



Review Article



Bioengineered Phyto Nanocarriers for Rheumatoid Arthritis: Synergistic Pathway Modulation and Translational Immunotherapy

Nagaraju Ravouru¹, Arun Rasheed², Jyothi Basini³, Aruna Kumari Dommaraju³, Rekha Devi Allagadda³, Prasanna Raju Yalavarthi^{3*}

¹Pharmaceutics Division, Institute of Pharmaceutical Technology, Sri Padmavathi Mahila Visvavidyalayam, Tirupati-517502, India

²Pharmaceutical Chemistry, Al-Shifa College of Pharmacy, Poonthavanam, Kerala-679325, India

³Pharmaceutics Division, Seven Hills College of Pharmacy (Autonomous), Venkatramapuram, Tirupati, IN-517561, India

ARTICLE INFO

Article History:

Received: July 15, 2025

Revised: August 12, 2025

Accepted: August 25, 2025

ePublished: January 5, 2026

Keywords:

Boswellic acid, Curcumin, Effusion, Guggulsterone, Immunomodulation, Nanomedicine, Personalized drug delivery, Synovial inflammation

Abstract

Background: Rheumatoid arthritis (RA) is a chronic, debilitating autoimmune disease characterized by synovial inflammation, immune-mediated joint destruction, and systemic manifestations. While current disease-modifying antirheumatic drugs (DMARDs) and biologics—have advanced disease control, long-term use is limited by toxicity and immunosuppression. These limitations underscore a growing need for integrative strategies that combine conventional immunomodulators with targeted phytotherapy and modern drug delivery technologies.

Objectives: This review explores mechanistically driven, combinatorial therapeutic approaches in RA that integrate Phytoconstituents, essential mineral cofactors, conventional DMARDs, and classical Ayurvedic formulations. Emphasis is placed on the application of nanobiotechnological platforms like solid lipid nanoparticles (SLNs), nanoemulgels and SMEDDSto enhance joint-targeted delivery, bioavailability, and immunological precision.

Methods: A structured review of preclinical, pharmacokinetic, clinical, and regulatory literature was conducted using databases such as PubMed, Scopus, and Web of Science. Articles were critically evaluated for their insights into inflammatory signaling modulation (e.g., NF- κ B, JAK/STAT, MAPK), pharmacological synergy, redox regulation, and nanocarrier-mediated macrophage targeting in RA. Policy frameworks from CDSCO, FDA, EMA, and AYUSH were also reviewed to contextualize translational feasibility.

Results: Several phytochemical-based combinations—such as curcumin with boswellic acids, and guggulsterone with methotrexate—exhibit additive or synergistic modulation of cytokine cascades, redox balance, and osteoclastogenesis. Nanocolloidal systems significantly enhance the pharmacokinetics and synovial targeting of lipophilic actives via passive (EPR effect) and active (e.g., folate receptor-mediated) uptake. These bioengineered platforms have demonstrated improved therapeutic outcomes minimized systemic toxicity. However, challenges persist in standardization of Phytoconstituents and clinical trial validation.

Conclusion: Integrative nanobiotechnology—bridging traditional phytotherapy with modern delivery science—represents a transformative paradigm for personalized and precision-based RA management. Guggul-based nanophytomedicine offers a compelling alternative or adjunct to conventional DMARDs by targeting inflammatory and oxidative networks with enhanced specificity. To fully harness these advances, future efforts must focus on harmonized regulatory models, robust clinical evaluation, and scalable manufacturing infrastructure.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that primarily affects the synovial joints, leading to chronic inflammation, progressive articular destruction, and significant functional disability. Globally, RA affects approximately 0.5–1% of the adult population, with a marked predominance in females and a typical onset between the fourth and sixth decades of life.¹ However, recent Indian epidemiological trends indicate a concerning increase in early-onset RA, especially

among urban young adults.² This shift may be attributed to emerging environmental triggers, sedentary lifestyles, dietary shifts, stress-related hormonal dysregulation, and genetic predispositions that together contribute to immune system imbalances and heightened auto-reactivity.³

