic Ovary Syndrome. J Endocr Soc. 2022 Oct 1;6(10):bvac128.
14. Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? Br J Clin Pharmacol. 2013 Mar;75(3):645–62.

# Elucidating the role of transferosomes for the management of gout: A comprehensive review

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**Abstract**

Millions of people throughout the world suffer from gout, a chronic inflammatory disease. It is predominantly brought on by uric acid crystals building up in the joints, which causes excruciating pain and swelling. Conventional therapies are accessible, but their efficacy and safety are frequently limited, highlighting the need for more sophisticated and dependable therapy alternatives. Nanotechnology has become a viable option for improving drugs delivery method in recent years. Strategies utilizing liposomes, polymeric nanoparticles, metal and non-metal oxide nanoparticles, and liquid crystalline nanoparticles have demonstrated promise in enhancing bioavailability and more precisely addressing inflammatory regions. Transferosomes, a unique class of ultra-deformable, lipid-based vesicles, have drawn a lot of interest as an innovative drug delivery system for the treatment of gout. A growing amount of data from preclinical and clinical research demonstrates that transferosome-based formulations are safe and effective, and they can address many of the drawbacks of conventional gout treatments.

**Keywords:** Transferosomes, joint inflammation, skin permeation.

## 1. Introduction

Gout is a painful and chronic inflammatory condition which is accompanied by the abnormal formation of uric acid crystals in the joints, characterized by intense pain and considerable swelling. The condition can persist for years, often affecting a person's quality of life. The underlying cause of gout is the formation of monosodium urate (MSU) crystals, which can deposit in various tissues throughout the body. The

formation of uric acid crystals requires serum uric acid (SUA) levels to rise above a certain threshold. Hyperuricemia is the primary factor in the development of gout as a pathogenic defect However, many persons who are diagnosed with hyperuricemia do not suffer from gout and even formation of UA crystals do not take place in them. Gout only develops in 5 percent of patients who have hyperuricemia levels that are higher than 9 mg/dL. Accordingly, it is hypothesized that the occurrence of gout is also influenced by other variables, such as a hereditary susceptibility (1). Figure 1 depicts the pathophysiology of gout and provides a clearer understanding of the disease.

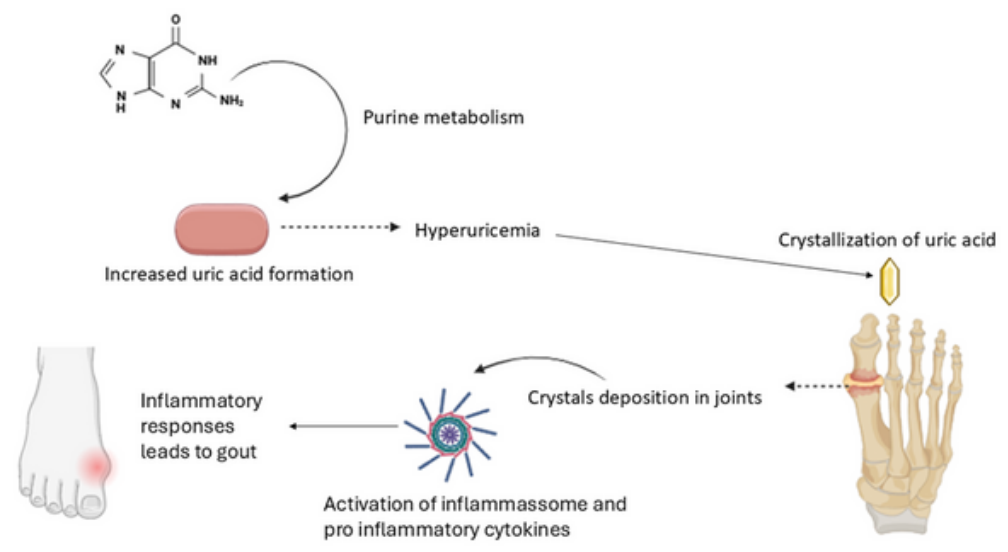


**Figure 1.** Pathophysiology of gout

In 2020, gout affected approximately 55.8 million people worldwide, with a 22.5% increase in age-standardized prevalence since 1990. Men were over three times more likely to have gout than women, and prevalence rose with age. By 2050, gout cases are projected to reach 95.8 million, primarily due to population growth. The age-standardized prevalence in 2050 is expected to be around 667 per 100,000 people (2). It can cause discomfort and may lead to several health complications. However, traditional therapies for gout have several drawbacks, including ineffective medication distribution to the affected tissues and the risk of adverse effects. Recent advancements in nanotechnology have given rise to a new medication delivery mechanism called transferosomes. This article explores the potential of transferosomes to revolutionize gout treatment by enhancing medication delivery efficacy while minimizing adverse effects. Future research must focus on the development and testing of therapeutic interventions for the prevention and treatment of gouty arthritis. Combining clinical and epidemiological evidence and animal experiments could significantly benefit this field (3).

## 2. Limitations of current treatment

Suboptimal gout care is caused by a variety of variables, including clinicians who don't adhere to established procedures, patients who don't adhere to their medicines, and communication gaps between doctors and their patients. Patients need to be reminded of the need of adhering to long-term treatment and other elements of sickness diagnosis and care. Low medication adherence may also be caused by a lack of motivation and an inability to purchase the prescription. Around one in a hundred people taking allopurinol may develop a usually mild skin rash, though in rare cases it can signal a serious allergic reaction. Renal issue is another risk with the treatment line (4).

## 3. Transferosomes®

Transferosomes® are novel lipid-based vesicles that are the modified form of liposomes and have also gained a lot of interest for the transdermal delivery of drugs. They are small, with a diameter of approximately 100 nm, and are referred to as transferosomes. The name comes from the words "transfere" in Latin and "soma" in Greek, which mean "to carry across" and "body," respectively. These tiny carriers

have properties like prosomes, which are cells involved in exocytosis. With this delivery carrier, drugs can be delivered to bodily tissues non-invasive. IDEA AG, a German company, has registered Transferosome as a trademark to refer to its technology for delivering drugs. Membrane-enclosed transferosomes with an activator on the outer edge; because of the edge activator, the lipid layer is ultra-deformable and flexible. Because of their ability to deform and squeeze through minute holes and constrictions in the skin, these vesicles permeate easily (5). Transferosomes offer a significant advantage over ordinary liposomes i.e. exceptional stability. Moreover, transferosomes are considerably enhanced by edge activators (anionic surfactants), which significantly boost their performance compared to liposomes. Numerous studies indicate that transferosomes can carry bioactive compounds and hydrophilic and lipophilic molecules with a molecular weight ranging from 200 to $10^6$. They have a transport efficiency of over 50% when applied to human skin. The transferosomes are amphiphilic vesicular systems (6). Figure 2. Shows how the vesicles penetrate through the skin's layers, starting from the outer stratum corneum, moving into the epidermis and dermis. They carry the drug safely across these barriers without degradation. Once they reach the systemic circulation, the vesicles release the drug gradually for effective absorption.

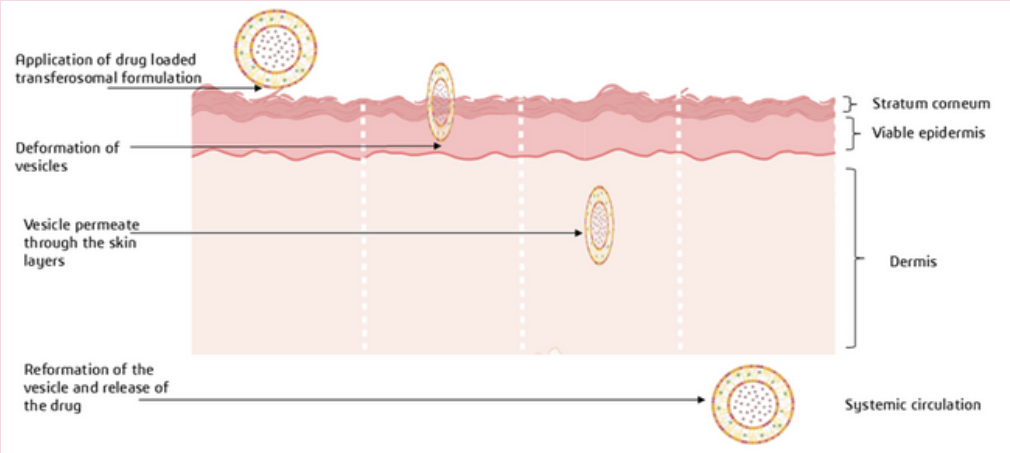


**Figure 2.** The mechanism of drug release and transferosome trafficking via the skin

## 4. Therapeutic applications of transferosomes

Transferosomes are novel vesicular drug carriers that improve transdermal drug absorption by getting past the limits of the epidermal barrier (7). These elastic vesicles, which are made of water, phospholipids, and surfactants, can distort to enter skin pores, increasing medication absorption and lowering toxicity (8). Transdermal vaccination, insulin delivery, and the injection of NSAIDs and steroidal hormones are merely a few of their many medical applications. Preparation techniques include reverse phase evaporation, modified hand shaking, and thin film hydration method (9). Transferosomes are intriguing possibilities for skin cancer treatment and other dermal and transdermal applications due to their adaptability and flexibility; multiple products are undergoing advanced clinical testing (10).

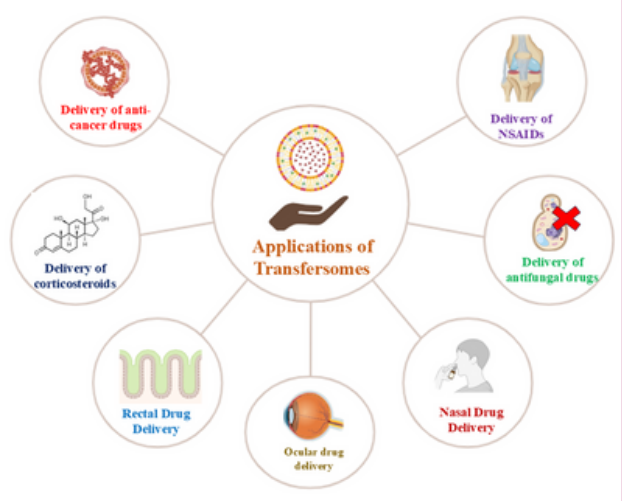


**Figure 3.** Different transferosome uses for delivering different agents using different delivery mechanisms

## 5. Key studies on transferosomes in gout treatment

Studies have shown that transferosomes can be used in the treatment of gout. These studies are key to understanding the effectiveness of transferosomes in treating this condition. Transferosomes have the potential to revolutionize drug delivery and improve treatment outcomes for a variety of conditions like arthritis, osteoarthritis, etc. Table 1 lists the potential therapeutic agents that can be delivered using transferosomes for the treatment of gout.

**Table 1.** Potential therapeutic agents delivered topically by ultra-deformable system for Gout

| Nanocarrier system | Drug | Method of Preparation | Result | Ref |
|---|---|---|---|---|
| Transferosome | Allopurinol | Thin film hydration method | Selected formulation demonstrated a drug permeation of 79.84%, with a flux of 13.06 µg/cm²/hr, indicates a significant enhancement in permeation compared to the standard allopurinol formulation, which exhibited a flux of only 7.05 µg/cm²/hr. | (6) |
| Transferosome | Indomethacin | Rotary evaporation sonication method | The Indomethacin-Hyaluronan transferosomal gel showed approximately 3.04-fold higher drug permeation than conventional Indomethacin gel and 1.73-fold higher than indomethacin-transferosomal gel. It also exhibited a 3.31-fold increase in flux over Indomethacin Gel and 1.85-fold over Indomethacin Gel,confirming its superior transdermal delivery performance. | (11) |
| Transethosome | Colchicine | Cold method | Colchicine-transethosomes exhibited high biocompatibility, high permeation, sustained delivery and lesser toxic effects as compared to 40% ethanol solution. | (12) |
| Transferosome | Dexibuprofen | Thin film hydration method | The selected formulation, Dexibuprofen transferosomal gel, followed sustained release by releasing the drug 38.1% in 4 hours. | (13) |

## 6. Conclusion and future prospects

Conventional oral therapies for gout often face significant limitations due to patient comorbidities, poor drug tolerance, and systemic side effects. In recent years, nanotechnology-based drug delivery systems such as liposomes, niosomes, ethosomes, and particularly transferosomes have emerged as promising alternatives, offering more targeted and effective approaches to gout management. Among these, transferosomes stand out due to their ultra-deformable lipid bilayers, which enable deep transdermal penetration and localized drug delivery directly to inflamed joints. This unique capability not only enhances drug bioavailability and prolongs release but also significantly reduces systemic toxicity, thereby improving anti-inflammatory and antigout effectsTransferosomes reduce systemic exposure, increase therapy effectiveness, and encourage improved patient adherence by precisely delivering therapeutic chemicals to the site of injury. Numerous commercially available transferosomal formulations, including Flexiseq, TDT-067, Transfersulin, Triamcinolone acetonide, and Diractin, have already shown improved targeted delivery and skin penetration. These pharmaceuticals have demonstrated clinical effectiveness in treating inflammatory disorders, diabetes, fungal infections, and osteoarthritis, highlighting the therapeutic usefulness and adaptability of transferosome-based administration. These achievements pave the path for additional research into using transferosomes as a vehicle to deliver a greater variety of medications. This system's versatility presents a great deal of promise for transdermal treatment of both acute and chronic diseases.

