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Review Article

Inflammation And Anti-Inflammatory Therapeutics: Molecular Mechanisms, Clinical Burden, Therapeutic Limitations, And Emerging Safer Alternatives

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ABSTRACT

Inflammation is a tightly regulated biological response that protects the host, clears injurious stimuli, and restores tissue homeostasis, yet its dysregulation underlies a large share of acute and chronic human disease. This review consolidates current understanding of the molecular architecture of inflammation, spanning pattern-recognition receptor signalling, cellular and chemical mediators, and the intracellular cascades (NF-κB, MAPK, JAK–STAT, and the NLRP3 inflammasome) that convert an initiating stimulus into a coordinated inflammatory programme. It examines the clinical footprint of inflammation, using C-reactive protein as a representative biomarker linking systemic inflammation to cardiovascular disease, type-2 diabetes, neurodegeneration, renal failure, and rheumatoid arthritis, and summarises the substantial and unevenly distributed global burden of immune-mediated inflammatory diseases. Conventional pharmacological strategies — NSAIDs, corticosteroids, DMARDs, biologic agents, and JAK inhibitors — are reviewed alongside their well-documented gastrointestinal, renal, cardiovascular, immunological, and economic costs, which together constrain long-term management. Against this backdrop, the review surveys plant-derived anti-inflammatory agents (curcumin, gingerols, eugenol, aloe vera constituents, epigallocatechin gallate, and Portulaca oleracea phytochemicals) as multi-targeted, comparatively safer alternatives, while acknowledging persistent barriers of bioavailability, standardisation, and clinical validation. Finally, it considers emerging strategies — nanocarrier-based delivery, rational combination regimens, biomarker-guided personalised therapy, and computational/AI-assisted drug discovery — that may narrow the gap between efficacy and safety. Taken together, the evidence indicates that no single therapeutic class offers both maximal efficacy and minimal risk, and that future progress will depend on integrating mechanistic pharmacology with safer delivery platforms and individualised treatment selection.

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INTRODUCTION

1.1 Definition and Historical Perspective

Inflammation is classically understood as the reaction of vascularised living tissue to harmful stimuli — pathogens, physical injury, or chemical irritants — and forms a core component of the innate, non-specific arm of host defence [1,2]. Biochemically, it can also be viewed as a state of heightened tissue catabolism: the accumulation of low-molecular-weight breakdown products raises local osmotic pressure, drawing fluid into the tissue and producing the oedema that is one of its most visible hallmarks [3].

Awareness of inflammatory disease is ancient. Egyptian medical papyri dating to roughly 1650 BCE already record descriptions consistent with tissue injury and its visible sequelae [4]. Centuries later, the Roman encyclopaedist Aulus Cornelius Celsus, writing in his treatise De Medicina in the first century CE, distilled the clinical presentation of inflammation into four cardinal signs — rubor (redness), calor (heat), tumor (swelling), and dolor (pain) — arising respectively from local vasodilation, increased regional blood flow and metabolism, fluid and cellular accumulation, and stimulation of sensory nerve endings by inflammatory mediators [5,6]. A fifth sign, functio laesa (loss of function), is traditionally attributed to Galen in the second century CE, although historians note that this attribution may be a later retrospective addition rather than a documented original contribution [7].

Between antiquity and the modern era, explanations of inflammation were dominated by the Hippocratic humoral theory, which framed disease as an imbalance among four bodily fluids [4]. This view persisted for well over a millennium until autopsy-based pathology — beginning with Giovanni Morgagni's organ-level correlations in 1761 and maturing through nineteenth-century histology — relocated disease from diffuse humoral imbalance to discrete tissue and, eventually, cellular lesions [4,6]. Rudolf Virchow's cellular pathology, published in 1858 and encapsulated in the principle omnis cellula e cellula ("every cell arises from another cell"), established the cell as the fundamental unit of both physiology and pathology and reframed inflammatory diseases, including atherosclerosis, as processes originating in cellular and vascular derangement [8]. Alongside Virchow, Julius Cohnheim and Carl Weigert extended the microscopic study of vascular and leukocytic changes during inflammation. Late in the same century, Ilya Metchnikoff's work on phagocytosis and Paul Ehrlich's studies of antibodies and complement established that much of the tissue damage seen in infection arises from the host's own immune response rather than from direct pathogen action [9].

The twentieth century added a biochemical dimension to this cellular framework. The identification of cytokines, complement components, and reactive oxygen species clarified that immune cells cause tissue injury largely through secreted molecules rather than by direct contact alone [10], and more recent work has implicated regulated cell-death pathways — apoptosis, necroptosis, and pyroptosis — in shaping how inflammation initiates and resolves [11]. Discovery of the prostaglandins in the 1930s by Ulf von Euler, followed by elucidation of their arachidonic-acid/cyclooxygenase biosynthetic pathway in the 1960s–70s and Sir John Vane's demonstration that aspirin-like drugs act by inhibiting prostaglandin synthesis, provided the molecular rationale for NSAID pharmacology and earned Vane, Bengt Samuelsson, and Sune Bergström the 1982 Nobel Prize in Physiology or Medicine [12]. Thus, the understanding of

inflammation has evolved from a purely descriptive clinical phenomenon into a multi-layered biological process involving receptor recognition, cellular recruitment, chemical signalling, and regulated cell death — the mechanistic layers addressed in Section 2.

1.2 Acute versus Chronic Inflammation

Acute inflammation is typically studied through models of microbial infection, in which monocytes are recruited to the injured or infected site after an initial wave of neutrophil infiltration, a process that can continue for several days [13]. Infection with Listeria monocytogenes, for example, drives strong monocytosis and Toll-like-receptor-dependent monocyte production in the bone marrow, leading to $CCR2^{+}$ classical monocyte recruitment that contributes both to pathogen clearance and to initiation of adaptive immunity [14,15,16]. This recruitment is coordinated chiefly by the chemokines CCL2 and CCL7 acting on bone-marrow monocytes [17,18].

Chronic inflammation, in contrast, persists over extended periods and underlies diseases such as atherosclerosis, in which lipid deposition within the arterial wall attracts monocytes that differentiate into macrophages and accumulate lipid to become foam cells within the developing plaque [19]. Both classical and non-classical monocyte subsets are recruited into plaques through chemokine-receptor signalling involving CCR2, CCR5, and CX3CR1 [20], and hypercholesterolaemia-associated monocytosis in animal models correlates with plaque burden and cardiovascular risk [21,22,23].

