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MOLECULAR AND CELLULAR INFLAMMATORY MODULATORS GOVERNING WOUND HEALING AND TISSUE REPAIR

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ABSTRACT: Inflammation is a critical protective response that involves a complex network of inflammatory modulators, which coordinate the body's detection, reaction to, and repair of tissue damage or infection. These modulators include cytokines, chemokines, adhesion molecules, lipid mediators, neuroimmune signals, and emerging regulators such as A3 adenosine receptors, formyl peptide receptors, CCN (cellular communication network) proteins, microRNAs, and the Nrf2 (Nuclear factor erythroid 2-related factor 2) pathway. These components work together to initiate and guide immune responses, ensuring effective tissue communication and resolution of inflammation. When functioning properly, inflammation supports healing, but when imbalanced or overactive, it can lead to chronic inflammatory diseases such as arthritis, cardiovascular disorders, autoimmune conditions, and metabolic dysfunction. Understand operate and interact has enabled the development of targeted therapies, including cytokine inhibitors and receptor specific drugs, to restore immune balance. Inflammatory modulators form an interconnected system that determines the intensity, duration, and outcome of inflammation, making them essential targets for improving treatments of chronic inflammatory conditions.

INTRODUCTION: Inflammation is one of the most complex and essential biological processes, acting as the body's immediate defence mechanism against harmful stimuli such as microbial invasion, physical injury, chemical exposure, and cellular stress [1]. It is deeply embedded in human physiology, orchestrated through a sophisticated communication system of molecular messengers known as inflammatory modulators [2].

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These modulators include classical agents such as pro-inflammatory and anti-inflammatory cytokines, chemokines, adhesion molecules, and lipid mediators, as well as emerging regulators that add depth and complexity to the inflammatory network [3, 4].

When a harmful event occurs, the body detects it through pattern recognition receptors, triggering a cascade in which pro-inflammatory cytokines like T N F-IL-1 and IL-6 rapidly activate immune pathways, increase vascular permeability, and initiate the recruitment of leukocytes to the affected site [5–7]. Chemokines act as directional signals, ensuring these immune cells migrate accurately toward the site of inflammation, while adhesion molecules allow their controlled exit from the

bloodstream into tissues. Lipid mediators such as prostaglandins and leukotrienes coordinate the early inflammatory response but also contribute to preventing excessive inflammation through specialized pro-resolving mediators [8, 9]. Beyond these well-established players, scientific advancements have uncovered newer modulators that shape inflammation at genetic, cellular, and systemic levels. For example, the A3 adenosine receptor fine-tunes inflammation by regulating cell survival and cytokine release under stress, while the formyl peptide receptor responds directly to infection-associated signals and promotes phagocytic activity [10]. CCN family proteins influence cell migration, adhesion, and tissue remodelling during inflammatory episodes, contributing to wound healing and fibrosis. MicroRNAs add a post-transcriptional layer of control by turning genes on or off depending on the inflammatory environment, and the Nrf2 signalling pathway helps limit oxidative stress and enhance cellular resilience [11].

These components function in a precise yet delicate balance, allowing inflammation to protect and repair tissues while preventing unnecessary damage [12]. However, when this balance is disrupted, acute inflammation may transition into a chronic state that silently damages organs over time. Prolonged cytokine elevation, continuous immune cell recruitment, and persistent oxidative stress are all factors that contribute to conditions such as rheumatoid arthritis, atherosclerosis, Type 2 diabetes, inflammatory bowel disease, Alzheimer's disease, and several autoimmune disorders [13]. Such chronic conditions often arise when regulatory mechanisms fail to resolve inflammation effectively, allowing harmful signalling to dominate. Understanding this shift from protective to pathological inflammation is essential for developing more effective therapeutic strategies. Modern treatments, including T N F inhibitors, IL-6 blockers, integrin-blocking drugs, and agents that activate Nrf2 pathways, demonstrate how targeting specific inflammatory modulators can significantly improve clinical outcomes [14, 15]. As research continues to uncover how these modulators interact and influence one another, the possibility of personalized anti-inflammatory therapies grows stronger. Studying inflammatory modulators is therefore not only essential for understanding the biology of healing and disease but also for developing next-generation interventions that can precisely regulate the immune response without compromising the body's natural defence mechanisms [16–18]. This introduction aims to provide a comprehensive foundation for understanding the vast landscape of inflammatory modulators, their mechanisms, and their profound impact on both health and disease, ultimately highlighting why they stand at the centre of modern anti-inflammation [19].

Some natural anti-inflammatory mediators helps to reduce the oxidative stress such as diosgenin has qualities that help fight oxidative stress and lessen inflammation. Numerous disorders, including diabetes, obesity, irregularities in blood and brain function, and allergy diseases, may benefit from it [20]. Poor wound healing in diabetic patients is associated with several diseases, including neuropathy, vascular disease, and deformities of the feet. At the cellular level, epidermal migration, an increase in acute inflammatory cells, and a decrease in cellular proliferation have all been observed. These biological changes might make people more vulnerable to wound infection. Improving and planning for the care of chronic wounds has been increasingly important in recent decades in an effort to extend life and improve human quality of life [21].

Cellular Receptors Modulating Wound Healing:
Upon an injury, the coagulation cascade is activated and endothelial cells and platelets engage immediately, causing clotting. Neutrophils and macrophages are drawn from the bloodstream as a result of an inflammatory response driven by mediators secreted during this early period. These cells then release growth factors and proinflammatory cytokines, which attract stromal cells and cause them to undergo division into myofibroblasts, which are in charge of wound healing and extracellular matrix deposition. These cells have a tendency to promote the proliferation of endothelial and epithelial cells in the wound site, resulting in neoangiogenesis and re-epithelialization, respectively. Tissue repair proceeds toward and concludes with scarring following the removal of clots and tissue debris by macrophages and extracellular hydrolases (matrix metalloproteases, elastase, and plasmin) [22, 23].