Furthermore, transferosome development's incorporation of Computer-Aided Drug Design (CADD) is expected to spur innovation in this area. In order to maximize skin penetration, CADD helps select for appropriate lipids and edge activators and predicts drug-excipient interactions, vesicle stability, and entrapment efficiency. With further study and technical development, transferosomes have the potential to revolutionize future treatment approaches and establish themselves as a key component of personalized, non-invasive drug delivery systems.

## References


1. Punzi L, Galozzi P, Luisetto R, Scanu A, Ramonda R, Oliviero F. Gout: one year in review 2023. Clin Exp Rheumatol. 2024 Jan 1;42(1):1-9.
2. Cross M, Ong KL, Culbreth GT, Steinmetz JD, Cousin E, Lenox H, Kopec JA, Haile LM, Brooks PM, Kopansky-Giles DR, Dreinhoefer KE. Global, regional, and national burden of gout, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology. 2024 Aug 1;6(8):e507-17.
3. Wen P, Luo P, Zhang B, Zhang Y. Mapping knowledge structure and global research trends in gout: a bibliometric analysis from 2001 to 2021. Frontiers in public health. 2022 Jun 29;10:924676..
4. Saxena S, Sahu R, Jain S. Current trends and gaps in gout management guidelines: A critical review. Journal of Health Physiotherapy and Orthopaedics (JHPO). 2025 Apr 20;2(2):7-10.
5. Opatha SA, Titapiwatanakun V, Chutoprapat R. Transfersomes: A promising nanoencapsulation technique for transdermal drug delivery. Pharmaceutics. 2020 Sep;12(9):855.
6. Tiwari R, Tiwari G, Singh R. Allopurinol loaded transferosomes for the alleviation of symptomatic after-effects of Gout: An Account of Pharmaceutical implications. Current Drug Therapy. 2020;15(4):404–19.
7. Madhumitha V, Sangeetha S. Transfersomes: A Novel Vesicular Drug Delivery System for Enhanced Permeation through Skin. Research Journal of Pharmacy and Technology. 2020;13(5):2493–501.
8. Akram MW, Jamshaid H, Rehman FU, Zaeem M, Khan J zeb, Zeb A. Transfersomes: a Revolutionary Nanosystem for Efficient Transdermal Drug Delivery. AAPS PharmSciTech [Internet]. 2021;23(1):7.
9. Moqejwa T, Marimuthu T, Kondiah PPD, Choonara YE. Development of Stable Nano-Sized Transfersomes as a Rectal Colloid for Enhanced Delivery of Cannabidiol. Pharmaceutics. 2022 Mar;14(4).
10. Mazyed EA, Abdelaziz AE. Fabrication of transgelosomes for enhancing the ocular delivery of acetazolamide: Statistical optimization, in vitro characterization, and in vivo study. Pharmaceutics. 2020 May 20;12(5):465.
11. Yuan M, Niu J, Xiao Q, Ya H, Zhang Y, Fan Y, et al. Hyaluronan-modified transfersomes based hydrogel for enhanced transdermal delivery of indomethacin. Drug delivery. 2022 Dec;29(1):1232–42
12. Zi M, Ke J, Jiang S, Cui X, Zhang J, Yuan S, Huang S, Wang J, Liu H, Zhang J, Peng C. Colchicine-loaded transethosomes enhances transdermal permeability and therapeutic effects of acute gouty arthritis via vesicle extrusion and lipid perturbation. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2024 Apr 20;687:133582.
13. Rafique M, Ali Z, Sohail S, Zahid F, Khan MI, ud Din F, Alamri A, Al Fatease A, Alqahtani T, Lahiq AA. Development of dexibuprofen loaded nano transfersomal gel with enhanced biopharmaceutical performance in complete Freund's adjuvant induced arthritis model. Journal of Drug Delivery Science and Technology. 2024 Sep 1;98:105928.

# A panoramic view of inflammation: Etiology, pathophysiology, and management strategies

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**Abstract**

Inflammation, a fundamental biological process, plays a pivotal role in host defense and disease pathogenesis. This paper explores the triggers, mechanisms, impact, and management of inflammation. It highlights infectious agents, chemical/physical factors, and autoimmunity as key initiators, activating cellular components such as macrophages and neutrophils via pathways such as NF-kB and inflammasomes. While acute inflammation promotes healing, its dysregulation leads to chronic diseases like rheumatoid arthritis, cardiovascular disorders, and fibrosis. Traditional treatment involves NSAIDs, corticosteroids, and DMARDs, while emerging therapies focus on precise targeting of immune pathways and metabolic immunomodulation. Lifestyle modifications, including anti-inflammatory diets, also play a critical role. Unresolved issues persist regarding the transition from acute to chronic inflammation, necessitating further research into novel therapy targets and a personalized approach for effective resolutions.

**Keywords:** Inflammasomes, cytokines, autoimmune diseases, anti-inflammatory therapy

## 1. Introduction

Inflammation is the body's natural response to harmful stimuli like pathogens, damaged cells, or irritants, serving as a first line of defense and playing a key role in eliminating threats and initiating tissue repair. While acute inflammation is essential for healing, chronic inflammation can contribute to serious health issues such as cancer, cardiovascular disease, and autoimmune disorders (1,2). It triggers increased blood flow, immune activity, and chemical release, causing redness, heat, swelling, pain, and loss of function (3).

Pattern-recognition receptors (PRRs) are key in identifying specific molecular structures. These structures can be Pathogen-Associated Molecular Patterns (PAMPs) found on microorganisms or Damage-Associated Molecular Patterns (DAMPs) released by damaged or dying cells. Once PRRs detect these patterns, they activate inflammatory signaling pathways which kick-starts the body's inflammatory response (4).

## 2. Understanding inflammation

Inflammation is a biological response of vascular tissues to harmful stimuli like pathogens, damaged cells, or irritants. Its main goal is to eliminate the cause of injury, clear necrotic cells, and initiate tissue repair. Cardinal signs are redness, heat, swelling, pain, and loss of function resulting from increased blood flow, permeability, and chemical mediators aiding the immune response and repair. It involves the innate and

adaptive immune system with immune and non-immune cells, chemical mediators, and signaling pathways (5). Inflammation is classified as acute and chronic.

### 2.1. Acute inflammation

The body's innate response to injury and infection involves neutrophils and plasma proteins. It is short-lived, lasting minutes to days, and aimed at eliminating pathogens and promoting healing.

### 2.2. Chronic inflammation

It persists for weeks to years, often due to unresolved acute inflammation or ongoing exposure to irritants. It involves macrophages, lymphocytes, and plasma cells, leading to tissue damage and repair. Chronic inflammation can contribute to diseases like cardiovascular disease, diabetes, cancer, and autoimmune disorders. Thus, while inflammation is essential for host defense and tissue repair, its dysregulation can lead to significant pathology (6). Inflammation activates immune cells and releases cytokines like IL-1β, IL-6, and TNF-α, leading to vascular changes and immune cell migration to restore health (7).

## 3. Triggers of inflammation

### 3.1. Infectious agents

Infectious agents like bacteria, fungi, and parasites are major triggers of inflammation. Bacterial components like TLRs on immune cells lead to the release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β) and the recruitment of neutrophils to the infection site. Viral infections activate innate immune response through recognition of viral nucleic acids by TLRs and RIG-I-like receptors, including interferon production and inflammation. Fungal pathogens like Candida albicans stimulate inflammasomes activation, while parasitic infection provokes chronic inflammatory responses through antigen presentation and cytokine secretion, contributing to pathogen clearance but may cause tissue damage (8).

### 3.2. Physical chemical triggers

Physical injury, such as trauma, burns, or radiation, damages cells and tissues, releasing Damage-Associated Molecular Patterns (DAMPs) that activate innate immune receptors and trigger inflammation (9). Chemical irritants like pollutants (e.g., particulate matter, ozone), cigarette smoke, and toxins induce oxidative stress, which activates inflammatory pathways like NLRP3 inflammasome (10). Exposure to asbestos fibers causes persistent inflammation by stimulating macrophages and releasing cytokines, contributing to fibrosis and carcinogenesis. Alcohol abuse also promotes inflammation by disrupting gur barrier integrity and increasing systemic endotoxin levels, which further activate an immune response. These physical and chemical triggers initiate inflammation that can be protective but may cause chronic tissue damage if unresolved (11).

### 3.3. Autoimmune causes

Autoimmune diseases arise when the immune system mistakenly targets self-antigens, leading to chronic inflammation and tissue damage (12). In conditions like rheumatoid arthritis and systemic lupus erythematosus (SLE), autoantibodies and immune complexes activate complement and recruit inflammatory cells, sustaining inflammation (13). Genetic predispositions, such as specific HLA alleles, and environmental factors contribute to the loss of self-tolerance. Molecular mimicry, where microbial antigen resembles self-Persistent Autoimmune inflammation disrupts normal tissue function and underlies many chronic diseases, highlighting the need for targeted immunomodulatory therapies (14).

## 4. Molecular and cellular mechanisms

### 4.1. Cellular mechanism

Inflammation involves immune and non-immune cells eliminating pathogens and repairing tissues, Macrophages regulate phagocytosis, cytokines production (TNF-α, IL-1β, IL-6), remodeling, and polarizing into M1 or M2 phenotypes. Neutrophils respond rapidly with granules, reactive oxygen species ROS and neutrophil extracellular traps NETs. Dendritic cells release histamine and leukotrienes to increase permeability.

Lymphocytes (Th1, Th17, B cells) drive chronic inflammation via IFN-γ, IL-17, and autoantibodies. Endothelial cells help leukocyte adhesion and migration by expressing ICAM-1 and VCAM-1 (15).

### 4.2. Molecular mechanism

Inflammation is driven by conserved signaling pathways activated by pattern recognition receptors (PRRs), pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) from microbes or stressed cells. PAMPs include microbial nucleic acids (unmethylated CpG motifs, double and single-stranded RNA) and components like peptidoglycans, lipoteichoic acid, and lipopolysaccharides (LPS). DAMPs include mitochondrial DNA, uric acid, S100 proteins, heat shock proteins, fibronectin, β-amyloid, advanced glycation end proteins (AGEs), and histone (16). These signals activate pathways like NF-kB, inducing transcription of pro-inflammatory cytokines (TNF-α, IL-1β) and chemokines (CXCL8) (17). The JAK-STAT pathway is triggered by IL-6 and IFN-γ, promotes leukocyte activation and chronic inflammation. Inflammasomes like NLRP3 activate caspase-1, maturing IL-1β and IL-18. Cytokines enhanced endothelial adhesion, molecule expression and acute phase response; chemokines attract neutrophils and monocyte/macrophages; lipid mediators (PGE2, LTB4) regulate vasodilation, pain, and cell movement. Reactive oxygen species ROS eliminate pathogens but contribute to oxidative tissue damage during chronic inflammation (18).

### 4.3. Regulation and resolution mechanism

To limit damage, inflammation is controlled by molecules “brakes”. Proteins like Tollip, SIRT1, and IRAK-M inhibit NF-κB activation, reducing cytokine production. Autophagy and lysosomal fusion clear debris, adding resolution. Transcription factors CREB and TFEB induce anti-inflammatory and tissue repair genes. Failure of these pathways can cause chronic inflammation, contributing to autoimmune disease, atherosclerosis, and metabolic syndrome (19).

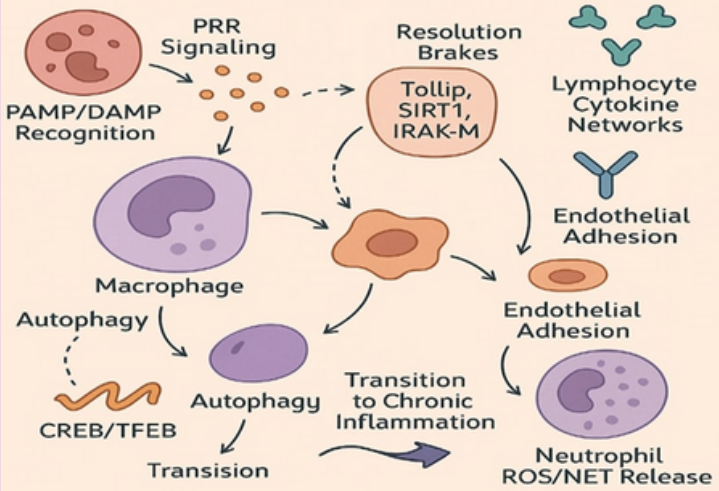


**Figure 1.** Mechanism of inflammation

## 5. Impact on inflammation

### 5.1. Physiological role (defense and healing)

Inflammation is crucial for host defense and tissue repair. Acute inflammation eliminates pathogens through immune cell recruitment and cytokine-mediated pathogen clearance (20). In tendon-bone healing, controlled inflammation clears debris and stimulates collagen synthesis. While immune cells like fibroblasts promote regeneration. Early-stage bone repair also relies on inflammatory signals to initiate callus formation. Similarly, skin wound healing involves immune cells releasing growth factors that coordinate tissue regeneration. These processes underscore inflammation’s protective role in restoring homeostasis (21).

### 5.2. Pathological consequences (chronic diseases, tissue damage)

Uncontrolled inflammation drives chronic diseases and tissue destruction. Long-term inflammatory signaling disrupts extracellular matrix (ECM) balance, leading to fibrosis and organ dysfunction. In bone, prolonged inflammation exacerbates osteoclast activities, increasing fracture risk and osteoporosis (22). Chronic

inflammation in wounds delays healing, causing pathological scarring or a non-healing ulcer. Overactive immune responses in autoimmune disorders like rheumatoid arthritis perpetuate joint damage, while oxidative stress from inflammatory mediators worsens tissue injury (23).