Materials and Methods

This review was compiled through a structured, non-systematic literature search of PubMed, Scopus, and Google Scholar, using combinations of the terms “inflammation,” “NF-κB,” “NLRP3 inflammasome,” “NSAIDs,” “corticosteroids,” “biologic therapy,” “JAK inhibitors,” and “plant-derived anti-inflammatory agents,” restricted primarily to peer-reviewed articles published in English. Reference lists of retrieved articles were hand-searched for additional relevant sources. Preclinical, clinical, and epidemiological studies were included where they contributed mechanistic insight, clinical relevance, or comparative safety data; conference abstracts and non-peer-reviewed sources were excluded except where no peer-reviewed alternative was available.

2. Molecular Mechanisms of Inflammation

The inflammatory response is initiated by receptor-mediated recognition of danger signals, propagated by cellular and chemical mediators, and executed through a small number of convergent intracellular signalling pathways. This section addresses each layer in turn; Figure 1 summarises how the components discussed in Sections 2.1–2.5 fit together.

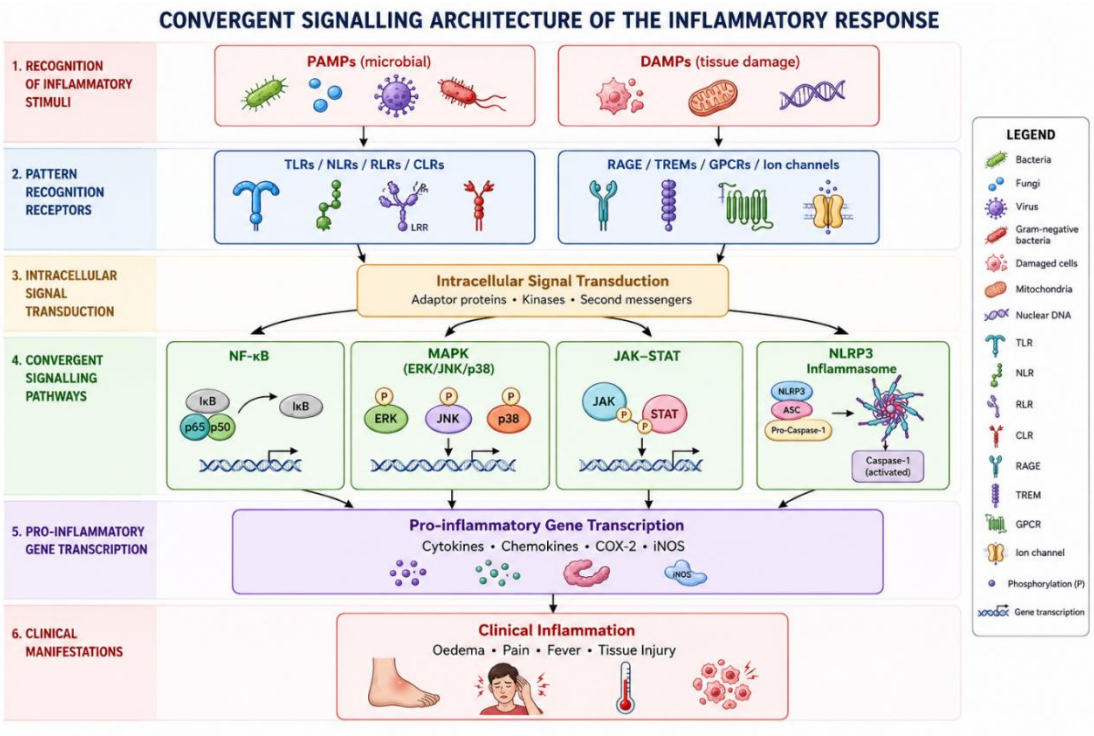

Figure 1. Convergent signalling architecture of the inflammatory response: PAMP/DAMP recognition converges, via NF-κB, MAPK, JAK–STAT, and NLRP3 inflammasome signalling, on pro-inflammatory gene transcription and the clinical manifestations of inflammation.

2.1 Recognition of Inflammatory Stimuli

Pathogen- and Damage-Associated Molecular Patterns

Innate immune cells detect microbial "non-self" through germline-encoded pattern recognition receptors (PRRs) that recognise conserved pathogen-associated molecular patterns (PAMPs) shared across microbial classes [24]. A parallel surveillance system recognises damage-associated molecular patterns (DAMPs) — endogenous molecules such as nucleic acids, proteins, ions, and metabolites that are normally sequestered or inert but become immunostimulatory once their location, concentration, or chemical state changes following cellular stress or injury [25]. Both PAMPs and DAMPs converge on classical PRR families, including Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and C-type lectin receptors (CLRs), while DAMPs are additionally sensed by non-PRR receptors such as the receptor for advanced glycation end-products (RAGE), TREMs, selected G-protein-coupled receptors, and ion channels [26,27]. Table 1 summarises representative PRR families, their cellular localisation, and their principal ligands.

Table 1. Representative pattern recognition receptor (PRR) families and their ligands.

PRR family	Receptor	Cellular localisation	Representative ligand	Origin of ligand
TLR	TLR1	Plasma membrane	Triacyl lipoprotein	Bacteria
TLR	TLR2	Plasma membrane	Lipoprotein	Bacteria, viruses, parasites, self
TLR	TLR3	Endolysosome	dsRNA	Virus

TLR	TLR4	Plasma membrane	LPS	Bacteria, viruses, self
TLR	TLR5	Plasma membrane	Flagellin	Bacteria
TLR	TLR6	Plasma membrane	Diacyl lipoprotein	Bacteria, viruses
TLR	TLR7 (human TLR8)	Endolysosome	ssRNA	Virus, bacteria, self
TLR	TLR9	Endolysosome	CpG-DNA	Virus, bacteria, protozoa, self
RLR	RIG-I	Cytoplasm	Short dsRNA, 5′-triphosphate dsRNA	RNA/DNA viruses
RLR	MDA5	Cytoplasm	Long dsRNA	RNA viruses
NLR	NOD1 / NOD2	Cytoplasm	iE-DAP / MDP	Bacteria
CLR	Dectin-1 / Dectin-2	Plasma membrane	β-Glucan	Fungi
Non-PRR DAMP receptor	RAGE	Plasma membrane	HMGB1, AGEs, S100 proteins	Self (damaged tissue)

TLR, Toll-like receptor; RLR, RIG-I-like receptor; NLR, NOD-like receptor; CLR, C-type lectin receptor; RAGE, receptor for advanced glycation end-products. Adapted from Cao [26] and Hudson & Lippman [28]

.RAGE illustrates how a single DAMP receptor can serve simultaneously as a disease biomarker and a druggable target. Genetic variants in RAGE, including the Gly82Ser coding polymorphism and two promoter variants, have been linked to chronic obstructive pulmonary disease and cardiovascular risk [29,30,31], while its soluble form (sRAGE) is inversely correlated with cardiovascular disease and several inflammatory states, acting as a natural ligand decoy [32,33,34]. Because RAGE-knockout mice are developmentally normal — and in aged-mouse studies appear to live longer than wild-type littermates [35] — RAGE blockade is considered a comparatively low-risk therapeutic strategy, and small-molecule inhibitors targeting either its extracellular ligand-binding domain or intracellular signalling region are under active development [36].