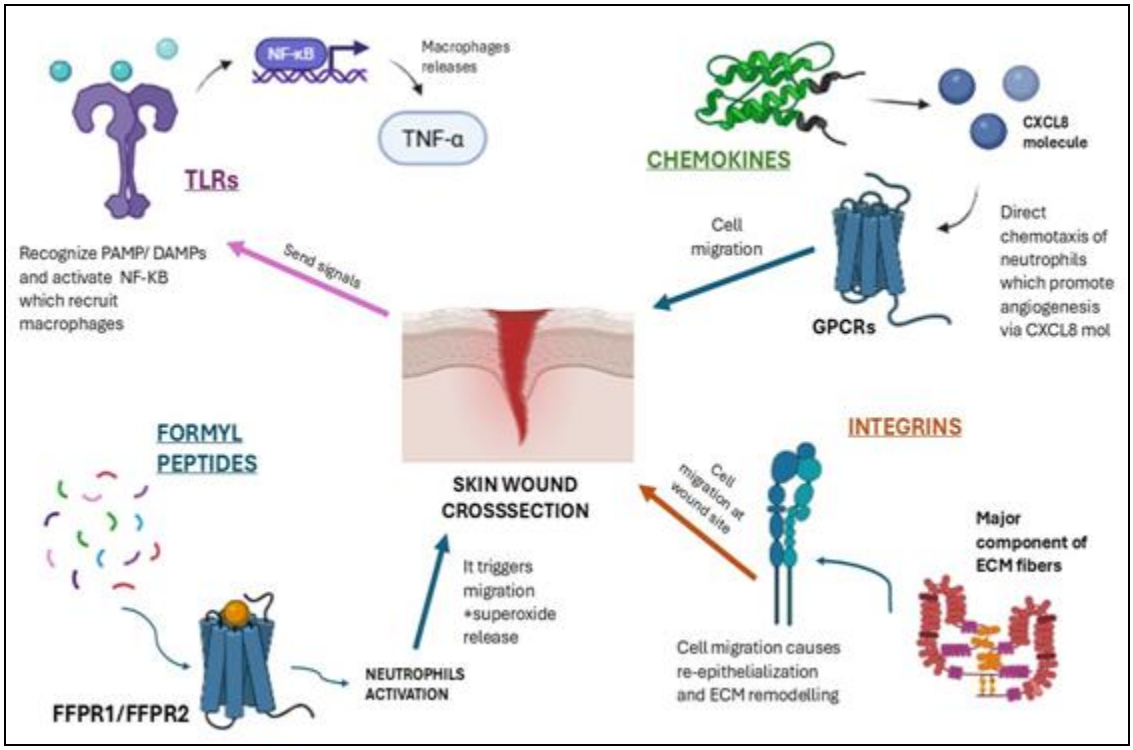

FIG. 1: INTERPLAY OF IMMUNE CELLS, RECEPTORS, AND SIGNALLING PATHWAYS DURING WOUND REPAIR

Toli-like Receptors: Toll-like receptors (TLRs) occupy a central position in both the initiation and fine-tuning of the innate immune response. They are expressed across a broad range of skin-resident immune and non-immune [24]. Cells and their importance in host defence stems from their ability to modulate both innate and adaptive immunity. TLRs are found on diverse cell populations, including macrophages, neutrophils, dendritic cells, Langerhans cells, mast cells, lymphocytes, endothelial cells, keratinocytes, and fibroblasts. As prototypical pattern recognition receptors (PRRs), they are capable of detecting pathogen-associated molecular patterns (PAMPs) and other foreign ligands, making them indispensable sentinels at the interface of the host and the external environment [25].

Chemokine Receptors: Chemokines are a family of small secreted proteins, typically ranging from 7 to 13 kDa in molecular weight, that have been shown to regulate a wide spectrum of biological processes beyond immune cell trafficking including angiogenesis, chemotaxis, and homeostasis. They are crucial in guiding the healing and closure of wounds. Based on the structural features they possess, the chemokine family is divided into four subfamilies [26–28]. Chemokines exert critical immunostimulatory effects during wound healing: platelet activation and the subsequent release of chemokines such as CXCL2 and CXCL8 stimulate neutrophils and monocytes, which in turn secrete additional chemokines including CCL2, CCL3, CCL4, and CCL5. This secondary release further activates lymphocytes, keratinocytes, and endothelial cells, amplifying and sustaining the reparative response [29].

Formyl Peptide Receptors: Gi-protein-coupled receptors (GPCRs) comprise the family of seven transmembrane domains known as formyl-peptide receptors (FPRs). FPR1, FPR2, and FPR3 are the three FPRs found in humans. Several chemoattractants regulate the neutrophil accumulation [30], such as IL-8 (CXCL8), CXCL7, and CXCL1, which rely on neutrophil-expressed CXCR2. However, in both humans and mice, neutrophils also express FPR1 (Fpr1) and FPR2 (Fpr2). Fpr1/Fpr2 are the first to detect chemotaxis signals in a mouse skin-wound healing model, which leads to rapid neutrophil infiltration. When agonists generated at the site of injury activate FPR1/FPR2 (Fpr1/Fpr2), a signaling cascade is triggered, leading to neutrophil migration, enhanced phagocytosis, and superoxide production [31].