### 5.3. Disease association

5.3.1. **Autoimmune disorders:** Rheumatoid arthritis is characterized by systemic inflammation, where cytokine imbalances (e.g., TNF-α, IL-6) accelerate joint erosion and increase cardiovascular mortality.

5.3.2. **Cardiovascular diseases:** Chronic inflammation in Rheumatoid arthritis promotes endothelial dysfunction, elevating cardiovascular mortality risk (24).

5.3.3. **Fibrosis:** TGF-β-driven inflammation in organs like the lings and liver results in ECM accumulation and functional decline (25).

## 6. Management and therapeutic approach

### 6.1. Conventional treatment

Conventional management of inflammation primarily involves pharmacological interventions aimed at controlling symptoms and preventing disease progression. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen are commonly used to reduce pain and swelling. Corticosteroids like prednisone provide potent anti-inflammatory effects, especially in acute exacerbation. Disease-modifying antirheumatic drugs (DMARDs), including methotrexate and sulfasalazine, are used in chronic conditions such as RA to slow down disease progression. Biologic agents targeting specific immune pathways, such as TNF inhibitors (e.g., adalimumab, infliximab) and interleukin blockers, have revolutionized treatment by providing targeted suppression of inflammation. These conventional therapies aim to control the inflammatory process, preserve tissue function, and improve quality of life. However, long-term use of some agents, especially NSAIDs and corticosteroids, carries risks such as gastrointestinal, cardiovascular, and immunosuppressive effects (26).

### 6.2. Emerging therapy

Recent advancement in inflammation management emphasizes precision targeting in immune pathways. Dual inflammasome inhibitors like ADS032, which block NLRP1 and NLRP3, offer broad therapeutic potential for skin and systemic disorders. NLRP3-specific inhibitors (Inzomelid, MCC950) show efficacy in neurodegenerative models by curbing chronic inflammation. Stem cell therapies, including mesenchymal cell and their exosomes, modulate neuroinflammation without exacerbating pathology, while hematopoietic stem cell transplantation achieves remission in refractory cases. Metabolic immunomodulation reprograms the T-cell pathway to reduce inflammation in colitis and multiple sclerosis models, minimizing systemic immunosuppression risk. Complement inhibitors (SAR445088, C5a blockers) and cytokine modulators (GM-CSF inhibitors) target upstream drivers of tissue damage and cognitive decline in Alzheimer's trials. Bruton Tyrosine Kinase and Janus kinase inhibitors refine B-cell and cytokine signaling in arthritis and bowel diseases. These approaches- spanning biologics, small molecules, and cellular therapies- prioritize specificity to enhance efficacy and safety, making a shift toward personalized anti-inflammatory medicine (27).

### 6.3. Lifestyle and prevention

Anti-inflammatory diets, particularly those rich in fruits, vegetables, whole grains, nuts, legumes, and omega-3 fatty acids, have demonstrated effectiveness in managing chronic inflammation and improving quality of life for patients with conditions such as rheumatoid arthritis and chronic pain. Clinical studies, including a 2023 pilot trial, show that adherence to an anti-inflammatory dietary pattern correlates with reduced pain, stress, depression, and better

sleep, likely due to decreased intake of pro-inflammatory foods and increased consumption of anti-inflammatory nutrients. These diets act by lowering pro-inflammatory mediators and oxidative stress, thereby reducing systemic inflammation. While not a cure, an inflammatory diet serves as a valuable adjunct to medical therapy. Integrating complementary lifestyle modifications regular physical activity, stress management, adequate sleep, smoking cessation, and weight control, further enhances anti-inflammatory effects and overall health outcomes. Together, these strategies help to manage inflammation and may reduce reliance solely on pharmacological treatment.


**Figure 2.** Inflammation management: Treatments and lifestyle

## 7. Challenges and future directions

### 7.1. Unresolved issues in inflammation research

Key unresolved questions include the precise mechanism driving the transition from acute to chronic inflammation in diseases like long COVID and autoimmune disorders. Current therapies often fail to resolve inflammation completely, as many pathways (e.g., NLRP3 inflammasome activity, cytokine storms) remain difficult to target without immunosuppressive side effects. Additionally, the interplay between inflammation, aging, and metabolic dysregulation is poorly understood, limiting tailored therapeutic strategies.

### 7.2. Potential areas for new therapies and research focus

Emerging approaches focus on modulating immune cell migration (e.g., targeting miR-199 to suppress neutrophil trafficking without immunosuppression) and restoring anti-inflammatory homeostasis (e.g., boosting endogenous anti-inflammatory lipids or mediators like resolvins). Innovation in precision medicine, such as single-cell profiling of immune-neuronal interaction, could uncover novel targets like thrombospondin-1 (TSP1) to resolve inflammatory pain. Additionally, the “amalgamation” hypothesis proposes rebalancing pro- % anti-inflammatory mediators rather than broadly suppressing inflammation, opening avenues for therapies targeting specific molecular checkpoints (28).

## 8. Conclusion

Inflammation is a double-edged sword, essential for defense and healing but harmful when dysregulated, driving chronic diseases like cancer and autoimmune disorders. Advances in understanding its molecular mechanisms (e.g., NLRP3, NF-κB) enable targeted therapies, though unresolved challenges in resolving chronic inflammation necessitate innovative strategies to restore immune balance.

## References


1. Oronsky B, Caroen S, Reid T. What exactly is inflammation (and what is it not?) Int J Mol Sci. 2022 Nov 28;23(23):14905.
2. Chavda VP, Feehan J, Apostolopoulos V. Inflammation: the cause of all diseases. Cells. 2024 Nov 18;13(22):1906.
3. Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation. Clin Exp Immunol. 2007 Feb;147(2):227–35.
4. Janeway CA. Approaching the asymptote? Evolution and revolution in immunology. Cold Spring Harb Symp Quant Biol. 1989;54 Pt 1(1):1–13.
5. Megha KB, Joseph X, Akhil V, Mohanan PV. Cascade of immune mechanism and consequences of inflammatory disorders. Phytomedicine. 2021 Oct 1;91:153712.
6. Ephraim R, Fraser S, Devereaux J, Stavely R, Feehan J, Eri R, et al. Differential gene expression of checkpoint markers and cancer markers in mouse models of spontaneous chronic colitis. Cancers (Basel). 2023 Sep 29;15(19):4793.
7. Lionakis MS, Netea MG. Candida and host determinants of susceptibility to invasive candidiasis. PLoS Pathog. 2013 Jan;9(1):e1003079.
8. Lim EY, Kim GD. Particulate matter-induced emerging health effects associated with oxidative stress and inflammation. Antioxidants (Basel). 2024 Oct 1;13(10):2050.
9. Mossman BT, Churg A. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med. 1998;157(5 Pt 1):1666–80.
10. Rosenblum MD, Remedios KA, Abbas AK. Mechanisms of human autoimmunity. J Clin Invest. 2015;125(6):2228–33.
11. Wucherpfennig KW. Mechanisms for the induction of autoimmunity by infectious agents. J Clin Invest. 2001 Oct 15;108(8):1097–104.
12. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017 Dec 14;9(6):7204–18.
13. Thermo Fisher Scientific. Inflammation overview [Internet]. [cited 2025 Apr 24]. Available from: https://www.thermofisher.com/in/en/home/life-science/cell-analysis/cell-analysis-learning-center/immunology-at-work/inflammation-overview.html
14. Kuprash DV, Nedospasov SA. Molecular and cellular mechanisms of inflammation. Biochemistry (Mosc). 2016 Nov 1;81(11):1237–9.
15. Crockett-Torabi E, Ward PA. The role of leukocytes in tissue injury. Eur J Anaesthesiol. 1996 May;13(3):235–46.
16. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev. 2018 Jan 1;281(1):8–27.
17. Rahtes A, Geng S, Lee C, Li L. Cellular and molecular mechanisms involved in the resolution of innate leukocyte inflammation. J Leukoc Biol. 2018 Sep 1;104(3):535–48.
18. Cioce A, Cavani A, Cattani C, Scopelliti F. Role of the skin immune system in wound healing. Cells. 2024 Apr 1;13(7):942.
19. Torres HM, Arnold KM, Oviedo M, Westendorf JJ, Weaver SR. Inflammatory processes affecting bone health and repair. Curr Osteoporos Rep. 2023 Dec 1;21(6):842–53.
20. Antar SA, Ashour NA, Marawan ME, Al-Karmalawy AA. Fibrosis: types, effects, markers, mechanisms for disease progression, and its relation with oxidative stress, immunity, and inflammation. Int J Mol Sci. 2023 Feb 1;24(4):3532.
21. Ma Z, Wu S, Guo Y, Ouyang S, Wang N. Association of advanced lung cancer inflammation index with all-cause and cardiovascular mortality in US patients with rheumatoid arthritis. Front Nutr. 2024;11:1267651.
22. Rajabally YA. Chronic inflammatory demyelinating polyradiculoneuropathy: current therapeutic approaches and future outlooks. Immunotargets Ther. 2024;13:99–110.
23. Andonian BJ, Hippensteel JA, Abuabara K, Boyle EM, Colbert JF, Devinney MJ, et al. Inflammation and aging-related disease: a transdisciplinary inflammaging framework. Geroscience. 2024 Feb 1;47(1):515–33.
24. Diet Review: Anti-Inflammatory Diet - The Nutrition Source [Internet]. [cited 2025 Apr 25]. Available from: https://nutritionsource.hsph.harvard.edu/healthy-weight/diet-reviews/anti-inflammatory-diet/
25. Nutrients | Special Issue: Anti-Inflammatory Diet and Chronic Inflammation [Internet]. [cited 2025 Apr 25]. Available from: https://www.mdpi.com/journal/nutrients/special_issues/SK6I8IB484
26. Foods you should eat to help fight inflammation - Harvard Health [Internet]. [cited 2025 Apr 25]. Available from: https://www.health.harvard.edu/nutrition/foods-you-should-eat-to-help-fight-inflammation
27. Nathan C. Nonresolving inflammation redux. Immunity. 2022 Apr 12;55(4):592–605.
28. Research suggests new approach for treating inflammation [Internet]. [cited 2025 Apr 26]. Available from: https://www.purdue.edu/research/features/stories/research-suggests-new-approach-for-treating-inflammation/

# Inflammation in focus: Lifestyle, diet, and pharmacological interventions

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## Abstract

Inflammation is a versatile physiological reaction critical for host defense and tissue repair, but when deregulated, it contributes to the pathogenesis of numerous chronic diseases. In this review, inflammation is investigated from an integrative perspective, with particular focus on how lifestyle, diet, and pharmacological interventions affect inflammatory processes. Acute and chronic inflammations are covered with importance on precipitating factors like infections, trauma, autoimmune diseases, malnutrition, and psychological stress. It is revealed that lifestyle factors like exercise regularly, good sleep, stress management, and abstinence from alcohol and tobacco play a significant role in modulating inflammatory pathways. In addition, immune function is well-regulated by dietary interventions like the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, as well as by certain anti-inflammatory foods. Common pharmacological therapies applied in the clinical management are also discussed here. Extensive work for the suppression of inflammation and overall well-being is provided by the knowledge of the synergy of diet, lifestyle, and pharmacology.

**Keywords:** Chronic inflammation, anti-inflammatory diet, lifestyle modification, cytokines, immune response, pharmacological interventions

## 1. Introduction

The ancient, ancestral word "inflammation" is derived from the Latin "inflammare," which means "to ignite or burn" (1). Three factors make inflammation problematic: not all threats, such as ischemia-reperfusion injury, blunt trauma, contact to toxins or crystal particulates, and auto-inflammatory diseases, always call for an inflammatory response; inflammation is an "equal opportunity offender" that "singes" both healthy and diseased tissues; and like any fire, there is always a chance of smoldering persistence or uncontrolled inflammatory extend (2). A multifaceted biological reaction to injurious stimuli is exemplified by inflammation, which involves the activation of immune cells and the release of signaling molecules. Immune cells that are engaged are macrophages, neutrophils, and T-cells, which are responsible for

releasing cytokines and other inflammatory mediators such as prostaglandins. These mediators and the common symptoms of inflammation, such as pain, swelling, heat, and redness are contributed to by the inflammatory response (3). Inflammation can be divided into two types: acute and chronic. Acute inflammation can be brought on by noxious substances, microbial invasion, or trauma-induced tissue injury. An immediate response to remove the cause of injury and facilitate healing is exemplified by acute inflammation (4). Subacute inflammation is the time between acute and chronic inflammation, and it can last anywhere from 2-6 weeks (5). Chronic inflammation, on the other hand, is continued for extended periods and is related with several diseases, such as cardiovascular disease, diabetes, cancer, and autoimmune diseases. Prolonged Inflammation, another name for chronic inflammation, is sluggish, persistent inflammation that lasts for several months to years (6).

Inflammation can be triggered by a number of variables like:

- **Infections:** A body's inflammatory response is created by pathogens such as bacteria, viruses, and fungi as the body tries to combat them (7).
- **Injuries:** The inflammatory response is triggered by physical injury to heal injured tissues (8).
- **Autoimmunity:** When normal tissues are erroneously targeted by the immune system, there is chronic inflammation, as occurs in autoimmune diseases including lupus and rheumatoid arthritis (9).
- **Unhealthy diet:** Low-grade chronic inflammation is able to induce by a diet that is rich in refined sugars, unhealthy fats, and processed foods (7).
- **Stress:** The synthesis of inflammatory cytokines is also heightened by psychological stress, which increases inflammation (10).