2.2 Cellular Mediators of Inflammation

Innate immune defence is carried out chiefly by macrophages, neutrophils, mast cells, and dendritic cells, which respond non-specifically to injury, complemented by antigen-specific T- and B-lymphocytes.

Macrophages, derived from circulating monocytes and resident tissue populations, are activated at sites of injury where they clear debris and secrete cytokines, chemokines, and growth factors that both drive and later resolve the inflammatory response. A key regulatory function is the clearance of apoptotic neutrophils; when this clearance fails, neutrophils undergo necrosis and release their toxic contents, perpetuating tissue damage and pushing the response toward chronicity [37]. Because of their longevity and re-activation potential, macrophages are considered at least as important as neutrophils in sustaining chemically induced or persistent tissue injury [38,39].

Table 2. Macrophage-driven cellular events across the phases of inflammation and tissue repair [37].

Phase	Key Cellular Events	Outcome

Injury	Tissue damage triggers release of danger signals and recruitment of neutrophils and monocytes/macrophages from the blood	Initiation of the inflammatory response
Inflammation	Neutrophils and activated macrophages accumulate at the site; macrophages phagocytose tissue debris and apoptotic neutrophils	Determines whether resolution or chronicity follows
Failure to resolve	Apoptotic neutrophils that are not cleared undergo necrosis, spilling their toxic contents	Chronic inflammation and progressive tissue damage
Successful resolution	Macrophages clear debris efficiently and signal recruitment of fibroblasts	Tissue repair and remodelling

Neutrophils constitute the first cellular line of defence; roughly 55–60% of bone-marrow output is devoted to their production, generating on the order of 100 billion neutrophils daily in a healthy adult and underscoring their centrality to antimicrobial defence. In chronic inflammatory states, however, neutrophils are frequently implicated in tissue damage, and autophagy has emerged as an important, still incompletely characterised, regulator of neutrophil differentiation, phagocytosis, cytokine release, degranulation, and extracellular trap formation [40].

Mast cells reside in essentially all vascularised tissues and, since their description in 1863, have been recognised chiefly for driving IgE-mediated allergic conditions such as asthma, allergic rhinitis, and urticaria. It is now appreciated that they also generate protective innate responses to bacterial and viral challenge and shape lymph-node architecture during adaptive immune induction, functioning as sentinel cells that couple pathogen sensing to downstream immunity [41,42,43].

Dendritic cells and T-lymphocytes complete the cellular circuit linking innate recognition to adaptive immunity: dendritic cells capture and present antigen to prime T-cell responses, while T-lymphocytes — through helper, cytotoxic, and regulatory subsets — determine the character, magnitude, and eventual resolution of the adaptive inflammatory response.

2.3 Chemical Mediators of Inflammation

Alongside cellular effectors, a family of small-molecule and peptide mediators shapes the vascular and functional changes of inflammation.

Histamine, released mainly from mast cells and basophils, is a vasodilator and smooth-muscle constrictor that increases vascular permeability, mucus secretion, and gastric acid output; through H2 receptors it can also exert anti-inflammatory feedback, including inhibition of neutrophil lysosomal enzyme release and activation of suppressor T-lymphocytes [44,45].

Bradykinin and related kinins (kallidin, met-lys-bradykinin) are generated proteolytically from kininogens by plasma and tissue kallikreins and produce smooth-muscle contraction, vasodilation, and increased capillary flow. Tissue kallikreins, which are biochemically distinct from plasma kallikrein, act on both high- and low-molecular-

weight kininogen pools and are comparatively resistant to protease-inhibitor blockade, making the tissue kinin pathway an important, partly independent contributor to local inflammatory oedema [46,47].

Prostaglandins, principally PGD2 in mast-cell-driven reactions, are generated from arachidonic acid via the cyclooxygenase pathway and modulate smooth-muscle tone, vascular permeability, pruritus, pain, and platelet function [48,49,50]. Leukotrienes (LTC4, LTD4, LTE4 — historically termed the slow-reacting substance of anaphylaxis) are produced by mast cells, basophils, eosinophils, neutrophils, and monocytes and reproduce many of histamine's biological effects, apparently in part through receptor-coupled G-protein signalling [51].

Cytokines released by mast cells and other leukocytes — including IL-1, IL-2, IL-4, IL-5, IL-6, TNF-α, and GM-CSF — orchestrate the late phase of allergic and inflammatory reactions by modulating macrophages, T- and B-lymphocytes, and eosinophils; IL-4 and TNF-α, for example, jointly up-regulate IgE receptor expression on antigen-presenting cells, while IL-5 supports eosinophil differentiation and survival [52,53,54].

2.4 Major Intracellular Signalling Pathways

2.4.1 NF-κB Pathway

Nuclear translocation of cytoplasmic NF-κB/Rel complexes is central to inflammation because it drives transcription of pro-inflammatory genes in response to pathogen- or stress-related stimuli [55]. NF-κB is markedly activated at inflamed sites in diverse diseases: in rheumatoid arthritis its subunits p50 and p65 are enriched in synovial lining and sublining mononuclear cells, correlating with elevated IL-1, IL-6, IL-8, and TNF-α production relative to osteoarthritis controls [55]; in asthmatic bronchial epithelium, its nuclear localisation parallels expression of cytokines, chemokines, iNOS, and COX-2 [56]; in Helicobacter pylori-associated gastritis, the density of NF-κB-positive gastric epithelial cells tracks disease severity; and in inflammatory bowel disease, antisense blockade of p65 in lamina propria macrophages reduces pro-inflammatory cytokine output [57]. NF-κB activation also contributes to neurodegenerative and atherosclerotic inflammation [58,59], and its central, disease-spanning role makes it one of the most heavily pursued targets for novel anti-inflammatory agents.

2.4.2 MAPK Pathway

Mitogen-activated protein kinase (MAPK) cascades are highly conserved eukaryotic signalling modules that integrate diverse inputs — hormones, growth factors, cytokines, GPCR ligands, TGF-β family signals, PAMPs/DAMPs via PRRs, and environmental stress — into coordinated transcriptional, translational, cell-cycle, apoptotic, and differentiation responses [60,61]. Three MAPK sub-families are of particular relevance to inflammation.