Conventional management of RA predominantly revolves around synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, and sulfasalazine, as well as biological agents including TNF- α

*Corresponding Author: Prasanna Raju Yalavarthi, Email: kanishka9002@gmail.com

© 2026 The Author(s). This is an open access article and applies the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>). Non-commercial uses of the work are permitted, provided the original work is properly cited.

inhibitors, IL-6 antagonists, and Janus kinase (JAK) inhibitors.⁴ While these interventions have significantly improved clinical outcomes over the past two decades, a substantial proportion of patients either exhibit inadequate therapeutic responses or develop adverse effects such as hepatotoxicity, myelosuppression, and increased susceptibility to infections.⁵ Additionally, the high cost and logistical burden of biologics remain barriers to accessibility in low- and middle-income countries.⁶

To address these limitations, the exploration of adjunctive and alternative therapies rooted in phytochemistry and traditional medicine has gained momentum. Phytoconstituents such as guggulsterone (from *Commiphora mukul*), boswellic acids (*Boswellia serrata*), and curcumin (*Curcuma longa*) have shown promising anti-inflammatory and immunomodulatory properties through well-established molecular mechanisms including NF- κ B inhibition, cyclooxygenase (COX) modulation, and MAPK pathway suppression.⁷ Trace minerals such as selenium and zinc also play crucial roles in regulating oxidative stress, immune homeostasis, and cytokine production—functions that are particularly relevant to the chronic inflammatory milieu of RA.⁸

Moreover, the integration of classical Ayurvedic formulations such as Simhanada Guggulu and Rasnadi Guggulu introduces a multidimensional approach to disease modulation. These herbo-mineral combinations are traditionally used to treat conditions closely resembling RA (e.g., *Amavata* in Ayurveda), and recent pharmacological research has substantiated their roles in cytokine suppression, free radical scavenging, and cartilage preservation.

A persistent challenge associated with herbal and mineral-based therapeutics lies in their inherently poor oral bioavailability, rapid systemic clearance, and interindividual pharmacokinetic variability. Specifically, guggul-derived bioactives despite their demonstrated pharmacological efficacy are characterized by limited aqueous solubility, low gastrointestinal permeability, and pronounced first-pass hepatic metabolism, all of which constrain their therapeutic potential.

To address these limitations, recent advances in nanotechnology have enabled the development of sophisticated drug delivery platforms such as solid lipid nanoparticles (SLNs), self-microemulsifying drug

delivery systems (SMEDDS), nanoemulgels, and co-crystallized formulations. These systems are engineered to enhance the solubility, physicochemical stability, and site-specific delivery of lipophilic phytoconstituents like guggulsterone.

Importantly, such nanocarriers exhibit preferential accumulation within inflamed synovial tissues via the enhanced permeability and retention (EPR) effect. When further functionalized for instance, through folate conjugation they facilitate active targeting of synovial macrophages, as evidenced in [Table 1](#). The pathophysiological milieu of RA, characterized by acidic pH, elevated reactive oxygen species (ROS), and overexpression of macrophage-specific receptors, provides a rationale for the design of stimuli-responsive nanocarriers. These systems can be tailored to exploit disease-specific microenvironmental cues, thereby optimizing the delivery and therapeutic efficacy of herbal actives in RA management.⁹

In this review, we consolidate and critically examine the scientific rationale, therapeutic outcomes, and translational viability of combinatorial therapeutic strategies for RA. Particular emphasis is placed on the nanocolloidal delivery of Guggul-based phytoconstituents, their potential synergy with conventional DMARDs and minerals, and the integration of these strategies within traditional Indian medicine frameworks. Regulatory hurdles and commercial challenges associated with these hybrid therapeutics are also discussed to provide a comprehensive perspective on their future in clinical rheumatology.