Integrin Receptors: Integrins represent the principal molecular mediators of cell attachment to the extracellular matrix (ECM) [32]. Based on their ligand specificity and/or phylogenetic comparison of the α subunits, integrins can be categorized into four subfamilies [66]. Integrin heterodimers exist in all multicellular organisms and are able to recognize the arginine-glycine-aspartic acid (RGD) pattern in extracellular ligands. The integrins α3β1, α6β1, α7β1, and α6β4 that belong to the laminin receptor subfamily can mediate cellular attachment to basement membranes in a variety of tissues. Integrins α4β1, α4β7, and α9β1 constitute a distinct subfamily. They are able to identify RGD-independent ECM ligands like fibronectin. Various kinds of wound cells interact actively with one another. Integrins and ECM proteins are important components of these interactions [33]. For instance, eliminating monocytes and neutrophils. For instance, in mice, skin wound re-epithelialization is delayed when neutrophil and monocyte integrin αMβ2 is eliminated, but it is accelerated when αvβ3 integrin, which is expressed in wounds by platelets, endothelial cells, macrophages, and fibroblasts, is eliminated [34].

Pathways Involved in Healing:

The Signalling Pathway MAPK: The MAPK (Mitogen-Activated Protein Kinase) pathway is organized as a three-tiered kinase module comprising the MAPK itself, a MAPK kinase (MEK or MKK), and a MAPK kinase kinase (MEKK or MKKK). Sequential and coordinated activation of these three enzymatic layers enables the pathway to regulate a diverse array of physiological and pathological outcomes, including cell growth, differentiation, stress responses, and inflammatory cascades. The MAPK framework branches into four primary signalling arms: ERK, JNK, p38/MAPK, and ERK5. In the context of wound repair, activation of the MAPK signalling pathway has been shown to accelerate healing by promoting cell migration and proliferation at the wound site [35].

PI3K/AKT Signalling Pathway: PI3K is a cytosolic lipid kinase that participates in cellular membrane metabolism, intracellular transport, and signal transduction. Structurally, it exists as a heterodimer composed of a regulatory subunit (p85) and a catalytic subunit (p110). Upon binding to growth factor receptors such as EGFR, PI3K induces conformational changes in AKT, thereby activating it. Activated AKT subsequently phosphorylates a range of downstream substrates including the apoptosis-regulating proteins Bad and Caspase-9 to govern cell proliferation, differentiation, survival, and migration. Additionally, protein kinase B (AKT) can initiate crosstalk with the NF-κB pathway through IKK activation. The downstream targets of PI3K/AKT include the mammalian target of rapamycin (mTOR) and transcription factors such as FoxO (Forkhead Box O), HIF-1α, and c-MYC. Wound healing has a particularly close functional relationship with PI3K/AKT signalling [36].

TGF - β Signalling Pathway: The TGF-β (Transforming Growth Factor-beta) family comprises secreted polypeptide signalling proteins that govern cell proliferation, differentiation, apoptosis, and wound repair. Within this pathway, the primary signal sources are TGF-β1, TGF-β2, TGF-β3, and BMPs (bone morphogenetic proteins), while Smad proteins serve as the canonical downstream transcriptional effectors. Evidence suggests that inhibiting TGF-β signal transduction may facilitate faster and potentially scarless wound closure [37]. TGF-β1 in particular is a master regulator of scar formation and wound healing: it promotes fibroblast proliferation and the conversion of stromal cells into fibroblasts. Furthermore, TGF-β1 drives the differentiation of fibroblasts into myofibroblasts, a process that is instrumental in wound contraction and closure [38-40].

NF-kB Signalling Pathway: The NF-κB signalling network is a master regulatory system that underpins the body's inflammatory response and is involved in the initiation and progression of numerous inflammatory diseases. Once translocated to the nucleus, activated NF-κB binds to promoter and enhancer elements of target genes, driving adhesion molecule production in endothelial cells and stimulating leukocyte and fibroblast proliferation alongside the broader inflammatory response [41, 42]. This pathway also exerts considerable influence over wound healing through its regulation of vascular regeneration. Studies have demonstrated that NF-κB signalling controls VEGF (Vascular Endothelial Growth Factor) transcription, such that pharmacological

blockade of NF-κB activation leads to a marked reduction in VEGF expression and capillary network formation [43].

New Paths and Targets:

Cytokine Signalling: Cytokines are the chemical communication molecules that cells employ to convey signals to one another. While this term was historically associated primarily with immune function, its scope is considerably broader [44]. Structurally, cytokines are classified into two major categories: Type I and Type II. Type I cytokines share a characteristic four-alpha-helix bundle architecture [45] and perform critical regulatory functions throughout the immune system. Type II cytokines, a category that includes interferons, participate in distinct biological processes. Importantly, cytokine classification does not restrict their functional reach — these molecules exert regulatory influence across a wide variety of cell types and physiological systems [46].

JAK/STAT Pathway: The JAK/STAT (Janus Kinase/Signal Transducer and Activator of Transcription) signalling pathway is vital for conveying messages from cytokines to the cell's interior. Initially linked to interferons, this pathway helps regulate immune responses [47]. When conditions are right, specific kinases (called JAKs) become active and begin a cascade of reactions that lead to gene expression changes in the nucleus [48, 49]. There are different JAK types, and they play specific roles in signalling pathways that affect immune cell functions. Once activated, STAT proteins are crucial for transmitting these signals and can even influence gene activity by binding to specific DNA regions. This pathway not only supports immune function but also impacts various bodily processes, highlighting the intricate ways our cells communicate and operate [50].

NLRP3 Inflammasomes and Inflammation: NLRP3 (NLR family pyrin domain containing 3) inflammasomes area part of our innate immune system that can respond to various stimuli. Unlike other inflammasomes that react to specific triggers, NLRP3 is quite versatile and can engage with numerous different signals related to danger or infection. It works through a two-step process: a priming phase that gets it ready and an activation phase where it responds to signals like cell damage or pathogens. This activation influences inflammatory responses, which is essential for fighting infections but can also lead to issues if not controlled. Learning about how NLRP3 works helps us understand the complexities of our immune reactions and how they can sometimes go awry, leading to diseases [51]. In summary, the advances in personalized healthcare, nanotechnology, epigenetics, microbiome studies, and understanding immune signalling pathways, among others, are paving the way for innovative treatments and better health outcomes.