Chronic inflammation-related diseases are encompassed by cardiovascular diseases, obesity, type 2 diabetes, inflammatory bowel diseases (IBD), and arthritis (11).

## 2. Managing Inflammation naturally and medically

Managing inflammation naturally and medically explores how everyday lifestyle choices, dietary habits, and modern pharmacological options can work together to reduce chronic inflammation shown in Figure 1. This balanced approach highlights the importance of integrating natural strategies with evidence-based medicine for optimal health.

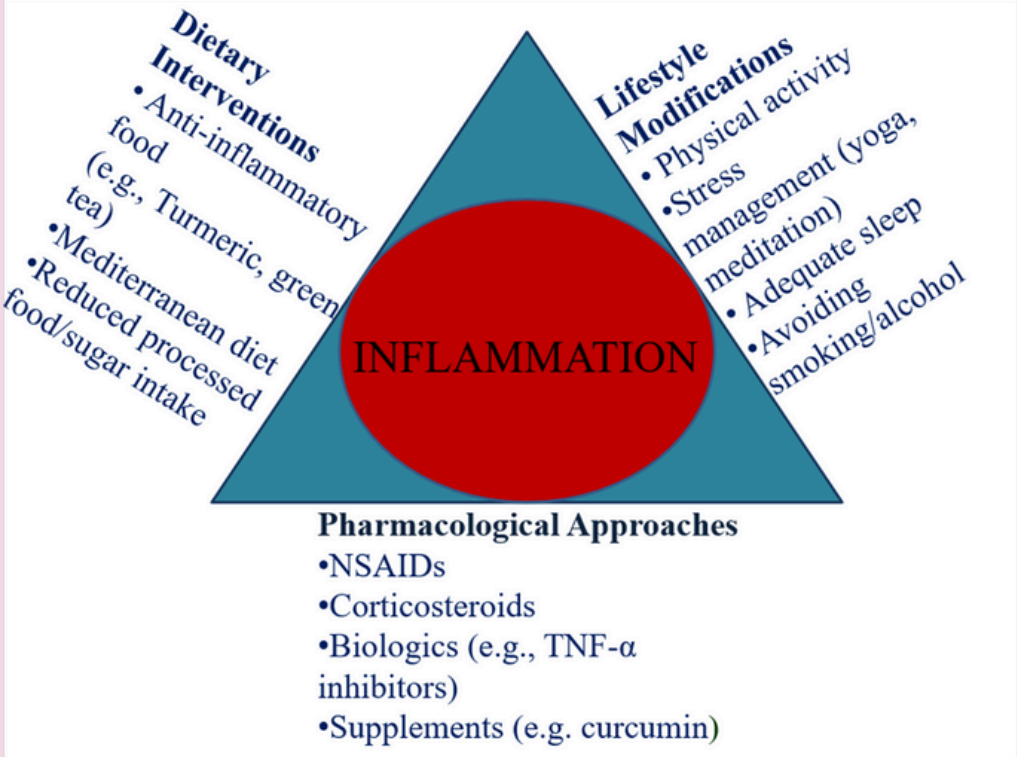


**Figure 1.** Managing inflammation naturally and medically

## 2.1. Role of lifestyle in managing inflammation

Lifestyle factors play a vital role in the parameter of inflammation. Certain habits can either exacerbate the inflammatory process.

### 2.1.1. Physical activity

Anti-inflammatory effects have found to be linked to regular physical exercise. Pro-inflammatory cytokine levels can be lowered by exercise, particularly moderate-intensity aerobic exercise and raise anti-inflammatory markers. The positive control of exercise on inflammation was indicated that systemic inflammation can be reduced by moderate exercise through the reduction of CRP and IL-6 levels (12). Such an effect is regarded as beneficial not only for athletes but also for patients suffering from chronic conditions like cardiovascular disease and arthritis.

### 2.1.2. Sleep

The other necessary element in managing inflammation is good sleep. Excessive inflammation has been found to be linked to chronic sleep deprivation. A research study of pro-inflammatory cytokines similar to IL-6 and tumor necrosis factor-alpha (TNF-α) correlate with sleep disturbance (13). Sleep plays an vital role in regulating immune function, and inflammatory processes may be amplified by inadequate sleep, rendering the body susceptible to disease.

### 2.1.3. Stress management

A significant influence on inflammation is exerted by chronic stress. The hypothalamic-pituitary-adrenal (HPA) axis is stimulated by stress, causing the release of cortisol. Although a short-term anti-inflammatory hormone is cortisol, dysregulation of this system is caused by chronic stress, facilitating systemic inflammation and increased release of pro-inflammatory cytokines for example: IL-6 and TNF-α (14). Inflammation can be brought down through the use of successful stress management interventions, including mindfulness, meditation, and relaxation strategies, through the equilibrium of immune function.

### 2.1.4. Avoiding smoking and alcohol

Chronic inflammation is known to be caused by excessive alcohol use as well as cigarette smoking. It found that smoking inhibits the immune system, promoting an elevation of inflammatory markers as well as oxidative stress. Also, inflammation has been reported to be enhanced by alcohol by the disruption of gut microbiota and an increase in intestinal permeability, which results in endotoxin translocation and systemic inflammation. These inflammatory effects may be alleviated by avoiding smoking and limiting alcohol consumption (15).

## 2.2. Dietary approaches

A key function is performed by diet in the regulation of inflammation. An unhealthy diet high in processed food, sugars, and unhealthy fats promotes chronic low-grade inflammation. However, an anti-inflammatory diet reduces inflammation, and overall health can be enhanced (16).

### 2.2.1. Anti-inflammatory diets

The anti-inflammatory properties of the Mediterranean diet and DASH diet have been extensively known. These diets stress consumption of fruits, vegetables, nuts, seeds, whole grains, legumes, and healthy fats like olive oil. The inflammatory markers were decreased, and cardiovascular health was enhanced by following a Mediterranean diet (17).

### 2.2.2. Beneficial foods

Several foods have demonstrated anti-inflammatory properties in Table 1 (18, 19).

**Table 1.** Functional foods with anti-inflammatory potential

| Food categories | Examples | Anti-inflammatory properties |
|---|---|---|
| Fruits and vegetables | Berries, spinach, broccoli, kale | Rich in antioxidants and polyphenols that reduce oxidative stress and neutralize free radicals. |
| Omega-3 fatty acids | Salmon,sardines,flaxseeds, walnuts | Support cardiovascular health and reduce the production of pro-inflammatory cytokines. |
| Spices | Turmeric, ginger, garlic | Contain bioactive compounds like curcumin and gingerol that modulate inflammatory pathways. |
| Green tea | Green tea (preferably fresh brewed) | Contains EGCG, a potent polyphenol known to reduce inflammation and support metabolic health. |
| Fermented foods | Yogurt, kefir, kimchi, sauerkraut | Probiotics that support gut microbiota and help regulate immune and inflammatory responses. |

### 2.2.3. Pro-inflammatory foods to avoid

Certain foods promote inflammation and should be limited or avoided:

- **Processed meats:** Rich in saturated fats and advanced glycation end products (AGEs), processed meats such as bacon and sausages contribute to systemic inflammation (20).
- **Refined carbs and sweetened beverages:** These foods induce a blood sugar and insulin spike, leading to the release of inflammatory cytokines (21).
- **Trans fats:** Trans fats, which are used in most processed and fast foods, promote inflammation and increase the risk of chronic diseases (22).
- **Micronutrients & gut health:** Micronutrients such as vitamin D and zinc serve a key function in regulating the immune system and inhibiting inflammation. Most inflammatory conditions, such as autoimmune disorders and cardiovascular disease, have been associated with a deficiency of vitamin D. The role of gut health is also central to inflammation. The gut microbiota regulates immune function, and the inflammatory reaction can be modulated. Production of pro-inflammatory cytokines is lessened by a balanced microbiota, while enhanced inflammation is associated with dysbiosis (imbalanced gut microbiota) (23).

## 2.3. Pharmacological interventions

While lifestyle and dietary changes are crucial in managing inflammation, pharmacological interventions are often necessary for more severe or chronic cases.

### 2.3.1. Commonly used drugs for inflammation

- **Non-steroidal anti-inflammatory drugs (NSAIDs):** Cyclooxygenase (COX) enzymes, responsible for prostaglandin production, which are the main inflammatory mediators, are inhibited by drugs such as ibuprofen and aspirin. Side effects, such as gastrointestinal irritation and cardiovascular toxicity, can be had from long-term use of NSAIDs (24).
- **Corticosteroids:** Highly effective anti-inflammatory drugs like prednisolone are distinguished by the repression of the immune response. Inflammation is very effectively brought down, but serious side effects like weight gain, osteoporosis, and susceptibility to infections are linked to corticosteroids (25).

- **DMARDs (Disease-modifying anti-rheumatic drugs) and biologics:** Disease-modifying anti-rheumatic drugs such as methotrexate and biologics such as anti-TNF agents (e.g., infliximab) are employed in autoimmune diseases such as rheumatoid arthritis. Specific molecules within the inflammatory process are targeted by these drugs, offering more targeted treatments (26).

### 2.3.2. Targeted therapies

More targeted therapy for chronic inflammation, especially in autoimmune disease and cancer, is provided by targeted therapies like monoclonal antibodies and kinase inhibitors. Certain proteins participating in the inflammatory response are targeted by monoclonal antibodies, and enzymes favoring inflammation are inhibited by kinase inhibitors (27).

### 2.3.3. Natural products & nutraceuticals

Natural compounds such as curcumin, resveratrol, and boswellia are being investigated more and more as adjuncts in the management of inflammation. Curcumin, a component of turmeric, inhibits several pro-inflammatory pathways In conventional medicine, Boswellia, or frankincense, has been utilized for centuries for anti-inflammatory purposes, and the acceptance is growing in current research for it as an adjuvant to treat inflammatory diseases (28, 29).

### 2.3.4. Risks of overuse

Although pharmacological treatments are very effective, serious side effects can be caused by the misuse or overuse of anti-inflammatory drugs, especially NSAIDs and corticosteroids. These medications must be used under medical supervision, and non-pharmacological alternatives must be sought for long-term control of inflammation (30).

## 3. Conclusion

Inflammation is a necessary physiological response essential for immune defense and tissue repair; nonetheless, its chronic and dysregulated persistence is fundamental to most disease processes. The review emphasizes the need to adopt a multi-faceted treatment strategy for inflammation, incorporating lifestyle, nutritional, and pharmacological therapies. Physical exercise, sufficient sleep, stress alleviation, and abstaining from smoking and alcohol use have been shown to exert measurable impacts on the regulation of inflammatory processes. Dietary patterns characterized by substantial intake of complete, nutrient-dense foods, such as the Mediterranean and DASH diets, are synergistic as they mitigate pro-inflammatory signals and bolster immune function. While pharmacotherapies remain essential for managing acute or severe inflammatory conditions, their efficacy is enhanced when integrated with sustained lifestyle and dietary interventions. The interdisciplinary connection in these domains highlights the necessity for a thorough and preventative strategy to tackle inflammation-driven disorders.

## 4. Future directions

Future research should aim to individualize anti-inflammatory therapies by using advancements in genomes, metabolomics, and microbiome phenotyping.These technologies can provide individualized tactics based on an individual's unique biological profile.Long-term clinical studies must be meticulously constructed to determine the sustained efficacy and safety of integrated lifestyle, nutritional, and pharmacological therapies. Furthermore, innovative treatment approaches, plant bioactives, microbiota-targeted therapeutics, and nutraceutical immunomodulators are being developed, characterized by reduced toxicity and enhanced efficacy in mitigating chronic inflammation. The use of digital health technology, including wearable sensors and mobile applications, can boost active patient participation, facilitate real-time monitoring of inflammatory biomarkers, and improve adherence to anti-inflammatory treatment. Collectively, these technologies possess the capacity to provide a more precise, proactive, and individualized framework for managing inflammation.

## References

1.Reddy VS, Sainihal R, Ushasri K, Bhavani B, Varshini N. A review article on anti-inflammatory activity in the plants. Journal for Innovative Development in Pharmaceutical and Technical Science (JIDPTS). 2025;8(1).