The extracellular signal-regulated kinases (ERK1/2) were the first mammalian MAPKs identified and are classically engaged by mitogenic and insulin signalling through the Ras–Raf–MEK cascade [62,63]. The c-Jun N-terminal kinases (JNKs), first purified as a c-Jun-phosphorylating activity from cycloheximide-treated liver, are activated not only by mitogens but robustly by environmental stress (heat shock, ionising radiation, oxidants), genotoxins, ischaemia–reperfusion injury, mechanical shear, vasoactive peptides, pro-inflammatory cytokines, and PAMPs/DAMPs [64,65]. p38 MAPK, identified as a stress- and IL-1-activated kinase closely related to the yeast osmosensor Hog1p, phosphorylates and activates MAPKAP kinase-2

(MK2), which in turn regulates the small heat-shock protein Hsp27 [66,67].

2.4.3 JAK–STAT Pathway

The Janus kinase–signal transducer and activator of transcription (JAK–STAT) axis transmits signals from membrane cytokine receptors to the nucleus, governing proliferation, differentiation, and apoptosis [68]. Its four kinase members — JAK1, JAK2, JAK3, and TYK2 — are differentially expressed across tissues and mediate immune modulation, antiviral defence, and haematopoiesis, but dysregulating mutations can cause severe immunodeficiency or malignant transformation [69,70]. Because the pathway sits directly downstream of numerous pro-inflammatory cytokine receptors, it has become one of the principal targets of the newest generation of oral anti-inflammatory drugs, the JAK inhibitors discussed in Section 4.5 [71,72].

2.4.4 NLRP3 Inflammasome

The NLRP3 inflammasome is an intracellular multiprotein platform that activates caspase-1 and drives secretion of IL-1β and IL-18 in response to infection and cellular damage; its aberrant activation has been implicated in cryopyrin-associated periodic syndromes, Alzheimer's disease, type-2 diabetes, and atherosclerosis [73,74,75]. Assembly is triggered by a heterogeneous set of signals — ionic flux, mitochondrial dysfunction, reactive-oxygen-species generation, and lysosomal damage — the precise integration of which remains incompletely understood [76]. Alongside NLRP3, several other PRR family members (NLRP1, NLRC4, AIM2, pyrin, and additionally NLRP2, NLRP6, NLRP7, NLRP12, and IFI16) can also nucleate inflammasomes, typically recruiting the adaptor ASC to activate pro-caspase-1 [77,78].

2.5 The Cytokine Network in Acute and Chronic Inflammation

Cytokines are secreted polypeptides that largely determine the composition of the inflammatory infiltrate, the activation state of resident and recruited cells, and the systemic response to injury. Most are pleiotropic and act locally or systemically in autocrine or paracrine fashion, and they operate within extensive networks characterised by both synergistic and antagonistic cross-talk [79]. Acute inflammation is dominated by IL-1, TNF-α, IL-6, IL-11, IL-8 and related chemokines, G-CSF, and GM-CSF, whereas chronic inflammation additionally recruits cytokines governing humoral immunity (IL-4, IL-5, IL-6, IL-7, IL-13) and cellular immunity (IL-1, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, interferons, TGF-β, and TNF-α/β), with several mediators — IL-1 chief among them — contributing to both phases. Table 3 summarises this distribution.

Table 3. Principal cytokines associated with acute versus chronic inflammation.

Phase	Cytokines / chemokines
Acute inflammation	IL-1, IL-6, IL-8, IL-11, IL-16, IL-17, TNF-α, eotaxin, G-CSF, GM-CSF
Shared (acute + chronic)	IL-1, IL-6, IL-11, IL-17, TNF-α, eotaxin, GM-CSF
Chronic inflammation (humoral)	IL-4, IL-5, IL-6, IL-7, IL-13
Chronic inflammation (cellular)	IL-2, IL-3, IL-9, IL-10, IL-12, IL-14, IL-15, interferons, TGF-β, TNF-β

Several mediators (e.g., IL-1, IL-6, TNF-α) contribute to both phases. Adapted from Dinarello [79].

TNF-α and TNF-β share a common receptor family and overlapping biology. TNF-α (cachectin), a 17-kDa trimeric product of activated macrophages, monocytes, fibroblasts, mast cells, and selected T and NK cells, induces fever both directly (via hypothalamic PGE2 synthesis) and indirectly (via IL-1 release), stimulates synovial collagenase and PGE2 production implicated in rheumatoid joint damage, and — together with IL-1 — drives hepatic acute-phase protein synthesis via secondary induction of IL-6 [80]. IL-1α and IL-1β, cloned in 1984 from a shared chromosomal locus, exert closely related pro-inflammatory effects that can be antagonised by the naturally occurring IL-1 receptor antagonist (IL-1Ra), which competes for IL-1 receptor binding [79,81]. IFN-γ-inducing factor (IGIF), later renamed IL-18, potentiates IFN-γ production, supports TH1 differentiation, and augments GM-CSF while suppressing IL-10 [82,83].

Counter-regulatory cytokines temper these pro-inflammatory signals. IL-11, a functional homologue of IL-6 produced by bone-marrow stromal cells and fibroblasts, supports acute-phase protein secretion, T-cell-dependent B-cell antibody production, and platelet production [84,85]. IL-6 itself — known historically under synonyms such as interferon-β2 and B-cell stimulatory factor 2 — drives B-cell maturation into antibody-secreting plasma cells and T-cell activation, while also providing negative feedback on TNF production; its dysregulated overproduction is documented in thyroiditis, type-1 diabetes, rheumatoid arthritis, systemic sclerosis, and several neoplasms [86,87]. TGF-β, existing as three isoforms acting through a shared high-affinity receptor, inhibits T- and NK-cell proliferation, recruits monocytes to injury sites when released from degranulating platelets, and promotes extracellular-matrix deposition; sustained expression can tip toward pathological fibrosis, and in animal models TGF-β synergises with TNF-α to accelerate collagen-induced arthritis [88,89,90].

3. Clinical Significance and Global Burden of Inflammatory Disease

3.1 C-Reactive Protein as a Clinical Biomarker of Systemic Inflammation

C-reactive protein (CRP), an acute-phase protein synthesised by hepatocytes under cytokine stimulation, is the most widely used laboratory marker of both acute infection and chronic low-grade inflammation [91,92,93]. Persistently elevated CRP is associated with cardiovascular disease and atherosclerosis [94], and altered CRP levels have also been reported in hemorrhagic stroke, Alzheimer's disease, and Parkinson's disease [95,96].

In cardiovascular disease specifically, high-sensitivity CRP (hs-CRP) assays permit detection of subtle vascular inflammation and are used to stratify coronary artery disease risk; elevated hs-CRP accompanies plaque development and independently predicts myocardial infarction, ischaemic stroke, and sudden cardiac death [97,98]. In type-2 diabetes mellitus, CRP together with TNF-α and IL-6 contributes to insulin resistance, and elevated CRP correlates with both disease risk and glycated haemoglobin (HbA1c) in elderly diabetic patients [99,100]. CRP has additionally been detected within Alzheimer's senile plaques and is associated with Parkinson's disease risk, severity, and prognosis [101,102]. In end-stage renal failure, inflammatory markers including CRP correlate with cardiovascular morbidity and mortality [103], and in rheumatoid arthritis, vascular inflammation contributes to accelerated atherosclerosis and elevated cardiovascular mortality [104].