Natural Anti-Inflammatory Modulators: Numerous disorders, including as allergies, cardiovascular dysfunction, metabolic syndrome, cancer, and autoimmune diseases, which have a substantial financial impact on both people and society at large, are primarily caused by an unregulated inflammatory response. This is true despite the fact that inflammation is a protective process our body performs in reaction to damaging stimuli such as allergens and/or tissue damage [52]. Numerous medications are available to regulate and suppress inflammatory crises; immuno-suppressants, steroids, and nonsteroid anti-inflammatory drugs are practical examples of these drugs that have side effects. In practice, however, we aim to apply the lowest effective dose with the most effectiveness and the fewest side effects. Therefore, to maximize pharmaceutical efficacy and minimize undesirable side effects, we must incorporate natural anti-inflammatory agents into prescription therapy. Prescription medication must include natural anti-inflammatory ingredients to optimize drug effectiveness and reduce unwanted side effects. Naturally, since herbal remedies are increasing medical research, we need to learn more about them. Complementary, alternative, and traditional medicine are the main sources of recommendations for herbal drugs; nevertheless, modern medicine must first validate these suggestions through scientific methods before putting them into practice. Many inflammatory mediators are generated and released during different types of inflammatory reactions [53, 54].

Turmeric: Curcumin, also known as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione, is a chemical compound with anti-inflammatory, anti-oxidant, and anti-tumour

properties. Curcumin's anti-inflammatory qualities are thought to be the foundation of its many biological actions and are crucial in the management of illnesses [55].

Curcumin is mostly obtained from the rhizome of *Curcuma longa L*. (Turmeric) of the Zingiberaceae family and the root tuber of *Curcuma aromatica Salisb.* In China, these traditional Chinese remedies have long been used to treat pain, inflammation, and other illnesses by increasing blood flow and removing blood stasis. In India, turmeric is a popular spice that has been used in Ayurveda to treat inflammatory conditions [56, 57].

Inducers, sensors, mediators, and effectors are the four parts of the inflammatory process. Different inflammatory triggers cause different physiological and pathological mechanisms of inflammation, which are currently unknown. Generally speaking, the main methods that drugs reduce inflammation include: controlling how target tissues react to inflammatory mediators; generating anti-inflammatory mediators; reversing the medium's effect on the target tissue; and influencing receptors and signaling cascades. By regulating inflammatory signaling pathways and inhibiting the production of inflammatory mediators, curcumin has anti-inflammatory properties [58].

Curcumin binds to Toll-like receptors (TLRs) and modifies downstream nuclear factor kappa-B (NF-κB), mitogen-activated protein kinases (MAPK), activator protein 1 (AP-1), and other signaling pathways to regulate inflammatory mediators and cure inflammatory diseases. Curcumin inhibits NF-κB via acting on Peroxisome proliferator-activated receptor gamma (PPARγ) [59, 60].

By controlling the Janus kinase/Signal transducer and activator of transcription (JAK/STAT) inflammatory signalling pathway, curcumin can also have anti-inflammatory effects [61, 62].

Furthermore, a number of inflammatory illnesses are influenced by the cytosolic multiprotein complexes known as the NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome. The NLRP3 complex is composed of a protease known as caspase-1, an apoptosis-associated speck-like protein with a caspase recruitment domain, and a sensor protein. One of curcumin's potential mechanisms for treating inflammatory illnesses is its ability to either directly reduce NLRP3 inflammasome assembly or inhibit NLRP3 inflammasome activation by inhibiting the NF-κB pathway [63].

Ginger: It has been shown that both fresh ginger, which is mostly made up of gingerols, and dried ginger extracts, which are a major source of shogaols, can prevent the synthesis of prostaglandin E2 (PGE2) when lipopolysaccharide (LPS) is present [64]. Depending on the length of the side chains, 10-gingerol showed the highest inhibitory impact. This activity was ascribed to the inhibitory effects of 6-, 8-, and 10-gingerols on COX-2(Cyclooxygenase-2) mRNA expression and the corresponding COX-2 enzyme. However, it was discovered that the The 6-, 9-, and 10-shogaols had a less noticeable inhibitory effect on the expression of COX-2 mRNA. In a rat paw edema model caused by carrageenan, the anti-inflammatory properties of ginger extract were evaluated at different dosages. The findings showed that in a dose-dependent manner (25-200 mg/kg), the extract decreased the levels of inflammatory mediators PGE2, TNF-α, IL-6, monocyte chemoattractant protein-1 (MCP-1), and myeloperoxidase (MPO) by 32% to 60%. 6-SG was more effective than other shogaols, and ginger extract's anti-inflammatory properties were shown to be noticeably stronger than diclofenac's at the same concentration. Ginger extract enhanced overall antioxidant capacity and inhibited carrageenan-induced histopathological damage at a dose of 200 mg/kg [65]. According to the scientists, the primary mechanisms underlying ginger extract's anti-inflammatory properties are the stimulation of inflammatory cells and the inhibition of cell migration [66–69].

6-GN was found to inhibit the expression of TNF-α and inducible nitric oxide synthase (iNOS) in mouse macrophages stimulated by LPS, lower the levels of IL-6, IL-8, and ROS in hepatic HuH7 cells stimulated by IL-1β, lower the levels of IL-8, IL-6, IL-1β protein, and mRNA in intestinal epithelial cell inflammation caused by Vibrio cholerae, and (iv) decrease the secretion and expression of TNF-α, IL-1β, IL-6, PGE2, COX-2, and iNOS in murine RAW 264.7 monocyte/macrophage-like cells exposed to LPS,

and (v) decreased the expression of iNOS and COX-2 protein in murine skin cells exposed to 12-O-tetradecanoylphorbol 13-acetate (TPA) either by changing or blocking a signalling pathway mediated by NF-θB (nuclear factor kappa-light-chain-enhancer of activated B cells) or by interacting with different endogenous mediators like PI3K/Akt/I kappaB kinases (IKK) and MAPK. Furthermore, it has been observed that 6-GN's anti-inflammatory properties are facilitated by its inhibitory action on the COX-2 enzyme [70].