2.Oronsky B, Caroen S, Reid T. What exactly is inflammation (and what is it not?). International journal of molecular sciences. 2022;23(23):14905.
3.Ansar W, Ghosh S, Ansar W, Ghosh S. Inflammation and inflammatory diseases, markers, and mediators: role of CRP in some inflammatory diseases. Biology of C reactive protein in health and disease. 2016:67-107.
4.Zotova N, Zhuravleva Y, Chereshnev V, Gusev E. Acute and chronic systemic inflammation: features and differences in the pathogenesis, and integral criteria for verification and differentiation. International Journal of Molecular Sciences. 2023;24(2):1144.
5.Hamidzadeh K, Christensen SM, Dalby E, Chandrasekaran P, Mosser DM. Macrophages and the recovery from acute and chronic inflammation. Annual review of physiology. 2017;79(1):567-92.
6.Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH. Chronic inflammation in the etiology of disease across the life span. Nature medicine. 2019;25(12):1822-32.
7.Suardi C, Cazzaniga E, Graci S, Dongo D, Palestini P. Link between viral infections, immune system, inflammation and diet. International journal of environmental research and public health. 2021;18(5):2455.
8Lieberthal J, Sambamurthy N, Scanzello CR. Inflammation in joint injury and post-traumatic osteoarthritis. Osteoarthritis and cartilage. 2015;23(11):1825-34.
9.Yasmeen F, Pirzada RH, Ahmad B, Choi B, Choi S. Understanding autoimmunity: mechanisms, predisposing factors, and cytokine therapies. International Journal of Molecular Sciences. 2024;25(14):7666.
10.Liu YZ, Wang YX, Jiang CL. Inflammation: the common pathway of stress-related diseases. Frontiers in human neuroscience. 2017;11:316.
11.Lazou A, Ikonomidis I, Bartekova M, Benedek T, Makavos G, Palioura D, Cabrera Fuentes H, Andreadou I. Chronic inflammatory diseases, myocardial function and cardioprotection. British Journal of Pharmacology. 2020;177(23):5357-74.
12.Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nature reviews immunology. 2011;11(9):607-15.
13.Miklowitz DJ, Portnoff LC, Armstrong CC, Keenan-Miller D, Breen EC, Muscatell KA, Eisenberger NI, Irwin MR. Inflammatory cytokines and nuclear factor-kappa B activation in adolescents with bipolar and major depressive disorders. Psychiatry research. 2016;241:315-22.
14.Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. Brain, behavior, and immunity. 2017;64:208-19.
15.Khasawneh M, Spence AD, Addley J, Allen PB. The role of smoking and alcohol behaviour in the management of inflammatory bowel disease. Best Practice & Research Clinical Gastroenterology. 2017;31(5):553-9.
16.Wu Q, Gao ZJ, Yu X, Wang P. Dietary regulation in health and disease. Signal Transduction and Targeted Therapy. 2022;7(1):252.
17.Singh RB, Nabavizadeh F, Fedacko J, Pella D, Vanova N, Jakabcin P, Fatima G, Horuichi R, Takahashi T, Mojto V, Juneja L. Dietary approaches to stop hypertension via Indo-Mediterranean foods, may be superior to DASH diet intervention. Nutrients. 2022;15(1):46.
18. Griffiths K, Aggarwal BB, Singh RB, Buttar HS, Wilson D, De Meester F. Food antioxidants and their anti-inflammatory properties: a potential role in cardiovascular diseases and cancer prevention. Diseases. 2016;4(3):28.
19. Stromsnes K, Correas AG, Lehmann J, Gambini J, Olaso-Gonzalez G. Anti-inflammatory properties of diet: role in healthy aging. Biomedicines. 2021;9(8):922.
20. da Silva A, Felício MB, Caldas AP, Hermsdorff HH, Bersch-Ferreira ÂC, Torreglosa CR, Shivappa N, Hébert JR, Weber B, Bressan J. Pro-inflammatory diet is associated with a high number of cardiovascular events and ultra-processed foods consumption in patients in secondary care. Public health nutrition. 2021;24(11):3331-40.
21. Koebnick C, Black MH, Wu J, Shu YH, MacKay AW, Watanabe RM, Buchanan TA, Xiang AH. A diet high in sugar-sweetened beverage and low in fruits and vegetables is associated with adiposity and a pro-inflammatory adipokine profile. British Journal of Nutrition. 2018;120(11):1230-9.
22.Grosso G, Laudisio D, Frias-Toral E, Barrea L, Muscogiuri G, Savastano S, Colao A. Anti-inflammatory nutrients and obesity-associated metabolic-inflammation: state of the art and future direction. Nutrients. 2022;14(6):1137.
23. L Bishop E, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. Journal of Bone and Mineral Research plus. 2021;5(1):e10405.
24. Fokunang C, Fokunang ET, Frederick K, Ngameni B, Ngadjui B. Overview of non-steroidal anti-inflammatory drugs (nsaids) in resource limited countries. Moj Toxicol. 2018;4(1):5-13.
25. Bain CR, Myles PS, Corcoran T, Dieleman JM. Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. Anaesthesia. 2023;78(3):356-70.
26. Drakopoulou M, Soulaidopoulos S, Oikonomou G, Tousoulis D, Toutouzas K. Cardiovascular effects of biologic disease-modifying anti-rheumatic drugs (DMARDs). Current vascular pharmacology. 2020;18(5):488-506.
27.Lai Y, Dong C. Therapeutic antibodies that target inflammatory cytokines in autoimmune diseases. International immunology. 2016;28(4):181-8.
28. Sethi V, Garg M, Herve M, Mobasheri A. Potential complementary and/or synergistic effects of curcumin and boswellic acids for management of osteoarthritis. Therapeutic Advances in Musculoskeletal Disease. 2022;14:1759720X221124545.
29.Azeez TB, Lunghar J. Antiinflammatory effects of turmeric (Curcuma longa) and ginger (Zingiber officinale). Inflammation and Natural Products. 2021:83-102.
30. Brennan R, Wazaify M, Shawabkeh H, Boardley I, McVeigh J, Van Hout MC. A scoping review of non-medical and extra-medical use of non-steroidal anti-inflammatory drugs (NSAIDs). Drug Safety. 2021;44:917-28.

# Treatment options for neuroinflammation: Focus on Huntington's disease

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## Abstract

Huntington's disease (HD) is rare but fatal inherited neurodegenerative disorder that clinically manifests as chorea, psychiatric disturbances, and progressive functional impairment. The most affected part is cerebral cortex and striatum leads to dysfunction in neurons and eventual cell death ensue. The current treatment options aim to decrease symptoms and slow down the progression of HD. Treatments such as tetrabenazine and deutetrabenazine target motor symptoms by reducing involuntary movements. Additionally, antipsychotic and antidepressant medications are utilised to treat HD's mental and cognitive symptoms. Research has led to the exploration of potential gene-based treatments and RNA interference (RNAi) techniques. Ongoing research into CRISPR-associated protein 9 (CRISPR-Cas9) and other techniques related to gene editing offer hope to eventually find a cure for this crippling illness.

**Keywords:** Huntington's disease, tetrabenazine, deutetrabenazine, gene editing techniques

## 1. Introduction

Huntington's disease (HD) is a type of progressive neurodegenerative disorder which involves uncontrollable movements, emotional problems and loss in thinking ability. As HD is inherited autosomally-dominant (1), it adheres to Gregor Mendel's theories of inheritance. An individual with pathogenic variation, known as a heterozygote, has a 50% chance of passing on the disease-causing allele to their progeny. The huntingtin (HTT) gene on chromosome 4 has an autosomal dominantly inherited CAG trinucleotide repeat expansion that causes HD. As a result, a mutant huntingtin (mHTT) protein with an unusually lengthy polyglutamine repeat is produced. Reduced penetrance is shown between 36 and 39 CAG repeats, but those with more than 39 repeats are guaranteed to have the disease (2). The anticipation will occur, when the gene is passing through the paternal line. For example, a kid born to a father with an intermediate CAG repeat length may have an increased pathogenic repeat length. This is because the male sperm exhibits bigger repetition sizes and more repeat variability compared to somatic tissues (3).

HD is of two types: (i) Adult onset HD, and (ii) Juvenile HD. Adult onset, the most prevalent kind, HD typically strikes people in their thirties or forties. Involuntary jerks, impatience, poor coordination, depression, and difficulties understanding and making decisions are some of the first signs and symptoms. At the final stage, the person's thinking and reasoning skills deteriorate. The life expectancy thereafter is for 15 to 20 years.

Juvenile HD manifests as emotional, mental, and mobility issues. Other symptoms include slurred speech, clumsiness, drooling, seizures and frequent falls. Compared to adult-onset HD, this form progresses more swiftly, and the patient typically lives for 10 to 15 years after the signs and symptoms first manifest (4).

## 2. Management and therapeutic approaches

Optimising quality of life and anticipating the patient's evolving demands as the illness worsens are the therapeutic goals. Pharmacological and non-pharmacological therapies are typically used in conjunction for achieving this.

### 2.1. Motor symptoms therapy (Chorea)

Tetrabenazine is the only medication that licensed by FDA for the treatment of chorea (5) in a dose between 50 and 75 mg daily. This synaptic vesicular amine transport inhibitor produces a long-term anti-choreic action. It modulates dopamine by selectively inhibiting VMAT2. The side effects include are sleeplessness, depression, restlessness and anxiety. With the addition of deuterium molecules, deutetrabenazine is a modified form of tetrabenazine. This leads to reduced metabolic variability and a longer half-life (6). The FIRST-HD study found that deutetrabenzine significantly reduces chorea when compared to a placebo. Additionally, the research states that deutetrabenazine may have fewer side effects (7).

### 2.2. Treatment for psychiatric symptoms

Non-pharmacological treatments for depression, anxiety, OCD and irritability include cognitive behavioural therapy and psychodynamic therapy. Although these methods may not be as effective when cognitive impairment is present. Pharmacological treatments include the serotonergic and noradrenergic actions of mirtazepine and venlafaxine, and selective serotonin uptake inhibitors like citalopram, paroxetine, fluoxetine & sertraline (8). Neuroleptics may be helpful in the treatment of psychosis and aggressiveness. Apathy has been treated with a variety of drugs, such as bupropion, methylphenidate, atomoxetine, modafinil, amantadine, and bromocriptine; however, no RCTs have been conducted (9).

### 2.3. Antisense oligonucleotides (ASOs) based therapies

Single-stranded oligonucleotide analogues known as ASOs can act through a variety of methods, including as RNA degradation, translation stalling, and splice manipulation, which eventually change the expression of proteins. The ASOs are located throughout the CNS and don't need require of viral as well as lipid carrier for simple and effective treatment (10). They attach to either pre-mRNA or mRNA. An ASO may be allele-specific, meaning it only targets mHTT and non-allele-specific, meaning it targets both mHTT and wild type HTT (wtHTT). WVE-120101, WVE-120102, and Tominersen, an allele-non-specific ASO, are the three ASOs presently undergoing clinical trials. Tominersen attaches itself to mHTT & wild type HTT mRNA. ASOs effectively reduce the Huntingtin gene when infused into non-primate cerebrospinal fluid. Since they do not reduce wtHTT, their allele-specificity may help prevent long-term adverse consequences. All HD patients can't be treated by WVE-120101 and WVE-120102 since they target SNPs, but when used together, they may be able to treat 80% of HD patients in Europe (11). The most promising ASO series: A1, A2, and A3. We found 40 and 10 fold increase in potency for A2 and A3, respectively, compared to A1.

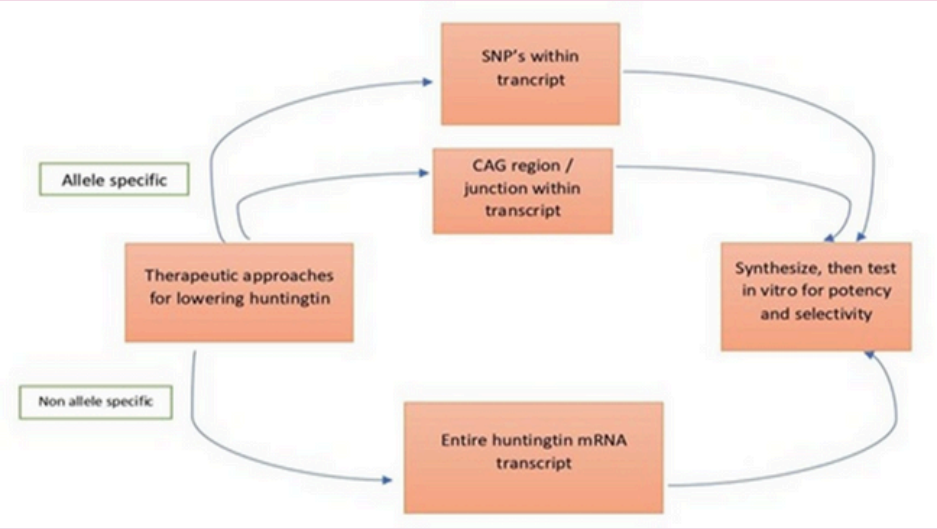


**Figure 1.** Targets for oligonucleotide therapy

## 2.4. FAN1 gene therapy

FAN1 was discovered to be widely expressed in both peripheral tissues and the central nervous system after being first discovered as KIAA1018 in a human brain cDNA collection (12). FAN1 haplotypes independently alter HD; uncommon genetic variations accelerate the start of HD by reducing the FAN1 protein's nuclease activity or DNA binding (13). One important modifier gene was the FAN1 gene, which codes for a nuclease that cleaves DNA during the process of repairing crosslinks between DNA strands. One possible protective factor for HD has been shown to be FAN1 (14).

## 2.5. Antibody therapy

A particular kind of monoclonal antibody called ANX005 blocks the C1q, which is the initial molecule in the innate immune system's complement cascade and serves mainly as the host's first line of defence against infections (15).