Etiology and Pathophysiology of RA: A Cellular and Molecular Perspective

RA is a complex, systemic autoimmune disorder driven by a dysregulated immune response that targets the synovial lining of joints. Its pathogenesis involves a finely orchestrated yet pathological interaction between genetic predisposition, environmental triggers, innate and adaptive immunity, and inflammatory cell signaling pathways, culminating in chronic inflammation and joint destruction.¹¹

Genetic and Epigenetic Drivers of Autoimmunity

The strongest genetic predisposition to RA lies within

Table 1. Classification, properties, and applications of nanocarriers used in RA therapeutics¹⁰

Nanocarrier type	Core composition	Key features	Targeting mechanism	Example phytochemical	Route of delivery
Solid lipid nanoparticles	Glyceryl monostearate, Compritol	High drug loading, biocompatible	EPR effect, passive	Guggulsterone	Oral, Topical
Self-microemulsifying drug delivery system	Surfactant+ oil phase	Enhanced solubility, lymphatic absorption	Passive	Boswellic acid	Oral
nanoemulsions	Oil-in-water stabilized systems	Thermodynamically stable, fast absorption	Passive	Curcumin	Topical, Oral
Polymeric Micelles	PEG-PLA, Poloxamers	Amphiphilic, stable in plasma	Folate-receptor mediated	Guggulsterone	Parenteral
Liposomes	Phosphatidylcholine, cholesterol	Biodegradable, flexible loading	CD44-mediated (HA-modified)	Resveratrol	Intra-articular, IV

the Major Histocompatibility Complex (MHC) class II region, particularly the HLA-DRB1 gene, which encodes the “shared epitope” (SE)—a five-amino acid motif located in the peptide-binding groove of HLA-DR molecules.¹² This sequence facilitates aberrant antigen presentation of citrullinated self-peptides by dendritic cells (DCs) to naïve CD4⁺ T cells, ultimately leading to a breakdown in central tolerance and the onset of autoreactive immune responses.¹³ In addition to HLA-related genes, polymorphisms in non-HLA loci such as *PTPN22* (a phosphatase that negatively regulates T-cell receptor signaling), *STAT4* (a transcription factor mediating IL-12/IL-23 pathways), and *CTLA4* (a checkpoint molecule involved in T cell anergy) further enhance aberrant T cell activation and survival.¹⁴

Epigenetic modifications also play a key role. Aberrant DNA methylation patterns and histone modifications have been observed in regulatory T cells (Tregs) and fibroblast-like synoviocytes (FLS), leading to altered gene expression profiles that favor chronic inflammation and abnormal tissue remodeling.¹⁵

Environmental Triggers and Molecular Mimicry

Environmental insults are critical contributors to RA pathogenesis, with tobacco smoking being the most prominent risk factor. Smoking induces post-translational modifications such as citrullination of proteins via activation of peptidylarginine deiminase (PAD) enzymes, especially in the lungs and gingival tissues.¹⁶ These modified peptides act as neoantigens and elicit the production of anti-citrullinated protein antibodies (ACPAs), which play a central role in disease onset by forming immune complexes and initiating complement activation.¹⁷ Furthermore, microbial agents such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have been shown to produce citrullinated epitopes and virulence factors that contribute to molecular mimicry, perpetuating the autoimmune process.¹⁸

Initiation of Synovial Inflammation: Immune Cell Recruitment and Crosstalk

The autoimmune cascade in RA begins with the infiltration of antigen-presenting cells—particularly dendritic cells and monocyte-derived macrophages—into the synovial compartment. These APCs present self-peptides via MHC class II molecules to autoreactive CD4⁺ T cells, leading to their clonal expansion and differentiation into pathogenic Th1 and Th17 subsets.¹⁹ Th1 cells produce interferon-gamma (IFN- γ), which promotes classical (M1) macrophage activation and enhances their pro-inflammatory activity. Th17 cells, in contrast, secrete IL-17A/F, IL-22, and GM-CSF, which activate FLS, neutrophils, and resident macrophages, establishing a self-amplifying inflammatory loop.²⁰