Ashawagandha: Withaferin's presence results in anti-inflammatory activity. The compounds 3-b-hydroxy-2,3-dihydrowithanolide F and withaferin A, which were extracted from *Withania somnifera*, exhibit encouraging antibacterial, antitumoral, immunomodulatory, and anti-inflammatory qualities.

Numerous conditions linked to inflammation in the body, including diabetes, cancer, neuro-degenerative illnesses, pulmonary, cardiovascular, and autoimmune disorders, are being researched in relation to *Withania somnifera*. Preclinical research has shown that this plant can control apoptosis and mitochondrial function while lowering inflammation by blocking inflammatory indicators such reactive oxygen species, nitric oxide, and cytokines like TNF-a and IL-6 [71].

In a mouse model of lupus, ashwagandha root powder was demonstrated to have a potential inhibitory effect in conditions such as proteinuria and nephritis. In a study using the HaCaT (human keratinocyte cell line), an aqueous solution from ashwagandha root was found to inhibit the NF-κB and MAPK (mitogen-activated protein kinase) pathways by increasing the expression of anti-inflammatory cytokines and decreasing the expression of pro-inflammatory cytokines like interleukin (IL)-8, IL-6, tumor necrosis factor (TNF-α), IL-1β, and IL-12. These results suggest that ashwagandha's anti-inflammatory qualities may be used to reduce skin irritation 72.

Animals administered Ashwagandha water extract (ASH-WEX) showed decreased reactive gliosis, inflammatory cytokine production (TNF-α, IL-1β, and IL-6), and nitro-oxidative stress enzyme expression in a preclinical study of the anti-neuroinflammatory properties of ASH-WEX against lipopolysaccharide-induced systemic neuroinflammation. Lipopolysaccharide (LPS)-induced regulation of the NFκB, P38, and JNK/SAPK MAPK pathways seems to be the molecular mechanism behind ASH-WEX's anti-inflammatory effects. According to the study's findings, *Withania somnifera* may be used to reduce inflammation in the nervous system linked to a number of neurological conditions [73].

Green Tea: According to recent research, polyphenols have anti-inflammatory and antioxidant qualities that improve health and help treat disorders linked to inflammation [74]. A variety of actions are produced by the absorption, metabolism, and delivery of polyphenolic chemicals to specific tissues or organs [75, 76]. By interacting with receptors on the surfaces of immune cells and enterocytes, the unabsorbed polyphenols can prevent pro-inflammatory signals. The gut microbes can metabolize the unabsorbed polyphenols [77]. Unabsorbed polyphenols and their metabolites can either reduce local inflammation or serve as prebiotics to encourage the growth of good bacteria, which will improve gut health. By directly functioning as antioxidants, triggering cytoprotective mechanisms, and blocking proinflammatory signaling transduction, dietary tea polyphenols have been shown to lower inflammation [78].

Resveratrol: Enzymes and pathways that generate inflammatory mediators and trigger the death of activated immune cells are regulated in part by RV. In this way, RV serves as a powerful anti-inflammatory and potential source of cancer treatment [79]. RV treatment has significantly reduced brain damage and decreased important inflammatory markers at the mRNA and proteomic levels. It has also been observed that the expression of Bcl-2(B-cell lymphoma 2), caspase3, and Bax-linked genes has changed. In rats with polycystic kidney disease, RV reduced blood urea nitrogen and creatine levels while lowering "two kidney/total body weight and density of cyst volume." Additionally, the investigation revealed decreased monocytic chemoattractant protein-1 (MCP-1) levels. Pro-inflammatory factors include complement factor B (CFB) and TNF-α. By

disrupting the pathway of the NF-κB signal, NF-κB (p50/p65) function was reduced 80.

Pro-inflammatory mediator triggering is lessened as a result of increased short-term expression of MyD88 (Myeloid Differentiation primary response 88). In mouse animal models, NTHi (Haemophilus influenza) did not activate the component MyD8 by inhibiting ERK1/2 expression. According to some experts, there is a non-steroidal activity that can be used therapeutically to treat a variety of illnesses that have a direct or indirect relationship to inflammatory diseases, either alone or in combination [81, 82].

Frankincense: The anti-inflammatory and anti-cancer properties of Boswellia species and their chemical compounds include 3-O-acetyl-11keto-β boswellic acid, α- and β-boswellic acids, 11-keto-β-boswellic acid and other boswellic acids, lupeolic acids, incensole, cembrenes, triterpenediol, tirucallic acids, and olibanumols. Frankincense operates by inhibiting a variety of processes, including oxidative stress, cyclooxygenase 1/2 and 5-lipoxygenase, leukotriene synthesis, and immune cell regulation from the innate and acquired immune systems. Frankincense also suppresses angiogenesis, invasion, metastasis, and proliferation via altering the transmission of signals that result in stoppage of the cell cycle Clinical research has discovered that le and its phytochemicals are useful against a variety of conditions, including osteoarthritis, multiple sclerosis, asthma, psoriasis, erythematous dermatitis, plaque-induced gingivitis, and irritation. While it had a beneficial effect on oedema related to brain tumors, frankincense did not reduce the size of gliomas. It has been demonstrated that the immune system benefits from decreased neutrophilic granulocyte invasion, mast cell stabilization, dropped T-effector cell differentiation and increased T-regulatory cell differentiation, decreased platelet Ca2+ mobilization, decreased immune cell and platelet infiltration in inflammatory tissues, and decreased leukocyte and its cell adhesive reaction [83].