## 2.6. CRISPR-Cas9 mediated therapy

There are two main parts of the CRISPR-Cas9 DNA-editing system i.e., single guide RNA (sgRNA) and a Cas9 nuclease which attaches with the Cas9 (16) and uses RNA-DNA base complementarity to guide it to a specific genomic location. When Cas9 binds to DNA, it causes a double-strand break (DSB) that triggers non-homologous end joining (NHEJ), a faulty DNA repair pathway that makes it easier to introduce random base insertions and deletions (17). These indels can result in a frameshift mutation, which can then cause nonsense-mediated mRNA decay to disrupt gene expression. Cell replacement therapy and CRISPR-Cas9 mediated gene editing could be used to treat HD in two ways: (1) using CRISPR to disrupt the endogenous mHTT gene to reduce its neurodegenerative effect, then integrating a functional striatal graft to replace lost cells, and (2) combining the benefits of both approaches to potentially treat HD more successfully (18). The study observed that the two plasmids of CRISPR-Cas9 i.e. CRISPR-gRNA1 (UTR targeted) and CRISPR-gRNA2 (exon1-intron) resulted in 79% and 58% reduction in mHTT production.

## 2.7. RNA interference therapy

Short interfering RNA (siRNA), short hairpin RNA (shRNA), bi-functional shRNA, and microRNA (miRNA) are all used in the gene-silencing technique known as RNA interference (19). When combined with brain progenitor stem cell therapy, RNAi therapy can lessen symptoms in animal models of HD. To improve motor function and lessen neuropathology, siRNA, shRNA, and miRNA therapies have been applied to animal models of HD. An artificial miRNA found in the adeno-associated viral vector AMT-130 generates a compound that lowers huntingtin (20). In several rodent models for HD, viral-based expression of shRNA targeting mutant htt mRNA in brain reduced transcript and protein levels by ~50–70% which improving behavioural and neuropathological phenotypes.

## 3. Conclusion

The development of contemporary technologies and the availability of numerous potential agents/molecules have made efficient treatments possible that will significantly enhance the outcomes for HD patients. These advancements are necessary to address the challenges posed by movement disorders, depression, anxiety, and psychosis, all of which have a significant negative impact on patients' overall well-being. Drugs that disrupt the effects of the mHTT protein and target its synthesis are the most promising.

## References

1.Sampaio C. Huntington disease–Update on ongoing therapeutic developments and a look toward the future. Parkinsonism & Related Disorders. 2024 May 1;122:106049.
2.Gatto EM, Rojas NG, Persi G, Etcheverry JL, Cesarini ME, Perandones C. Huntington disease: Advances in the understanding of its mechanisms. Clinical parkinsonism & related disorders. 2020 Jan 1;3:100056.
3.Ross CA, Margolis R. Huntington disease. Medicine. 2020;76:305-38.
4.Devadiga SJ, Bharate SS. Recent developments in the management of Huntington's disease. Bioorganic chemistry. 2022 Mar 1;120:105642.
5.Cheng Y, Zhang S, Shang H. Latest advances on new promising molecular-based therapeutic approaches for Huntington's disease. Journal of Translational Internal Medicine. 2024 May 21;12(2):134-47.
6.Gupta H, Perkins W, Stark C, Kikkeri S, Kakazu J, Kaye A, Kaye AD. Deutetrabenazine for the treatment of chorea associated with Huntington's disease. Health Psychology Research. 2022 Jun 28;10(5):36040.
7.Andhale R, Shrivastava D. Huntington's disease: a clinical review. Cureus. 2022 Aug 27;14(8).

8. Rojas NG, Cesarini ME, Peker G, Da Prat GA, Etcheverry JL, Gatto EM. Review of Huntington's disease: from basics to advances in diagnosis and treatment. Journal of Neurology Research. 2022 Oct 22;12(3):93-113.
9. Molnar MJ, Molnar V, Fedor M, Csehi R, Acsai K, Borsos B, Grosz Z. Improving mood and cognitive symptoms in Huntington's disease with cariprazine treatment. Frontiers in Psychiatry. 2022 Feb 10;12:825532.
10. Palaiogeorgou AM, Papakonstantinou E, Golfinopoulou R, Sigala M, Mitsis T, Papageorgiou L, Diakou I, Pierouli K, Dragoumani K, Spandidos DA, Bacopoulou F. Recent approaches on Huntington's disease. Biomedical reports. 2022 Nov 21;18(1):5.
11. Ferguson MW, Kennedy CJ, Palpagama TH, Waldvogel HJ, Faull RL, Kwakowsky A. Current and possible future therapeutic options for Huntington's disease. Journal of central nervous system disease. 2022 Apr 7;14:11795735221092517.
12. Deshmukh AL, Porro A, Mohiuddin M, Lanni S, Panigrahi GB, Caron MC, Masson JY, Sartori AA, Pearson CE. FAN1, a DNA repair nuclease, as a modifier of repeat expansion disorders. Journal of Huntington's disease. 2021 Feb 9;10(1):95-122.
13. Kim KH, Hong EP, Lee Y, McLean ZL, Elezi E, Lee R, Kwak S, McAllister B, Massey TH, Lobanov S, Holmans P. Posttranscriptional regulation of FAN1 by miR-124-3p at rs3512 underlies onset-delaying genetic modification in Huntington's disease. Proceedings of the National Academy of Sciences. 2024 Apr 16;121(16):e2322924121.
14 Dhingra H, Gaidhane SA. Huntington's disease: understanding its novel drugs and treatments. Cureus. 2023 Oct 23;15(10).
15. Kim A, Lalonde K, Truesdell A, Gomes Welter P, Brocardo PS, Rosenstock TR, Gil-Mohapel J. New avenues for the treatment of Huntington's disease. International journal of molecular sciences. 2021 Aug 4;22(16):8363.
16. Eje O, Ogbonna CV, Onoyima CS, Nduka FO. Huntington Disease: mechanism of Pathogenesis and recent developments in its therapeutic strategies: a review. J Chem Rev. 2023;5(2):129-42.
17. Dos Santos NT, do Bomfim FR. Gene editing by CRISPR/CAS9 for treatment of Huntington disease. Int. J. Dev. Res. 2020;10:38631-5.
18. Dos Santos NT, do Bomfim FR. Gene editing by CRISPR/CAS9 for treatment of Huntington disease. Int. J. Dev. Res. 2020;10:38631-5.
19. Kumar A, Kumar V, Singh K, Kumar S, Kim YS, Lee YM, Kim JJ. Therapeutic advances for Huntington's disease. Brain sciences. 2020 Jan 12;10(1):43.
20. Kotowska-Zimmer A, Przybyl L, Pewinska M, Suszynska-Zajczyk J, Wronka D, Figiel M, Olejniczak M. A CAG repeat-targeting artificial miRNA lowers the mutant huntingtin level in the YAC128 model of Huntington's disease. Molecular Therapy-Nucleic Acids. 2022 Jun 14;28:702-15.

# Linoleic acid: A modulator of inflammatory pathways in breast cancer


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## Abstract

Linoleic acid (LA) is an essential polyunsaturated fatty acid that plays a critical role in various physiological functions. It is an omega-6 fatty acid that has several health advantages, especially for cellular, cardiovascular, and skin health. However, a balanced approach to intake is necessary due to its impact on inflammation and cancer risk. Dietary LA binds to fatty acid binding protein 5 (FABP5) of malignant cells in triple negative breast cancer (TNBC), an extremely aggressive cancer that has few treatment options. This binding activates a mammalian target of rapamycin (mTOR) growth pathway in cancer cells, triggering a signalling cascade that promotes cell proliferation in triple-negative breast cancer. To promote a better omega-6 to omega-3 ratio, it is advised to balance LA intake with omega-3 fatty acids. For optimum health, whole, less processed foods should be prioritised.



**Keywords:** Linoleic acid, inflammation, breast cancer


## 1. Introduction

The influence of our diet and food consumption on health outcomes is now substantiated by ample evidence. Over the past decades, dietary guidelines have advocated for reduced consumption of saturated fats and trans fats, and their replacement with polyunsaturated fats. Polyunsaturated fatty acids (PUFAs) are of two types. Omega-3 fatty acids and omega-6 fatty acids. Linoleic acid (LA) is an omega-6 Fatty acid that humans must obtain from their diet, alongside alpha-linolenic acid (ALA), an omega-3 fatty acid. While bacteria, protozoa, and plants can readily synthesize LA, mammals lack this de novo capability (1). LA is rich in dietary sources like meat, eggs, nuts, seeds, and vegetable oils. Linoleic acid is abundant in soybean, corn, and sunflower oils. Both the increasing availability of vegetable oils and the suggestive evidence of their capacity to lower blood cholesterol levels spiked their intake by 20-fold. The consumption of linoleic acid grew significantly as a result of this dietary modification (2). Although necessary for many physiological processes, a new study indicates that consuming too much LA may affect the onset and progression of cancer.

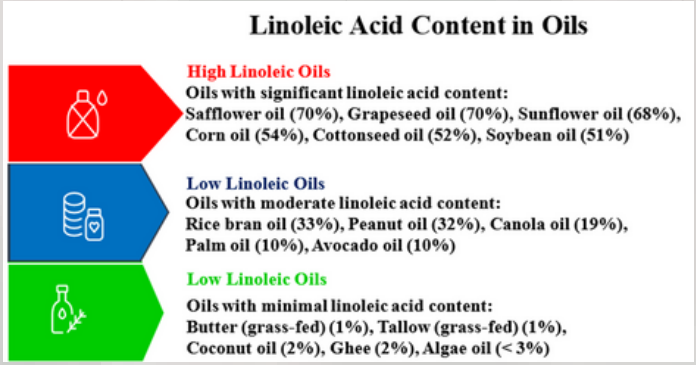


**Figure 1.** Approximate linoleic acid content in cooking oils

## 2. Beneficial effects of linoleic acid

Linoleic acid plays several important roles in human health (Table 1)

**Table 1.** Physiological role of linoleic acid

| Benefit | Description | Ref |
|---|---|---|
| Skin health | Maintains skin barrier, improves hydration, and helps treat dry skin and eczema. | (3) |
| Cholesterol regulation | Lowers LDL (bad) cholesterol, reducing risk of cardiovascular disease. | (3) |
| Cell function | Essential component of cell membranes, supports structural integrity. | (3) |
| Growth & development | Critical for proper growth, especially in infants and children. | (3) |
| Immunomodulatory effect | Supports immune function and helps manage inflammation (in balanced amounts). | (4) |
| Reproductive healtH | Supports hormonal balance and reproductive system function. | (5) |
| Wound healing | Enhances tissue repair and speeds up the healing process. | (6) |

## 3. Linoleic acid inflammation and cancer

The overall role of LA in cancer is complex and appears to be cancer-type specific. The association between LA intake and cancer risk has produced inconsistent findings. A meta-analysis encompassing multiple prospective cohort studies reported no significant association between dietary or serum LA levels and breast cancer risk. Similarly, studies on colorectal and prostate cancers have not consistently demonstrated a clear link between LA consumption and cancer incidence (7). But according to a review of animal studies, linoleic acid can affect the growth and advancement of tumours, although it may not have a significant impact on the initiation of tumours for many cancer types (8).

High-fat diets (HFDs) rich in LA promote carcinogenesis and accelerate the growth of tumours in cases of breast cancer models. Serna et al. reported “LA induces Akt2 activation, invasion, an increase in NFκB–DNA binding activity, miR34a upregulation and miR9 downregulation in MDA-MB-231 cells” (9). Human research has also discovered a sequence of signalling events that are triggered by the up-regulation of prostaglandin E2 and cyclooxygenase activity brought on by linoleic acid. These studies have characterised important proteins and signalling events that contribute to the acceleration of cell proliferation in breast cancer. Inflammation has a pivotal role in cancer initiation and progression. Especially, chronic inflammation can create a microenvironment that facilitates cell proliferation and metastasis. Newevidence indicates that the metabolism of LA to oxylipins might have detrimental impacts on tumor development and metastasis (10). Oxylipins are generated through various pathways, including the cyclooxygenase pathway, lipoxygenase (LOX) pathway, and cytochrome P450 metabolic pathway. Different classes of oxylipins have opposing effects. The oxylipins derived from omega-6 fatty acids are proinflammatory and proangiogenic, while oxylipins derived from omega-3 fatty acids are anti-inflammatory.

Although they might have significant biological consequences, oxylipins formed from LA have not received as much research attention as eicosanoids derived from AA. Serum oxylipin levels were recently assessed in participants undergoing screening for ovarian, colorectal, lung, and prostate malignancies. A positive correlation between ovarian cancer and five oxylipins was found. These findings highlight the serious negative consequences of increasing LA oxidation or ingestion (11).

Fatty acid–binding protein 5 (FABP5) is a lipid chaperone that is highly expressed in TNBC cells and is associated with poor prognosis. LA binds to FABP5 forming a complex that directly interacts and activates mTORC1 the eventually leads to tumour growth (12).