3.2 Global Burden of Immune-Mediated Inflammatory Diseases

Immune-mediated inflammatory diseases (IMIDs) — including asthma, rheumatoid arthritis, inflammatory bowel disease, psoriasis, multiple sclerosis, atopic dermatitis, and type-1 diabetes — share dysregulated immune pathways and collectively impose a substantial global health burden. Epidemiological estimates put the affected population at roughly 67.58 million individuals worldwide, with an age-standardised incidence rate of 908.69 per 100,000 [105,106]. Despite the availability of biologics and targeted small molecules, persistent disease activity, incomplete remission, and long-term complications keep the disease burden high, and chronic management imposes considerable economic and health-system strain [107,108].

Trend data suggest a more nuanced picture: while age-standardised mortality and disability-adjusted life years (DALYs) attributable to IMIDs have generally declined, incidence continues to vary substantially by disease and region. In 2021, the global age-standardised incidence rate was estimated at 823.28 per 100,000, with asthma the leading contributor followed by atopic dermatitis and psoriasis — indicating improving survival but persistently high disease occurrence [109]. Geographic and socioeconomic disparities are pronounced: lower socio-demographic-index regions tend to show higher mortality and DALYs, reflecting constrained healthcare access and delayed diagnosis, whereas higher-income regions report higher recorded incidence, likely reflecting more comprehensive diagnostic and surveillance capacity [110]. Projections to 2046 anticipate an overall decline in incidence, mortality, and DALYs, but persistent geographic inequality, underscoring the continued need for region-specific public-health strategies [109].

4. Conventional Anti-Inflammatory Therapies

NSAIDs remain among the most widely prescribed drug classes worldwide for their combined analgesic, antipyretic, and anti-inflammatory activity [111]. Their long-term use, however, carries well-characterised risk, motivating continued development of corticosteroids, DMARDs, biologic agents, and JAK inhibitors as alternative or complementary strategies. Table 4 provides a comparative overview of these five drug classes before each is discussed in turn.

Table 4. Comparative overview of conventional anti-inflammatory drug classes.

Class	Primary molecular target	Representative agents	Principal limiting toxicity
NSAIDs	COX-1 / COX-2	Ibuprofen, diclofenac, celecoxib	GI ulceration/bleeding; cardiovascular events with COX-2-selective agents
Corticosteroids	Glucocorticoid receptor → NF-κB / phospholipase A2	Prednisolone, dexamethasone, methylprednisolone	Immunosuppression, metabolic and adrenal effects with prolonged use

DMARDs	Folate metabolism (MTX); varied	Methotrexate, sulfasalazine, leflunomide	Hepatotoxicity, cytopenias, GI intolerance
Biologics — TNF inhibitors	TNF-α (soluble/membrane)	Etanercept, infliximab, adalimumab	Immunogenicity (anti-drug antibodies), infection risk
Biologics — IL-6 / IL-17 inhibitors	IL-6 or IL-17 signalling	Siltuximab, secukinumab, ixekizumab	Infection risk, infusion reactions, cytopenias
JAK inhibitors	JAK1/2/3, TYK2	Tofacitinib, baricitinib, upadacitinib	Viral reactivation (e.g., BK viraemia), over-immunosuppression at high dose

4.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Classification

NSAIDs are grouped chemically into salicylates (aspirin, sulfasalazine), para-aminophenol derivatives (paracetamol — though it has little true anti-inflammatory activity), indole/indene acetic acids (indomethacin, etodolac, sulindac), hetero-aryl acetic acids (diclofenac, ketorolac, tolmetin), aryl-propionic acids (ibuprofen, ketoprofen, naproxen, and related agents), anthranilic acids/fenamates (mefenamic acid), enolic acids/oxicams (piroxicam, meloxicam), alkanones (nabumetone), pyrazolidinediones (phenylbutazone), and diarylheterocyclic selective COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib) [112]. A parallel classification by COX selectivity distinguishes non-selective agents (ibuprofen, diclofenac, aspirin, naproxen) from moderately COX-2-preferential agents (celecoxib, meloxicam), strongly COX-2-selective agents (rofecoxib), and weak dual inhibitors (sodium salicylate, nabumetone), summarised in Table 5.

Table 5. Classification of NSAIDs by relative COX-1/COX-2 selectivity.

Group	Selectivity profile	Representative agents
1	Poorly selective — inhibits both COX-1 and COX-2	Ibuprofen, diclofenac, aspirin, piroxicam, naproxen
2	Preferential COX-2 selectivity (~5–50-fold)	Celecoxib, meloxicam, nimesulide, etodolac
3	Strongly COX-2 selective (>50-fold)	Rofecoxib, NS-398
4	Weak inhibitor of both isoforms	Sodium salicylate, nabumetone

Adapted from Antman et al. 112.

Mechanism of Action

All NSAIDs act by inhibiting cyclooxygenase (COX), the enzyme that converts membrane-derived arachidonic acid, via the unstable intermediates PGG2 and PGH2, into the primary prostaglandins (PGD2, PGE2, PGF2, PGI2) and thromboxane A2 [113,114]. COX-1 is constitutively expressed and subserves "housekeeping" functions including gastric cytoprotection, renal blood-flow regulation, and platelet aggregation, whereas COX-2 is highly inducible at inflamed sites by cytokines, hormones, growth factors, and hypoxia, and is also expressed by endothelial and several tumour cell types [115,116,117]. A splice variant, COX-3, was later identified but appears to lack meaningful prostaglandin-synthesising activity in human tissue [118,119]. Figure 2 depicts this cascade and the point at which NSAIDs intervene.