Capsaicin: Capsaicin, the active ingredient in chilli peppers produced from plants in the genus Capsicum, is the most frequently eaten chilli in the world. A naturally occurring chemical group consisting of capsaicin and related compounds is called capsaicinoids. Primarily having anti-pain, anti-inflammatory effects. Dura mast cells are activated and vascular permeability is increased by trigeminal nerve stimulation; capsaicin inhibits these effects. Vasodilation, catecholamines, and sensory neuropeptides are released when capsaicin is taken. According to numerous studies, capsaicin effectively reduces blood pressure and cholesterol, enhances digestion, helps prevent cardiovascular illness, and relieves and prevents migraine headaches. The pathophysiology and potential treatment of neuroinflammatory diseases may be affected by the results of these investigations [84].

Quercetine: Green tea, onions, and apples are among the plants and vegetables that contain quercetin, a flavonoid component. For example, quercetin, quercetin-3-O-βglucoside (Q3G), quercetin-4′-O-β-glucoside (Q4′G), and quercetin-3,4′-di-O-β-glucoside (Q3,4′G) have been identified as the predominant onion flavonoids 5. It's interesting to note that cooking techniques have an impact on the final flavonoid content; boiling lowers the levels of Q4′G, whereas microwave heating for oneminute increases the overall quercetin abundance by 1.5 times. atherosclerosis: Quercetin reduces cellular lipid buildup, enhances autophagy, and inhibits mammalian Ste20-like kinase 1 (MST1) during the course of atherosclerosis by suppressing the generation of ox-LDL-induced RAW264.7 macrophage foam cells, a model for foam cells. In human umbilical vein endothelial cells (HUVECs), a model of vascular endothelial damage in the early stages of atherosclerosis, quercetin ameliorates glucosamine-induced apoptosis and inflammation. Quercetin and docosahexaenoic acid (DHA) together inhibit the phosphorylation of ERK1/2 and JNK1/2, as well as the mRNA expression of NF-κB subunits p50 and p65, in LPS-stimulated [85].

Pycnogenol: According to some, pycnogenol has beneficial pharmacological properties since it contains procyanidins, phenolic acids, bioflavonoids, and catechins. These qualities include antioxidant and anti-inflammatory properties. Flavonoids, mainly procyanidins and phenolic chemicals, make up the well-known strong antioxidant pycnogenol. Several procyanidins from the bark of French maritime

pines (*Pinus pinaster*) are found in pycnogenol, a standardized extract. The ability of pycnogenol to reduce oxidized ascorbate is probably going to boost the vitamin's activity in the vicinity of the wound, encouraging the production of collagen. The high binding of pycnogenol components to collagen and their potent inhibitory effect on matrix metalloproteinases (MMPs) likely play a significant role in wound healing. Pycnogenol will also aid in the inflammatory, or early, stage of the wound-healing process [86].

Cannabidiol: Hemp, or *Cannabis sativa* L., is a perennial herbaceous plant that belongs to the Cannabaceae family. The flowery tops contain the largest concentration of cannabinoids, such as delta-9 tetrahydrocannabinol and cannabidiol (CBD), a cannabinoid that does not produce a psychoactive effect. CBD did not influence IL-8 release, in contrast to VEGF release, which solely shown an inhibitory trend. A concentration-dependent decrease of MMP-9 was observed with 50% inhibition at 5 μM, suggesting that CBD inhibited the extract's ability to stimulate the release of MMP-9 (Matrix Metallopeptidase 9) [87]. CBD usually suppresses the immune system and lowers inflammation, but it can also increase cytokine production in certain conditions. THC and CBD both reduced or boosted the production of IFN-γ and IL-2 by mouse splenocytes under optimal or suboptimal stimulation. It has been established that these two cannabinoids either increase or decrease HIVgp120-specific T cell responses. A recent study found that ajulemic acid was synthesized with great care, resulting in a molecule that exhibited anti-inflammatory qualities but was essentially devoid of CB1 action. HU-320 and HU-239 showed anti-inflammatory therapeutic effects in a mouse model of collagen-induced arthritis, but none of them showed a cannabimetic profile *in-vivo*. It stopped the in vitro production of TNF-a by RAW 264.7 cell ROIs and murine macrophages. Additionally, it stopped serum TNF-a levels from rising following an LPS attack [88].

Devil's Claw: The mother tuber, the main tuber of the perennial tuberous plant Devil's claw, has a taproot that can reach a depth of two meters, and creeping annual stems originate from it. Devil's claw extract successfully lowered a number of oxidative stress and inflammatory indicators, including prostanoid, cytokine, and serotonin colon levels, demonstrating that the extract can potentially be used to treat ulcerative colitis [89]. Pure harpagoside's mode of action demonstrated that it moderately reduced the arachidonic acid pathway's cyclooxygenases 1 and 2 (COX-1/2) and nitric oxide production in human blood. In accordance with the concentration of each component, devil's claw can have a range of medicinal effects, although harpagoside is the main [90].