B cells also contribute significantly to disease progression. Within the inflamed synovium, they undergo antigen-driven maturation and class switching in ectopic lymphoid

structures, ultimately differentiating into plasma cells. These plasma cells secrete high-affinity autoantibodies, including rheumatoid factor (RF) and ACPAs.²¹ When bound to citrullinated proteins, these antibodies form immune complexes that engage Fc γ receptors on macrophages and neutrophils, thereby triggering further cytokine production and complement-mediated inflammation.²²

Synovial Hyperplasia and Pannus Formation

A defining feature of RA is the transformation of synovial tissue into a hyperplastic, invasive pannus that actively erodes cartilage and bone. FLS in RA acquire a transformed, apoptosis-resistant phenotype characterized by high proliferative capacity and expression of inflammatory mediators.²³ Upon stimulation by cytokines such as IL-1 β , TNF- α , and IL-6, FLS secrete matrix metalloproteinases (MMP-1, MMP-3, and MMP-13) that degrade extracellular matrix components including type II and IX collagen, contributing to progressive cartilage destruction.²⁴

These activated FLS also express RANKL (Receptor Activator of Nuclear Factor κ B Ligand), which binds to RANK receptors on pre-osteoclasts, promoting their differentiation into mature bone-resorbing osteoclasts. This process is mediated through activation of the NF- κ B and NFATc1 signaling axes, resulting in localized bone erosion. Furthermore, angiogenesis—driven by vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1- α (HIF-1 α)—enhances leukocyte infiltration and sustains the inflammatory microenvironment, supporting pannus expansion.²⁵ These integrated events are summarized schematically in Figure 1.

Cytokine Networks and Inflammatory Signaling Pathways

The inflammatory environment in RA is shaped by a tightly regulated yet dysbalanced cytokine milieu. Among the central mediators, TNF- α (primarily from macrophages and Th1 cells) promotes endothelial activation, upregulation of adhesion molecules, and secretion of IL-1 β and IL-6.²⁶ IL-6, produced by FLS and monocytes, supports B cell maturation and triggers hepatic synthesis of acute-phase proteins. IL-1 β further activates FLS, induces MMP production, and amplifies

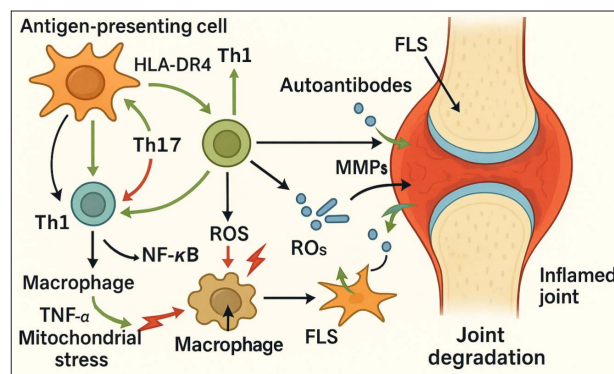


Figure 1. Immunopathogenesis of RA: Cellular and molecular crosstalk

inflammation via NF- κ B activation. IL-17, secreted by Th17 cells, promotes neutrophil recruitment and synergizes with IL-6 and RANKL, while IFN- γ enhances macrophage activation and antigen presentation.²⁷

A consolidated overview of the major cytokines involved in RA pathogenesis—along with their cellular sources and downstream effects—is provided in Table 2. These cytokines exert their effects through key intracellular signaling cascades. The NF- κ B pathway (canonical p65/p50 dimer) controls the transcription of pro-inflammatory genes including IL-6, TNF- α , and COX-2. The JAK/STAT pathway is essential for signal transduction downstream of IL-6, IFN, and GM-CSF receptors, and has become a target for JAK inhibitors in clinical use. Additionally, the MAPK cascade—comprising ERK, JNK, and p38 kinases—regulates FLS proliferation, cytokine expression, and MMP production.²⁸