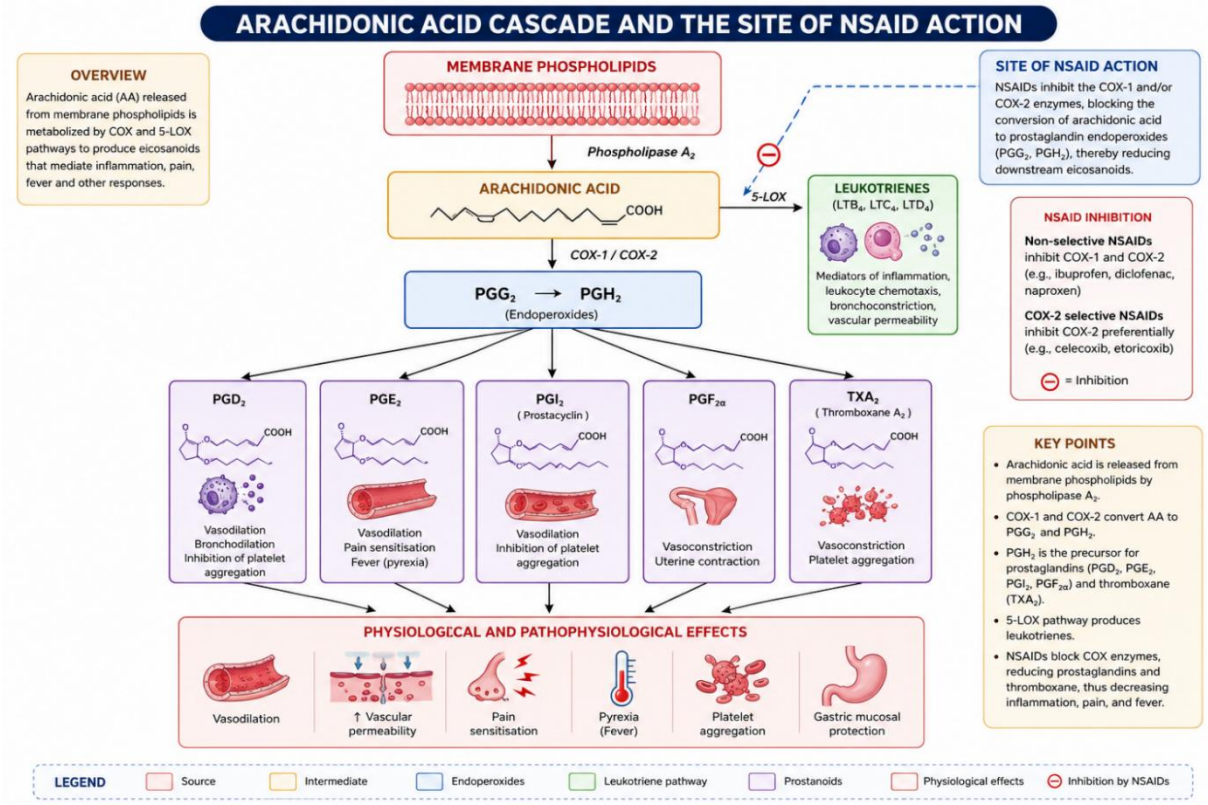

Figure 2. The arachidonic acid cascade. Phospholipase A2 liberates arachidonic acid from membrane phospholipids; the cyclooxygenase (COX-1/COX-2) branch yields prostaglandins and thromboxane, while the 5-lipoxygenase (5-LOX) branch yields leukotrienes. NSAIDs act by inhibiting COX-1/COX-2.

Therapeutic Benefits and Limitations

Reduced synthesis of vasodilatory prostaglandins (PGE2, PGI2) underlies the anti-inflammatory and analgesic actions of NSAIDs, while suppression of PGE2-mediated hypothalamic thermoregulatory signalling accounts for their antipyretic effect [120]. These benefits are offset by COX-1-dependent loss of gastric cytoprotection, producing gastrointestinal ulceration, bleeding, and perforation risk [121,122]. Selective COX-2 inhibitors were developed specifically to preserve efficacy while sparing the gastric mucosa; large trials (CLASS for celecoxib, VIGOR for rofecoxib) confirmed reduced GI complication rates relative to non-selective NSAIDs, although this advantage narrowed in patients co-prescribed low-dose aspirin [123,124].

4.2 Corticosteroids

Corticosteroids are divided into glucocorticoids, used for their anti-inflammatory and immunosuppressive activity, and mineralocorticoids, which govern salt and mineral balance [125]. Their anti-inflammatory action begins with induction of lipocortin-1, which suppresses phospholipase A2 and thereby blocks eicosanoid production at its source, while glucocorticoid–receptor complexes additionally inhibit promoter activity of pro-inflammatory genes and reduce cytokine secretion largely through restraint of NF-κB [126,127,128]. A single corticosteroid dose produces transient lymphocytopenia within hours through redistribution rather than destruction of circulating lymphocytes, while paradoxically inducing neutrophilia via bone-marrow release and reduced margination [127].

Methylprednisolone and dexamethasone illustrate the class's clinical range. In hospitalised COVID-19 patients, intravenous methylprednisolone pulse therapy reduced mortality and extended survival while lowering CRP and supporting platelet counts [129]; low-dose short-course regimens (1–2 mg/kg/day for 5–7 days) shortened hospital stay and reduced respiratory-support needs with a safety profile comparable to standard care [130]. Dexamethasone, available in numerous oral, injectable, and topical formulations, remains a reference agent for severe inflammatory and allergic conditions, with reported dose equivalence of roughly 6 mg dexamethasone to 32 mg methylprednisolone, though methylprednisolone's greater pulmonary tissue penetration has been associated with more favourable outcomes in some COVID-19 cohorts [129,131,132].

4.3 Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

Methotrexate (MTX), in clinical use since the 1980s, remains the anchor DMARD for rheumatoid arthritis owing to its efficacy, dosing flexibility, tolerability, and favourable safety-to-efficacy ratio, and current guidelines endorse it as first-line monotherapy or combination therapy in treatment-naïve patients [133,134]. A 13-year longitudinal study of 248 patients recorded a five-year continuation rate of 79%, with laboratory abnormalities in only 2.9 per 100 patient-years; of the 19% who discontinued, most did so for gastrointestinal or oral-ulcer adverse effects rather than lack of efficacy [135], and MTX has also demonstrated a survival benefit in rheumatoid arthritis [136].

Sulfasalazine, generally used in combination given its comparatively modest standalone efficacy, causes most of its toxicity — chiefly gastrointestinal and cutaneous effects accounting for over 25% of discontinuations — early in treatment, making long-term use relatively safe once tolerated; rare but serious risks include agranulocytosis (typically within the first six weeks), DRESS syndrome, and hepatotoxicity, warranting monthly monitoring initially and quarterly thereafter [137,138,139]. It is considered compatible with pregnancy and lactation, although temporary oligospermia warrants discontinuation in men three months before attempting conception [140,141].

Leflunomide, an oral pyrimidine-synthesis inhibitor with well-documented long-term efficacy, most commonly causes diarrhoea, elevated liver enzymes, alopecia, and rash, most of which are mild, transient, and resolve without discontinuation; long-term safety appears to improve with continued use, and discontinuation rates remain modest even in psoriatic arthritis [142,143].