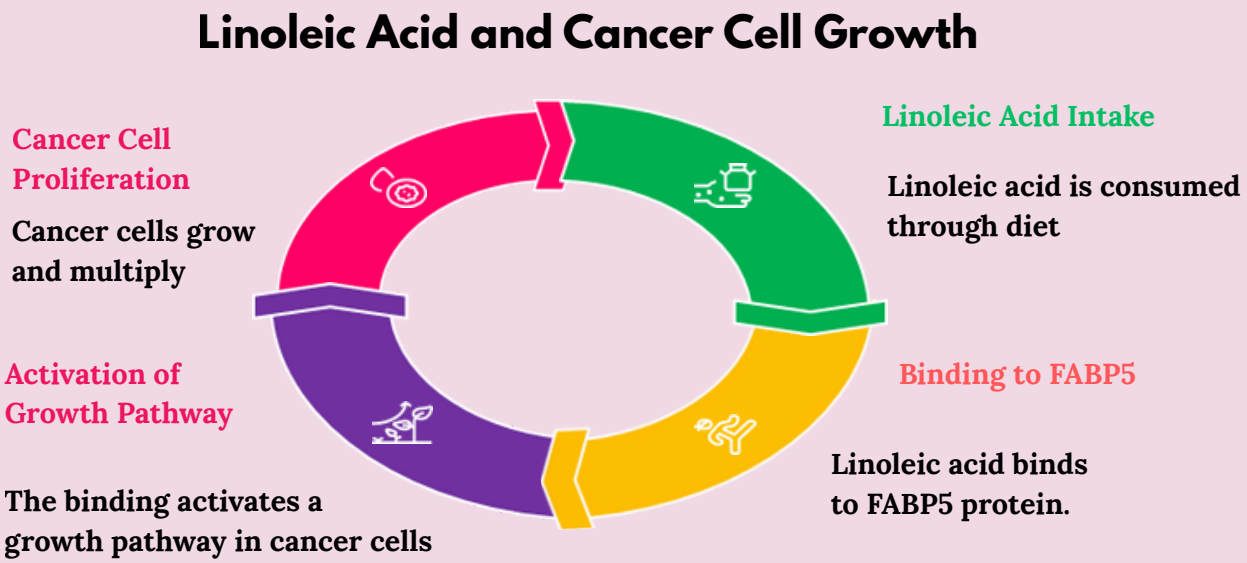


**Figure 2.** Linoleic acid and cancer cell growth cycle

## 4. Dietary considerations and recommendations

Given the complex role of LA in cancer biology, dietary recommendations should focus on balance and moderation. While LA is crucial for health, imprudent intake, particularly from processed foods rich in omega-6 PUFAs, may contribute to an inflammatory environment conducive to cancer progression. Incorporating a balanced intake of omega-3 fatty acids, that possess an anti-inflammatory nature, may help to reduce the potential adverse effects of high LA consumption. Maintaining optimal omega-6 PUFAs/ omega-3 PUFAs is essential for mitigating many diseases, including cancer.

## 5. Future directions

The significance of linoleic acid in cancer and its possible effects on dietary recommendations need to be better understood. Specific Subtypes of Cancer Research to be carried out to assess how LA affects the genesis and development of tumours. Because genetic, epigenetic, and microbial variables may affect LA metabolism, individual differences in metabolic responses to linoleic acid should be investigated. Long-term cohort studies can assist differentiate between causation and correlation and further clarify the association between linoleic acid intake and cancer incidence over time. The molecular and cellular processes via which linoleic acid may either cause or prevent various subtypes of cancer should be the main focus. Research comparing plant-based, Mediterranean, and ketogenic diets with or without LA may shed light on the compound's potential link to cancer.

## 6. Conclusion

The relationship between linoleic acid and cancer is multifaceted, with evidence suggesting both protective and detrimental effects depending on various factors, including cancer subtype, dietary context, and individual metabolic responses. While small amounts of LA from vegetable oils are generally safe, excessive intake, especially from frequent use or high consumption of processed food may lead to higher levels than the body requires. Further research is necessary to illuminate the mechanisms underlying these associations and to develop personalized dietary guidelines aimed at TNBC prevention and management. In the interim, adopting a balanced diet plentiful of whole foods and low in processed fats remains a prudent approach to health maintenance.

## References


1. Malcicka M, Visser B, Ellers J. An evolutionary perspective on linoleic acid synthesis in animals. Evolutionary biology. 2018 Mar;45:15-26.
2. Field CJ, Schley PD. Evidence for potential mechanisms for the effect of conjugated linoleic acid on tumor metabolism and immune function: lessons from n− 3 fatty acids. The American journal of clinical nutrition. 2004 Jun 1;79(6):1190S-8S.
3. Djuricic I, Calder PC. Beneficial outcomes of omega-6 and omega-3 polyunsaturated fatty acids on human health: An update for 2021. Nutrients. 2021 Jul 15;13(7):2421.
4. Gropper SS, Smith JL. Advanced nutrition and human metabolism. Cengage Learning; 2013.
5. Szczuko M, Kikut J, Komorniak N, Bilicki J, Celewicz Z, Ziętek M. The role of arachidonic and linoleic acid derivatives in pathological pregnancies and the human reproduction process. International journal of molecular sciences. 2020 Dec 17;21(24):9628.
6. Lin TK, Zhong L, Santiago JL. Anti-inflammatory and skin barrier repair effects of topical application of some plant oils. International journal of molecular sciences. 2018 Jan;19(1):70.
7. Zock PL, Katan MB. Linoleic acid intake and cancer risk: a review and meta-analysis. Am J Clin Nutr. 1998 Jul;68(1):142-53. doi: 10.1093/ajcn/68.1.142. PMID: 9665108.
8. Welsch CW. Relationship between dietary fat and experimental mammary tumorigenesis: a review and critique. Cancer research. 1992 Apr 1;52(7_Supplement):2040s-8s.
9. Serna-Marquez N, Diaz-Aragon R, Reyes-Uribe E, Cortes-Reynosa P, Salazar EP. Linoleic acid induces migration and invasion through FFAR4-and PI3K-/Akt-dependent pathway in MDA-MB-231 breast cancer cells. Medical oncology. 2017 Jun;34:1-2.
10. Leahy C, Osborne N, Shirota L, Rote P, Lee YK, Song BJ, Yin L, Zhang Y, Garcia V, Hardwick JP. The fatty acid omega hydroxylase genes (CYP4 family) in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD): an RNA sequence database analysis and review. Biochemical pharmacology. 2024 May 1:116241.
11. Mouradian M, Kikawa KD, Johnson ED, Beck KL, Pardini RS. Key roles for GRB2-associated-binding protein 1, phosphatidylinositol-3-kinase, cyclooxygenase 2, prostaglandin E2 and transforming growth factor alpha in linoleic acid-induced upregulation of lung and breast cancer cell growth. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2014 Apr 1;90(4):105-15.
12. Koundouros N, Nagiec MJ, Bullen N, Noch EK, Burgos-Barragan G, Li Z, He L, Cho S, Parang B, Leone D, Andreopoulou E. Direct sensing of dietary ω-6 linoleic acid through FABP5-mTORC1 signaling. Science. 2025 Mar 14;387(6739):eadm9805.

# Brain Teasers

1. I'm a molecule that's small and hot,
   I signal pain in every spot.
   Released when cells scream in despair,
   I make sure your brain is aware.

2. I'm not a germ, but I act like one.
   Processed and fried, I sneak in through fun.
   I'm edible but inflammatory too—
   What kind of trigger am I? Who?

3. No pill, no doc, but I reduce the flame,
   I walk the block and play the game.
   Regular, moderate — I'm the key,
   To keeping inflammation far from thee.

**UNSCRAMBLE WORDS (Inflammatory Mediators)**

| | |
|---|---|
| Tseekolnueri | EasrsPeot |
| Nyikbraidn | Ncaiossieod |
| Ihemstain | Tosyicekn |

**Answers on Page 102**

# APTI Forum News

**1. Dr. Vaishali Londhe**, Professor, Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's NMIMS, has received the **Best Poster Presentation** Award at **CRS Singapore 2025** Connecting Continents in Delivery science held at National University Health System, Singapore on 19th-21st February 2025 with a cash prize of 100 SGD. The topic presented was "Hesperidin Loaded Dissolving Microneedles for the Treatment of Rheumatoid Arthritis".

**2. Dr. Shailesh Sharma**, Director and Professor at Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, has been conferred the prestigious **Shodh Ratan Award 2025** at the **APTI & IPGA National Conference** in Palampur's Sri Sai University. The award recognizes his exceptional contributions to research, patents, and publications. Dr. Sharma dedicated the honour to his research team, emphasizing collaborative success. The college's management lauded his achievement, highlighting his impact on pharmacy education and innovation.


**3. Dr. S. Akilandeswari**, Dean, School of Pharmacy, Dhanalakshmi Srinivasan University, Trichy, has been conferred with the **AVRS Women in Science Award 2025** issued by Antiviral Research Society in recognition of her dedicated and tireless service to the pharmaceutical field. The award was presented during the International Conference on "Role of Artificial Intelligence in Drug Design, Discovery, and Development," organized by the Antiviral Research Society (AVRS) on 5th April 2025 at Srivilliputhur, and was conferred by Dr. Murugesh, Senior Professor, RTD, MMC, Madurai, Tamil Nadu.

**4. Students from Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela won nine prizes at HEALTHACON 2025**

A prestigious inter-college fest held at Saraswati Group of Colleges, Gharoan. The Bela pharmacy college team dominated cultural and technical events, winning four 1st prizes (in bhangra, mehndi art, and rangoli competition, face painting) and five 2nd prizes (in quiz competition, tattoo making, poster making, formulation challenge, and model competition), demonstrating excellence in both creativity and academics. Dr. Shailesh Sharma, director of the college, praised the students, saying, "Their dedication and hard work have made the college proud. These achievements reflect their all-round development beyond academics." The management committee also congratulated the students and faculty co-ordinators, Jaspreet Kaur and Ravinder Kaur, for the great achievement.

**5. Amar Shaheed Baba Ajit Singhand Jujhar Singh Memorial College of Pharmacy, Bela, an autonomous college, celebrated World Health Day**

A health checkup camp was organized by the Care and Cure Club. The event aimed to promote community well-being by offering free health checkups, including blood pressure, blood sugar, and fever screening of the

shopkeepers, customers at banks, petrol pump stations, and residents of Bela village. Dr. Shailesh Sharma, Director of Pharmacy College, graced the occasion and appreciated the club's efforts in spreading health awareness among the villagers. The initiative was led by Dr. Satnam Singh, Coordinator of the Care and Cure Club, along with club members Dr. Navjot Kaur, Mrs. Navjit Kaur, Mrs. Ravinder Kaur, Mrs. Ramandeep Kaur, Mrs. Rupinder Kaur, Harpreet Kaur, Jaspreet Kaur, and volunteers who actively participated in conducting the health checkups.


**6. Bela Pharmacy College celebrated World Asthma Day**

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy (An Autonomous), Bela celebrated World Asthma Day with an engaging and educational event organized by the Synthetic Discovery Club of the Pharmaceutical Chemistry Department. The event not only educated students and faculty about asthma but also encouraged active participation in spreading awareness within the community. Students presented a play on World Asthma Day to raise public awareness about asthma, its prevention, and the importance of practices like yoga in managing respiratory health. Dr. Monika Gupta, Head, Pharmaceutical Chemistry Department, shared her insights, underlining asthma as a growing health concern.


**7. Oration seminar on "Building healthier futures"**

Amity Institute of Pharmacy, Amity University Mumbai, organized an oration seminar on "Building Healthier Futures" on May 7, 2025, focusing on the theme "Healthy Beginning, Hopeful Future." Director of the institute, Prof. Dr. Suneela Dhaneshwar, addressed the audience and emphasized the value of a balanced diet, conventional Indian cooking and cuisine, as well as the importance of menstrual hygiene. Hon. Vice Chancellor Prof. Dr. A. W. Santhosh Kumar highlighted the significance of the quality and quantity of food. Esteemed speakers included Prof. Rekha Diwekar, an expert in Heritage Food, Kitchen Chemistry & Nutrition, who spoke on "The History, Mystery, and Chemistry of Food," and Ms. Swati Bedekar, Founder of Vatsalya Foundation& Sakhi Project, known as the "Pad Woman of Vadodara," who addressed on "Upsurge of Sakhi: From Humiliation to Dignified Menstruation." The seminar saw enthusiastic participation of students and faculty from various domains, promoting awareness on nutrition and menstrual health while fostering a culture of well-being and informed dialogue.


## Upcoming Conference

This year the 74th edition of The Indian Pharmaceutical Congress (IPC) will be organized from December 19 to 21, 2025 at the Bangalore International Exhibition Centre (BIEC), Bengaluru. The theme is 'AI & Technology in Pharma: Educate, Innovate, Empower,'. IPC 2025 is organized by the Indian Pharmaceutical Congress Association (IPCA) and hosted by the Association of Pharmaceutical Teachers of India (APTI).


# PHARMA NEWS ROUND-UP

**March 19, 2025:** Tech Mahindra has announced a pharmacovigilance (PV) autonomous solution built with NVIDIA AI software to automate and optimise pharmacovigilance workflows thereby advance drug safety management. The solution integrates the NVIDIA AI Enterprise software platforms, viz. NVIDIA NeMo, NVIDIA NIM microservices, and NVIDIA AI Blueprints. This streamlines case intake, data transformation, quality control, and compliance management, rendering a seamless and intelligent PV workflow. Additionally, the LLM-powered AI agents within the solution autonomously handle case classification, prioritisation, and verification of pharmacovigilance emails to minimize the risk of human error.

**March 25, 2025:** A patented bioprinting technology, Reactive Jet Impingement (ReJI) has been devised by Newcastle University scientists that creates cell-filled gels closely resembling human tissues. The technique involves jetting two different liquids at each other—one containing cells in a cross-linking solution and the other a polymer solution. These solutions combine mid-air to create a cell-filled hydrogel that can be printed on nearly any surface. The technology has been patented in both the US and Europe and has been funded by Versus Arthritis.

**March 28, 2025:** The annual change in the wholesale price index has led to modest increase of 1.74% in Maximum Retail Price (MRP) of Scheduled formulations from April 1. The essential medicines, impacted with the price change include paracetamol, antibiotics such as azithromycin used to treat bacterial infections, anti-anaemia medicines, vitamins, and minerals, to name a few.