Systemic Manifestations and Oxidative Stress

Although RA is joint-centric, its systemic inflammatory burden is substantial. Persistent cytokine signaling, mitochondrial dysfunction, and NADPH oxidase activation result in excessive production of ROS, which not only contribute to synovial injury but also impair endothelial function and exacerbate vascular disease. Oxidative stress inhibits Treg functionality and further skews the immune balance toward a pro-inflammatory state.³⁰

RA-associated extra-articular complications include interstitial lung disease (ILD), characterized by alveolar macrophage infiltration and fibrotic remodeling; cardiovascular disease due to arterial stiffness and accelerated atherogenesis; and anaemia of chronic disease, predominantly mediated by IL-6-driven hepcidin overproduction that impairs iron mobilization.³¹

The pathogenesis of RA represents a multidimensional network of genetic predisposition, immunologic dysregulation, oxidative stress, and tissue remodeling. Key molecular pathways such as NF- κ B, JAK/STAT, MAPK, and RANKL/OPG constitute the backbone of joint destruction and systemic spread. This mechanistic understanding lays the foundation for both established immunotherapies and novel integrative approaches, including phytochemical interventions and nanocolloidal delivery platforms designed to disrupt pathological loops with precision and reduced toxicity.³²

Glycosaminoglycans (GAGs) and Collagen

GAGs, particularly hyaluronic acid and chondroitin sulfate,

are indispensable for maintaining the viscoelasticity of synovial fluid and the compressive resilience of articular cartilage. Hyaluronic acid, through its high molecular weight and hydrophilic nature, facilitates joint lubrication and shock absorption. In RA, increased hyaluronidase activity leads to depolymerization of hyaluronic acid, resulting in diminished synovial viscosity and impaired joint mechanics. Simultaneously, aggrecanases such as ADAMTS-4 and ADAMTS-5 cleave chondroitin sulfate-rich domains of aggrecan, compromising cartilage's load-bearing capacity and accelerating matrix disintegration.^{33,34}

Collagen types II and IX, which form the structural scaffold of articular cartilage, are degraded by matrix metalloproteinases (MMP-1, MMP-13), leading to a loss of tensile strength and facilitating pannus-mediated invasion of the cartilage matrix. This enzymatic degradation not only destabilizes the extracellular matrix but also unveils cryptic neoepitopes, which may act as autoantigens and perpetuate the autoimmune response characteristic of RA. Notably, collagen exhibits a paradoxical role—while its degradation contributes to inflammation, exogenous collagen peptides have shown promise in modulating immune responses and promoting tissue repair.³⁵

Phytochemical and Mineral Therapeutics: Molecular Targets in RA Modulation

Recent scientific advancements have reaffirmed the therapeutic potential of phytoconstituents and trace minerals in the management of chronic inflammatory diseases such as RA. These naturally derived agents offer a multifaceted approach by modulating various cellular signaling pathways, altering gene expression and restoring immune homeostasis—all critical factors in the complex pathophysiology of RA. Their roles, once confined to adjunctive or traditional systems of medicine, are now increasingly recognized as part of evidence-based integrative strategies, especially when delivered through advanced pharmaceutical technologies.