4.4 Biologic Agents

Etanercept, the first biologic approved for rheumatoid arthritis, is an Fc-fusion soluble TNF receptor construct, distinct in binding behaviour from the chimeric monoclonal antibody infliximab and the fully human antibody adalimumab: infliximab binds both monomeric and trimeric TNF, whereas etanercept preferentially and less stably binds the active trimeric form [144,145,146]. These structural differences also translate into differing immunogenicity, summarised in Table 6.

Table 6. Differing risk of anti-drug antibody formation among anti-TNF biologics.

Agent	Structure	Reported antibody risk
Infliximab	Chimeric human–mouse monoclonal antibody	Highest concern; human anti-chimeric antibodies (HACA) can form against the murine variable region
Adalimumab	Fully humanised monoclonal antibody	Lower reported incidence of neutralising antibodies, attributed to fully human structure; human anti-human antibodies (HAHA) still reported in some patients
Etanercept	Fc-fusion soluble TNF receptor	No reported neutralising antibodies; non-neutralising antibody formation reported in ≈ 16% of patients

Adapted from Atzeni & Sarzi-Puttini [147].

IL-6 signals through a membrane receptor (IL-6R) that dimerises with the signal-transducing glycoprotein gp130; unusually, the soluble form of IL-6R facilitates rather than blocks signalling. Siltuximab, a chimeric anti-IL-6 antibody approved in 2014 for multicentric Castleman's disease, has also been investigated in several IL-6-driven malignancies and cachexia syndromes, though its use carries increased risk of upper respiratory infection and other adverse effects including cytopenias and hyperuricaemia [148,149,150].

IL-17 blockade with secukinumab improves outcomes in plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis relative to placebo or etanercept and received FDA approval in 2015; ixekizumab, a second anti-IL-17 antibody, followed for plaque psoriasis in 2016 [151,152].

4.5 Janus Kinase (JAK) Inhibitors

First-generation JAK inhibitors — ruxolitinib, tofacitinib, and baricitinib — block multiple JAK isoforms, whereas newer agents achieve greater selectivity: filgotinib, upadacitinib, and solcitinib are JAK1-selective; decernotinib and PF-06651600 target JAK3; and several compounds (BMS-986165, NDI-031232, NDI-031407, PF-06700841, SAR-20347) are TYK2-selective.

Tofacitinib, first studied for prevention of transplant rejection, proved efficacious but was associated with unacceptable over-immunosuppression — including BK viraemia, nephropathy, and post-transplant lymphoproliferative disease — likely reflecting the high doses (10–15 mg twice daily) and concurrent potent immunosuppressants used in those trials [153,154]. Baricitinib has shown activity in interferon-signature autoinflammatory conditions but has similarly required comparatively high doses (mean 8.5 mg/day) associated with BK viraemia [155,156]. Upadacitinib, engineered for JAK1-selective allosteric binding outside the ATP pocket shared with JAK2, is metabolised via CYP3A but can be co-administered with other CYP3A substrates including statins; in the BALANCE-1 and BALANCE-2 Phase II trials it

showed efficacy, in combination with MTX, in rheumatoid arthritis patients who had failed MTX or TNF-inhibitor therapy [157,158].

5. Limitations and Adverse Effects of Conventional Therapies

The efficacy of conventional anti-inflammatory drugs is counterbalanced by organ-specific and systemic toxicity that limits long-term use and motivates the search for safer alternatives.

5.1 Gastrointestinal Toxicity

NSAID-associated mucosal injury ranges from minor petechiae and erosions to ulceration with bleeding, perforation, or obstruction, occasionally fatal [159]. Minor epithelial breaks are usually repaired rapidly through "restitution," a division-independent migration of healthy epithelial cells across an intact basement membrane, but this repair capacity can be overwhelmed with continued COX-1 inhibition [160]. Risk rises sharply with age, dose, treatment duration, and prior peptic ulcer history, and elderly patients face a three- to six-fold increase in serious upper-GI events [161,162].

5.2 Renal Toxicity

An estimated 1–5% of NSAID users develop renal adverse effects, spanning acute deterioration of renal function, papillary necrosis, acute interstitial nephritis, hyperkalaemia, and sodium/fluid retention [163]. Acute effects are generally dose- and duration-dependent and reversible, but a history of acute renal injury increases susceptibility to chronic renal failure [164,165].

5.3 Cardiovascular Risk

Both selective COX-2 inhibitors and traditional non-selective NSAIDs carry increased cardiovascular hazard proportional to the degree of COX-2 inhibition. Placebo-controlled trials of celecoxib, rofecoxib, and valdecoxib recorded increased thrombotic events, and rofecoxib was ultimately withdrawn from the market after its association with myocardial infarction became clear [166,167,168]. Population-based studies and meta-analyses subsequently confirmed that this cardiovascular signal extends to some traditional NSAIDs, notably diclofenac, and that risk scales with dose potency [169,170,171].

5.4 Immunogenicity, Infection Risk, and Cost of Biologic Therapy

Anti-TNF biologics can provoke neutralising or non-neutralising anti-drug antibodies, with risk varying by molecular structure: the chimeric antibody infliximab is most prone to antichimeric antibody formation, the fully humanised adalimumab less so, while etanercept has not been reported to generate neutralising antibodies though non-neutralising antibody formation occurs in roughly 16% of patients [147]. Rituximab, a B-cell-depleting biologic, is associated with infusion reactions (fever, chills, rash, bronchospasm, hypotension) typically within the first infusion, mitigated by pretreatment with an antihistamine and paracetamol, and requires ongoing surveillance for infection, tuberculosis reactivation, and lymphoma [172]. Beyond immunological risk, the high acquisition cost of biologic agents remains a substantial barrier to equitable access and long-term adherence.

6. Herbal and Plant-Derived Anti-Inflammatory Agents

Given the toxicity profile of conventional anti-inflammatory drugs, considerable research attention has turned to plant-derived agents that act through multiple, often complementary, molecular targets while offering a comparatively favourable safety margin. The principal limitations of this class remain poor oral bioavailability, inconsistent standardisation of extracts, and a relative scarcity

of large, well-controlled clinical trials. Table 7 summarises the agents discussed below, together with olive leaf extract as a benchmark example of a standardised, mechanistically validated phytomedicine.

Table 7. Selected plant-derived anti-inflammatory agents and their proposed mechanisms.