**March 31, 2025:** Sun Pharma Advanced Research Company announced submission of an Investigational New Drug (IND) application to support the next phase of development of SBO-154 US Food and Drug Administration (USFDA). For evaluation of SBO-154 in treatment of solid tumors, the company has planned a global phase 1 dose-escalation and expansion study.

**April 7, 2025:** Sun Pharma has acquired rights from South Korea-based Daewoong Pharmaceutical to manufacture and commercialise novel potassium-competitive acid, Fexuprazan tablets in India. The drug showed over 95% healing efficacy in Erosive Esophagitis, a Phase 3 study.

**April 9, 2025:** ZIM Laboratories Ltd has entered into a licensing and supply agreement with UAE-based Globalpharma Co to commercialize oral thin film products, manufactured using ZIM Labs' proprietary oral thin film (OTF) technology platform

**April 23, 2025:** The Indian Council of Medical Research (ICMR) has sent a recommendation to the Drugs Technical Advisory Board for a selective ban on all formulations above 100 mg of Nimesulide for individuals under 18 and over 60. This recommendation has been made considering the safety concerns such as liver damage and gastrointestinal issues associated with use of this drug. Additionally, ICMR has suggested introducing a black box warning on labels and has categorically advised to curb its use in women trying to conceive.

**April 28, 2025:** Dr. Reddy's Laboratories has expanded its partnership with Sanofi Healthcare to introduce prefilled injection of monoclonal antibody, nirsevimab, under brand name Beyfortus. This novel drug has shown to be effective in prevention of respiratory syncytial virus caused lower respiratory tract disease in newborns, infants in children up to 24 months of age.

**May 2, 2025:** For abrogation of the misuse and regulate exports of opioid, Tapentadol to West Africa, the Indian government is planning to regulate Tapentadol under the Narcotic Drugs and Psychotropic Substances Act.

**May 21, 2025:** Hillchol, Bharat Biotech's oral Cholera Vaccine, has completed phase III clinical trials in 1,800 participants across various age groups and ten clinical sites in India. The study demonstrated non-inferiority of developed vaccine against Ogawa and Inaba serotypes in Indian adults and children.

**May 31, 2025:** Moderna's updated COVID-19 vaccine, mNEXSPIKE has been granted approval by USFDA for individuals aged 65 and older with underlying health conditions that increase their risk to contract COVID-19. This approval marks the first endorsement under stricter regulatory guidelines.

**June 2, 2025:** ISB 2001, a biotechnology based drug arising from collaboration between New York-based scientific research group Ichnos Sciences and Indian drug maker Glenmark has shown a 79% overall response rate in a Phase 1 study. The study was demonstrated the usefulness of this drug which targets two sites on the tumour cell and the body's T-cells in the treatment of relapsed or refractory multiple myeloma (RRMM), a rare form of blood cancer that affects plasma cells in bone marrow.

**June 2, 2025:** AstraZeneca's new breast cancer pill, Camizestrant, is a hormone therapy which exerts its action by stopping estrogen from attaching to cancer cells, thereby abolishing its growth. When used in conjunction with other medicines, Camizestrant, combined with other medicines, helped patients live to live for a median of 16 months, making it promising drug in tackling breast cancer.

Sources: https://economictimes.indiatimes.com/
www.expresspharma.in

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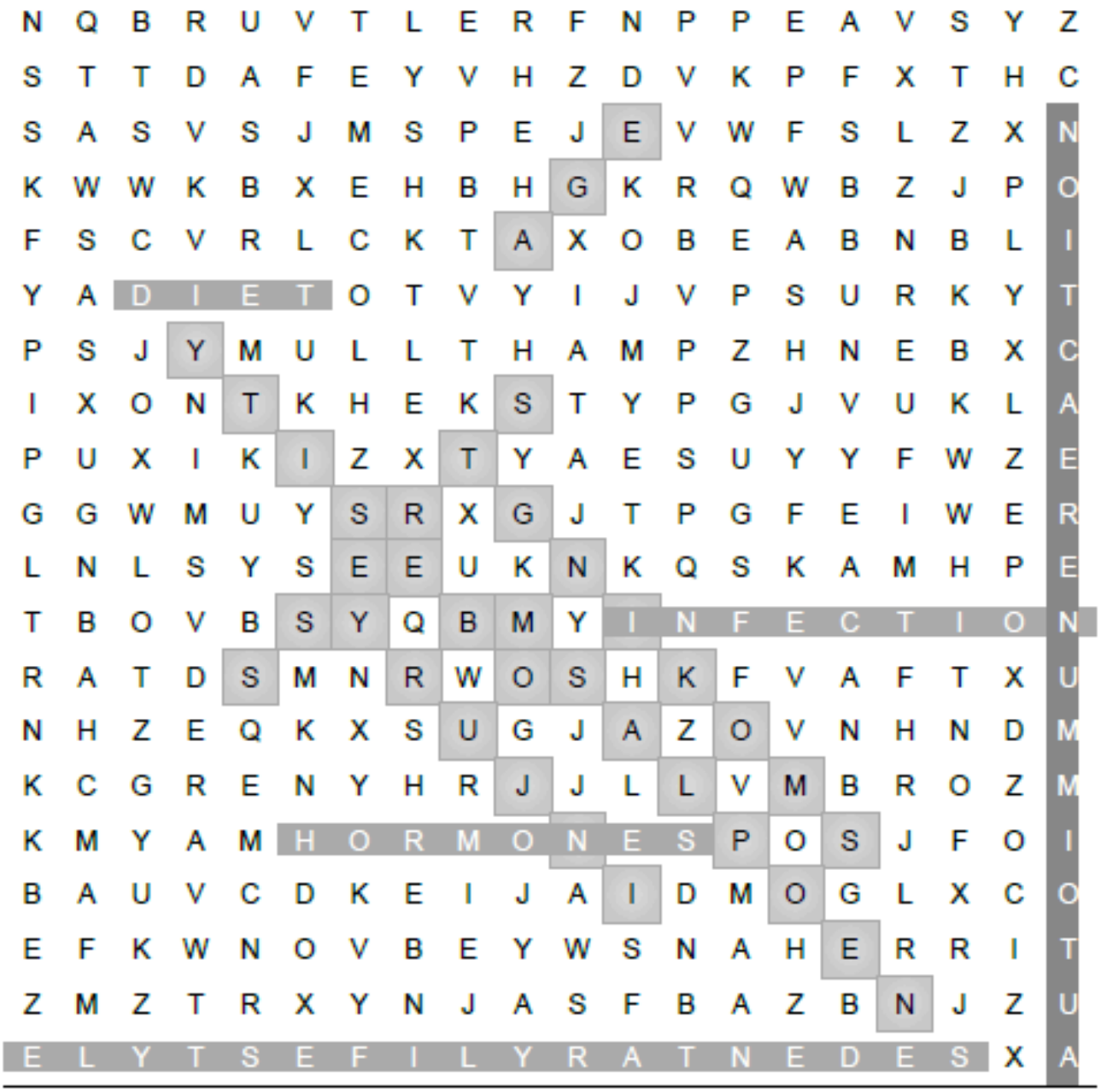
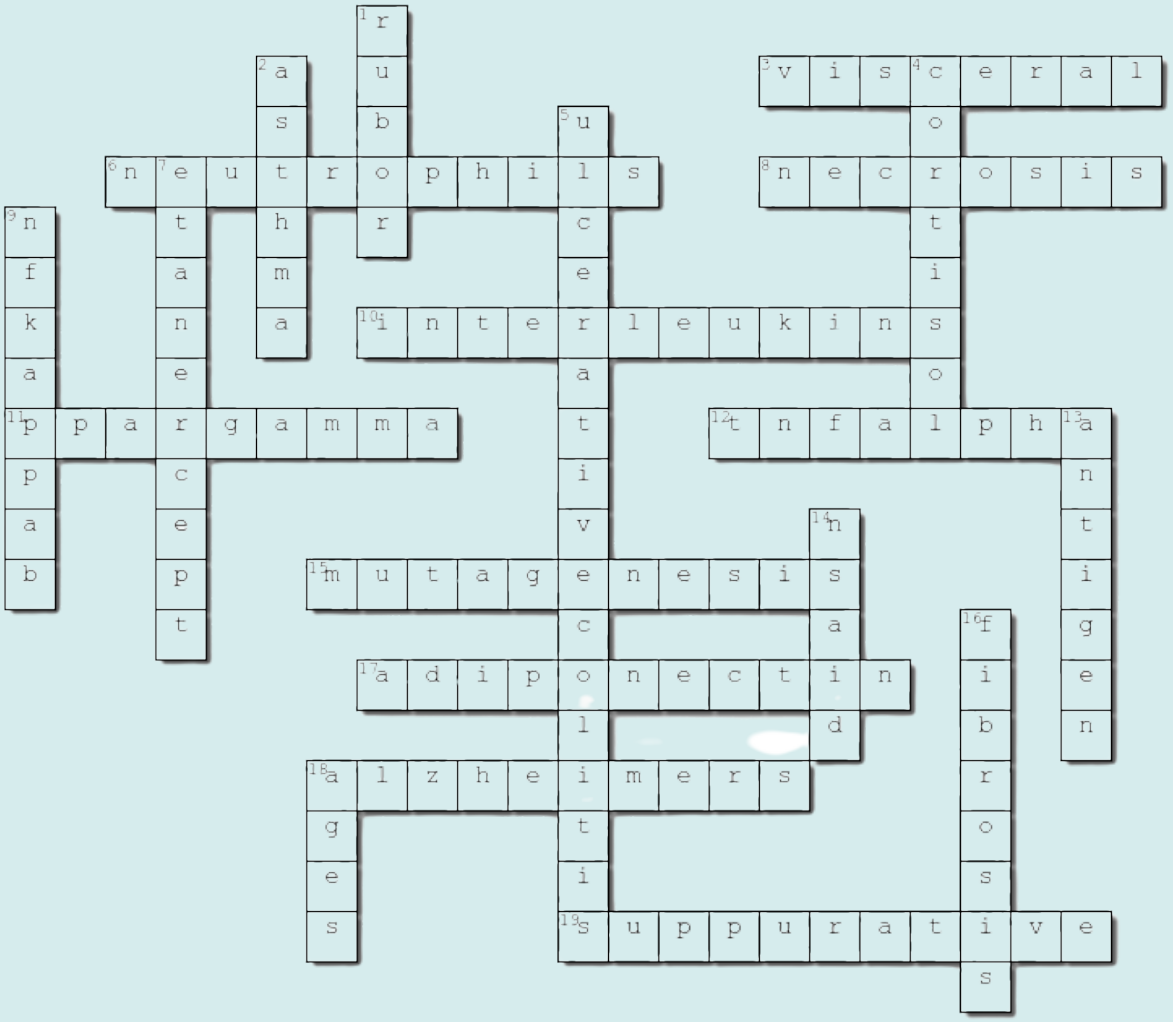
# Contributing Factors to Inflammation



AGE
AUTOIMMUNEREACTION
DIET
HORMONES
INFECTION
INJURY
NEOPLASM
OBESITY
SEDENTARYLIFESTYLE
SMOKING
STRESS

Name:_____

Complete the crossword puzzle below



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## Across

**3.** Type of fat releasing cytokines (**visceral**)
**6.** First responders to inflammation, a type of white blood cell (**neutrophils**)
**8.** Tissue death from inflammation (**necrosis**)
**10.** Signaling molecules in inflammation (**interleukins**)
**11.** Nuclear receptor with anti-inflammatory roles (**ppargamma**)
**12.** Inflammatory cytokine from macrophages (**tnfalpha**)
**15.** DNA mutation process caused by inflammation (**mutagenesis**)
**17.** Anti-inflammatory hormone from fat (**adiponectin**)
**18.** Age-related brain inflammation (**alzheimers**)
**19.** Inflammation with pus (**suppurative**)

## Down

**1.** Sign of inflammation that causes redness (**rubor**)
**2.** Lung condition with airway inflammation (**asthma**)
**4.** Natural hormone mimicked by corticosteroids (**cortisol**)
**5.** Chronic inflammatory bowel disease (**ulcerativecolitis**)
**7.** TNF-alpha blocker biologic (**etanercept**)
**9.** Signaling pathway for inflammation (**nfkappab**)
**13.** Immune-triggering molecule (**antigen**)
**14.** Pain-relieving and anti-inflammatory drug (abbr.) (**nsaid**)
**16.** Tissue scarring from chronic inflammation (**fibrosis**)
**18.** Advanced glycation end products (abbr.) (**ages**)

## Brain Teaser Answers

1. Prostaglandin
2. TransFat
3. Excerise

## UNSCRAMBLE WORDS (Inflammatory Mediators)

Tseekolnueri : Leukotrienes
Nyikbraidn : Bradykinin
Ihemstain : Histamine
EasrsPeot : Proteases
Ncaiossieod : Eicosanoids
Tosyicekn : Cytokines

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## LOTUS LOGO STORY

As a lotus is able to emerge from muddy waters un-spoilt and pure it is considered to represent a wise and spiritually enlightened quality in a person; it is representative of a woman who carries out her tasks with little concern for any reward and with a full liberation from attachment. Lotus-woman in the modern sense of women's qualities: she is superbly intelligent, highly educated, and totally committed to individualism. She is politically astute and works incessantly for a better and more humane society. She is exquisite in her taste for music, art and culture, abounds in social graces and performs brilliantly in communication.