TABLE 1: NATURAL ANTI-INFLAMMATORY MODULATORS

Drug name	Biological source	Mechanism	Uses	Chemical structure	Ref.
Turmeric (Curcumin)	*Curcuma longa* (dried rhizome), Family – Zingiberaceae	In addition to interacting with Toll-like receptors (tlrs), it regulates genes such as NF-kappab, mitogen-activated protein kinases (MAPK), activator proteins 1 (AP-1), peroxisome proliferators-activated receptor gamma (PPAR gamma), Janus kinase signal transducers and activation of transcription (JAK/STAT) pathways, and inhibits the formation of the NALP3 inflammasome.	Historically employed for managing discomforts like pain and swelling; currently utilized in treating conditions such as osteoarthritis and certain types of cancers.	$C_{21}H_{20}O_6$.	53, 56, 91, 92
Ginger (Gingerols and Shogaols)	*Zingiber officinale* (rhizome), Family – Zingiberaceae	Inhibits phosphoinositide 3-kinases/akt and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κb). (PI3K/AKT), I-kappa-B kinase (IKK), and mitogen-activated protein kinases (MAPK); it also lowers the levels of pro-inflammatory cytokines like tumor necrosis, cyclooxygenase-2 (COX-2) expression, and indoleamine 2,3-dioxygenase (inos) activity.	Effective against arthritis symptoms like swelling and discomfort; comparable to celecoxib in certain studies.	$C_{17}H_{26}O_4$	65, 93

TABLE 2: NATURAL ANTI-INFLAMMATORY MODULATORS

Drug name	Biological source	Mechanism	Uses	Chemical structure	Ref.
Green Tea (Polyphenols)	*Camellia sinensis* (leaves and buds), Family – Theaceae	Functions as an antioxidant; inhibits inflammatory signals; promotes digestive well-being through probiotic actions.	Reduces swelling, strengthens defense mechanisms, and maintains harmony in digestive flora.	$C_{22}H_{18}O_{11}$	94, 95
Resveratrol (RV)	Found in *Vitis vinifera* (grape skin), *Polygonum cuspidatum* (Japanese knotweed), Family – commonly Vitaceae or Polygonaceous	Signalling pathways like NF-κb, ERK1/2, and induce inflammation-related genes.	Utilized for treating brain swelling, safeguarding kidneys against damage, and possibly enhancing outcomes in certain cancers through supplementary means.	$C_{14}H_{12}O_3$	96
Frankincense (Boswellia spp.)	Resin from Boswellia species, Family – Burseraceae	Inhibits leukotrienes, cyclooxygenases (COX-1/2), lipoxygenase (5-LOX); it also diminishes the presence of immune cells in tissues.	Beneficial for conditions such as osteoarthritis, asthma, psoriasis, multiple sclerosis, and cerebral edema.	$C_{20}H_{32}O$	83
Capsaicin	Found in Capsicum species (chili peppers), Family – Solanaceae	Prevents trigeminal nerve pain by decreasing blood vessel leakage, regulates neurotransmitters.	Mainly anodyne; employed for headaches, cardiac wellness, and neurological inflammation.	$C_{18}H_{27}NO_3$	84, 97

TABLE 3: NATURAL ANTI-INFLAMMATORY MODULATORS

Drug name	Biological source	Mechanism	Uses	Chemical structure	Ref.
Quercetin	*Allium cepa* (onion) peel and outer layer, Family – Amaryllidaceae	Blocks NF-kappab, p38 MAP kinase ½, c-Jun N-terminal kinases ½; decreases fat storage and swelling.	Promotes blood vessel strength, decreases heart disease likelihood, and functions as an anti-oxidant.	$C_{15}H_{10}O_7$	85
Pycnogenol (French Maritime Pine Bark Extract)	Extract of *Pinus pinaster*, Family – Pinaceae	The antioxidant blocks matrix metalloproteinases by binding to collagen, thereby stabilizing connective tissues.	Utilized in promoting tissue regeneration, managing immune responses, and mitigating free radical damage.	$C_{30}H_{26}O_{12}$	86
Cannabidiol (CBD)	Extracted from *Cannabis sativa*, Family – Cannabaceae	Inhibits MMP-9, TNF-α; modulates cytokines; suppresses immune overactivation.	Applied in arthritis, neuroinflammation, and immune-related disorders.	$C_{21}H_{30}O_2$	88
Devil's Claw (Harpagophytum procumbens)	*Harpagophytum procumbens* (tuberous root), Family – Pedaliaceae	Inhibits COX-1/2 and nitric oxide production.	Utilized in treating arthritis symptoms, ulcers, and inflamed disorders.	$C_{24}H_{30}O_{11}$	89, 90

Inflammatory Modulators Risk and Side Effects: The gastrointestinal mucosa, cardiovascular system, hepatic system, renal system, and hematologic system are all known to be harmed by NSAIDs. The suppression of COX-1, which stops the synthesis of prostaglandins that shield the gastric mucosa, might be the cause of the negative consequences in the stomach. Patients with a history of peptic ulcers are more prone to sustain harm. The usage of COX-2 selective NSAIDs is a less hazardous alternative because it is COX-1 specific [98]. Because COX-1 and COX-2 promote prostaglandin synthesis, which affects renal hemodynamics, there are unfavorable effects on the kidneys. In patients with normal renal function, lowering prostaglandin synthesis does not pose any significant concerns; however, in patients with renal failure, prostaglandins become very important and can create problems when suppressed with NSAIDs. Among the potential consequences include renal papillary necrosis, nephrotic syndrome/interstitial nephritis, acute renal failure, and fluid and electrolyte deficits [99]. NSAID use might increase the chance of

cardiovascular side effects, such as atrial fibrillation, thromboembolic events, and MI. The NSAID with the most documented increase in adverse cardiovascular events appears to be diclofenac [100]. Hepatic side effects are less likely; hospitalization for liver-related reasons is extremely rare, as is the risk of hepatotoxicity (higher aminotransferase levels) linked with NSAIDs.