Plant source	Principal active constituent(s)	Proposed anti-inflammatory mechanism
Curcuma longa (turmeric)	Curcumin	NF-κB inhibition; downstream suppression of cytokines, COX-2, iNOS
Zingiber officinale (ginger)	Gingerols	COX inhibition, reduced prostaglandin synthesis
Ocimum sanctum (holy basil)	Eugenol	Antioxidant activity; cytokine suppression
Aloe vera	Polysaccharides, glycoproteins, aloin	Bradykinin modulation; prostaglandin/cytokine suppression
Camellia sinensis (green tea)	Epigallocatechin gallate (EGCG)	Antioxidant activity; NF-κB and MAPK pathway interference
Portulaca oleracea (purslane)	α-Linolenic acid (omega-3), flavonoids, ascorbic acid	Competitive eicosanoid modulation; antioxidant scavenging
Olea europaea (olive leaf)	Oleuropein, hydroxytyrosol, tyrosol	Reduced TNF-α, IL-1β, COX-2 and NO; RBC/lysosomal membrane stabilisation (Fayez et al., 2023)

6.1 Curcuma longa (Turmeric)

The principal active constituent of turmeric rhizome is curcumin, a diarylheptanoid polyphenol. Its anti-inflammatory activity is attributed largely to inhibition of NF-κB activation, which curtails downstream transcription of pro-inflammatory cytokines, COX-2, and inducible nitric oxide synthase, positioning curcumin as a multi-target modulator of the same central pathway exploited by corticosteroids (see Section 2.4.1).

6.2 Zingiber officinale (Ginger)

Ginger rhizome contains gingerols, pungent phenolic compounds that inhibit cyclooxygenase activity in a manner mechanistically analogous to conventional NSAIDs, thereby reducing prostaglandin synthesis at the site of inflammation while apparently sparing the gastric-protective COX-1 pool to a greater extent than synthetic non-selective NSAIDs.

6.3 Ocimum sanctum (Holy Basil / Tulsi)

Holy basil leaves are a source of eugenol, a phenylpropanoid with combined antioxidant and cytokine-suppressive activity. By scavenging reactive oxygen species and dampening pro-inflammatory cytokine output, eugenol is thought to interrupt the oxidative-stress/cytokine feed-forward loop that sustains chronic low-grade inflammation.

6.4 Aloe vera

Aloe vera gel contains polysaccharides, glycoproteins, and anthraquinones (including aloin) that have been reported to reduce bradykinin-mediated pain signalling and to modulate prostaglandin and cytokine output at the tissue level, supporting its traditional topical and oral use in inflammatory and wound-healing contexts, although rigorous dose–response and mechanistic data remain comparatively limited relative to curcumin or EGCG.

6.5 Camellia sinensis (Green Tea)

Green tea leaves are rich in catechins, of which epigallocatechin gallate (EGCG) is the most extensively studied. EGCG exerts broad antioxidant activity and has been reported to interfere with NF-κB and MAPK signalling, thereby suppressing downstream pro-inflammatory cytokine and COX-2 expression in a manner that overlaps mechanistically with several of the pathways discussed in Section 2.4.

6.6 Portulaca oleracea (Purslane)

Purslane is a succulent, widely distributed leafy vegetable notable among common food plants for its comparatively high omega-3 fatty acid (α-linolenic acid) content, alongside flavonoids, alkaloids, and ascorbic acid. Its anti-inflammatory activity is attributed to a combination of omega-3-mediated eicosanoid modulation — competitively diverting arachidonic-acid metabolism toward less inflammatory lipid mediators — and direct antioxidant scavenging by its phenolic constituents. Preliminary experimental studies support anti-inflammatory and analgesic activity, though clinical evidence in humans remains limited and would benefit from standardised extract characterisation of the kind applied to olive leaf extract and other well-studied phytomedicines.

7. Emerging and Safer Therapeutic Strategies

7.1 Nanotechnology-Based Drug Delivery

Nanocarrier platforms — liposomes, polymeric nanoparticles, and solid lipid nanoparticles — are being explored to overcome the poor aqueous solubility and rapid systemic clearance that limit many plant-derived anti-inflammatory compounds (notably curcumin), while also enabling site-directed delivery of conventional NSAIDs and biologics that could reduce off-target gastrointestinal, renal, and cardiovascular exposure.

7.2 Combination Therapy

Rational combination of a low-dose conventional NSAID with a standardised herbal anti-inflammatory compound, or of a biologic with a conventional DMARD, aims to achieve synergistic efficacy at reduced individual doses, potentially lowering the cumulative toxicity burden associated with monotherapy at full therapeutic dose.

7.3 Personalised Medicine

Biomarker-guided treatment selection — for example, using CRP or cytokine profiling (Section 3.1) — together with pharmacogenomic characterisation of drug-metabolising enzymes, offers a route to matching patients to the anti-inflammatory regimen most likely to be both effective and well tolerated, reducing exposure to agents unlikely to benefit a given individual.

7.4 Molecular Docking and AI-Assisted Drug Discovery

Computational docking against validated inflammatory targets (COX isoforms, NF-κB components, JAK kinases, NLRP3) and machine-learning-assisted screening of natural-product libraries are accelerating identification of

candidate anti-inflammatory molecules with predicted target selectivity, potentially shortening the discovery timeline for safer next-generation agents ahead of experimental validation.

8. Future Perspectives

Continued progress in anti-inflammatory therapeutics is likely to depend on several converging trends: precision-medicine approaches that stratify patients by inflammatory phenotype rather than diagnosis alone; multi-target agents capable of modulating more than one node of the NF-κB/MAPK/JAK–STAT/NLRP3 network simultaneously; systems-biology approaches that map how these pathways interact across tissues and disease states; AI-assisted drug design to accelerate lead identification and optimisation; and rigorous standardisation of herbal and plant-derived candidates so that their reported efficacy can be reproduced and validated in controlled clinical trials, following the model already applied to agents such as olive leaf extract.

9. CONCLUSION

Inflammation is executed through a layered system of receptor recognition (PAMPs/DAMPs and PRRs), cellular effectors (macrophages, neutrophils, mast cells, dendritic cells, lymphocytes), chemical mediators (histamine, kinins, prostaglandins, leukotrienes), and a small number of convergent signalling pathways — NF-κB, MAPK, JAK–STAT, and the NLRP3 inflammasome — whose dysregulation underlies a substantial share of global disease burden, as reflected in CRP-linked outcomes across cardiovascular, metabolic, neurodegenerative, renal, and rheumatological disease. Conventional pharmacological control of this system — NSAIDs, corticosteroids, DMARDs, biologics, and JAK inhibitors — remains effective but is constrained by gastrointestinal, renal, cardiovascular, immunological, and economic costs that limit long-term use. Plant-derived agents such as curcumin, gingerols, eugenol, aloe vera constituents, EGCG, and purslane phytochemicals offer multi-targeted, comparatively safer alternatives, but require better standardisation and clinical validation before they can be positioned as substitutes rather than adjuncts to conventional therapy. Nanotechnology-enabled delivery, rational combination regimens, biomarker-guided personalised treatment, and computational drug discovery represent the most promising near-term routes to narrowing the long-standing gap between anti-inflammatory efficacy and safety.

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Conflicts of Interest

The authors declare no conflicts of interest relevant to the content of this review

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