New Trends in Healthcare:

Personalized Healthcare: You might have heard about the buzz around personalized healthcare, which is all about tailoring medical treatments to each individual's specific needs and traits. It's often confused with precision medicine, but they aren't exactly the same [101]. The term personalized medicine first popped up in an article by a Canadian doctor back in 1971, where he stressed treating patients as unique individuals rather than just focusing on their diseases. Fast forward to the late '90s, when the Human Genome Project made significant strides, and suddenly, personalized medicine was the talk of the town. The Wall Street Journal even featured a piece titled New Era of Personalized Medicine: Targeting Drugs for Each Unique Genetic Profile back in April 1999, putting this fresh concept on the map [102]. Nowadays, personalized medicine involves making key decisions regarding disease prevention, diagnosis, and treatment based on a person's genetic makeup. It's revolutionary in how we view and handle healthcare today [103].

Nanotechnology in Medicine: Let's talk about nanotechnology, which uses tiny materials like nanoparticles and nanorobots in medicine. This field, known as nanomedicine, plays a significant role in diagnosing and treating diseases. Often, drugs don't perform well in the body because they don't dissolve or circulate effectively. Nanotechnology can help solve these issues. By designing drugs at a nanoscale, scientists can tackle challenges such as poor drug absorption, unwanted side effects, and the need for higher doses [104]. The beauty of nanotechnology lies in its ability to make drug delivery easier, less toxic, and more effective. It essentially helps in delivering medications directly to the right parts of the body, letting them do their job without affecting other areas. Some advanced drug systems are crafted to release their contents in response to specific triggers, making treatment much more efficient [105].

Epigenetic Controls: Now, let's dive into epigenetics. This fascinating area focuses on how certain chemical changes can impact gene expression without altering the underlying DNA sequence. Researchers have proposed that the various chemical modifications, known as epigenetic changes, create a sort of code that finely tunes the structure of our DNA [106]. For example, when specific proteins stick to DNA or histones, they can either promote or suppress gene activity. It's been found that DNA methylation, which often occurs in gene promoter regions, is particularly important active genes usually have less methylation, while silenced genes tend to be hyper-methylated. This whole process can dictate a cell's behavior and identity, which helps explain why different cell types, like skin or nerve cells, function so differently despite sharing the same DNA [107].

The Microbiome's Role: Did you know that the bacteria living in our gut play a vital role in our immune system? Research shows that mice without these gut bacteria (known as germ-free mice) face a variety of immune issues [108]. For example, they lack certain types of immune cells like Th17 and have a reduced ability to fight off infections. Interestingly, certain types of beneficial gut bacteria, like Clostridium, can help boost these immune cells [109]. They trigger the production of critical signalling molecules that promote the development of immune cells capable of defending against diseases like cancer. In fact, some studies have shown that the right mix of gut bacteria can even enhance the effectiveness of cancer treatments. As we learn more about these tiny allies, understanding their role in our health becomes increasingly important [110].

Stem Cell Therapy: Stem cells hold huge promise for treating a wide range of diseases. The ability of mesenchymal stem cells (MSCs), often referred to as mesenchymal stromal cells, to differentiate into many cell types, including fat, bone, and cartilage, makes them special [111]. They're easy to find gathered from various tissues and are known for being pretty safe to use without serious ethical concerns. These cells don't just sit around; they

actively help heal the body through their ability to send important signals to other cells, reduce inflammation, and support new blood vessel growth. They're currently investigation for treating conditions ranging from diabetes to heart disease and autoimmune illnesses. Even though we still have many questions about how best to use MSCs, their potential as a tool for cell therapy is undeniable [112].

Patents:

TABLE 4: RECENT PATENTS ON INFLAMMATORY MODULATORS

Patent Name	Approved by / Published	Description
Benzimidazoles as Modulators of IL-17	U.S. Patent Application US 20250122181 A1, BeiGene Ltd	Small-molecule benzimidazole compounds that inhibit IL-17A; used for psoriasis, RA, MS, allergies
Small Molecule IL-17A Modulators	U.S. Patent Application US 20250154318 A1, BeiGene Ltd	Fused bicyclic compounds that reduce IL-17 activity; used for autoimmune and inflammatory diseases
Methods of Treatment of Inflammation-Related Condition Using Pluripotent Anti-inflammatory and Metabolic Modulators	U.S. Patent No. 12,280,029 (Granted), Institut Pasteur de Montevideo	Metabolic and anti-inflammatory modulators for treating inflammation disorders
Pluripotent Anti-inflammatory and Metabolic Modulator (Application)	U.S. Patent Application US 20250099411 A1, Institut Pasteur	Describes dosing and therapeutic use for inflammation, obesity
GPR35 Agonist Compounds	International Application WO 2022224212 A1	GPR35 agonists for IBD, IBS, ulcerative colitis, Crohn's disease
GPR35 Modulators	U.S. Patent Application US 20210380590, Prometheus Biosciences Inc.	GPR35 receptor modulators used for inflammatory bowel disease (IBD)

Measuring Wound Healing: Wound contraction and macroscopic appearance were the two factors evaluated for excision wound healing. In order to assess the macroscopic appearance and wound contraction, the skin wound area was measured and photographed on days 0, 7, 14, and 21 after the damage [113, 114]. A digital camera (Sony Cybershot, Japan) was used to take pictures, and a digital calliper was used to measure the wounds [115].

CONCLUSION: Inflammation is a critical and tightly regulated process in wound healing, governed by cytokines, chemokines, cellular receptors, and key signalling pathways such as MAPK, PI3K/AKT, TGF-β, NF-κB, and JAK/STAT. Balanced inflammatory responses promote effective tissue repair, whereas dysregulation leads to delayed healing and chronic inflammatory conditions. Natural anti-inflammatory agents, including curcumin, ginger, resveratrol, and quercetin, demonstrate multi-targeted therapeutic potential with fewer adverse effects compared to conventional drugs. Advances in molecular targeting, nanotechnology, and personalized medicine offer promising strategies to enhance wound healing outcomes. A deeper understanding of inflammatory modulators is essential for developing safer and more effective therapeutic interventions.

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