Guggulsterone, the bioactive compound extracted from *Commiphora mukul*, exemplifies the mechanistic versatility of phytochemicals. It inhibits the nuclear factor-kappa B (NF- κ B) pathway—a central mediator in RA pathogenesis by preventing the phosphorylation and degradation of the inhibitor I κ B α , thereby blocking the translocation of NF- κ B dimers into the nucleus. As a result, transcription of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), and inducible nitric oxide synthase (iNOS) is

Table 2. Key phytochemicals for RA and their molecular mechanisms of action²⁹

Phytoconstituent	Source plant	Primary molecular targets	Signaling pathways affected	Evidence type
Guggulsterone	<i>Commiphora mukul</i>	NF- κ B, COX-2, FXR	NF- κ B, Nrf2	<i>In vivo</i> , Clinical
Curcumin	<i>Curcuma longa</i>	JAK2, STAT3, IL-6, TLR4	JAK/STAT, MAPK, MyD88	<i>In vitro</i> , <i>In vivo</i>
Boswellic acids	<i>Boswellia serrata</i>	5-LOX, MMP-3, IL-1 β	MAPK, Nrf2	<i>In vivo</i>
Resveratrol	<i>Vitis vinifera</i>	SIRT1, RANKL, STAT3	NF- κ B, SIRT1, RANK/RANKL	<i>In vivo</i>
Kaempferol	Leafy greens, <i>Camellia sinensis</i>	TLR4, NF- κ B, c-Fos	MAPK, NFAT	<i>In vitro</i>

significantly downregulated in activated macrophages and FLS. Furthermore, guggulsterone exhibits antagonistic activity at the farnesoid X receptor (FXR), a nuclear receptor involved not only in bile acid homeostasis but also in inflammatory responses. FXR inhibition has been shown to reduce the expression of chemokines and adhesion molecules, further contributing to its anti-inflammatory effects. The compound also enhances antioxidant enzyme activity, including glutathione peroxidase and catalase, thereby counteracting ROS-mediated synovial damage and preserving chondrocyte viability under oxidative stress.^{36,37}

Boswellic acids derived from *Boswellia serrata*, particularly Acetyl-11-keto- β -boswellic acid (AKBA), demonstrate powerful anti-arthritic properties through both enzymatic inhibition and transcriptional regulation. AKBA is a specific inhibitor of 5-lipoxygenase (5-LOX), thereby reducing leukotriene biosynthesis and neutrophil infiltration into the synovium. In fibroblasts, boswellic acids attenuate the expression of matrix metalloproteinases (MMPs), especially MMP-3 and MMP-9, which are critical mediators of cartilage degradation. Recent evidence also suggests that boswellic acids may activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, leading to transcriptional upregulation of cytoprotective genes such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1), enhancing cellular resistance to oxidative and electrophilic insults.^{38,39}

Curcumin, the principal polyphenol found in *Curcuma longa*, is widely studied for its broad-spectrum pharmacological activity. At the molecular level, curcumin inhibits multiple signaling cascades relevant to RA, including the mitogen-activated protein kinase (MAPK) family—p38, JNK, and ERK—as well as the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, particularly STAT3 phosphorylation induced by IL-6. These inhibitory effects disrupt downstream expression of pro-inflammatory genes and reduce the differentiation of pathogenic Th17 cells. Moreover, curcumin interferes with Toll-like receptor 4 (TLR4) and its downstream adaptor MyD88, thereby dampening innate immune activation at the level of synovial macrophages. Its epigenetic influence has also been noted, including inhibition of histone acetyltransferase activity and suppression of pro-inflammatory microRNAs such as miR-155, which modulate cytokine production and T cell survival. Through its potent ROS scavenging capacity and ability to stabilize mitochondrial membranes, curcumin further protects against apoptosis in chondrocytes and synoviocytes under inflammatory stress.^{40,41}

Resveratrol, a stilbenoid phytoalexin primarily found in grapes and peanuts, has emerged as a potent immunomodulatory agent with relevance to autoimmune diseases. It activates Sirtuin 1 (SIRT1), a class III histone deacetylase involved in chromatin remodeling and inflammation control. SIRT1 activation by resveratrol

results in deacetylation of the p65 subunit of NF- κ B, leading to transcriptional repression of TNF- α and IL-6 in synovial macrophages. Additionally, resveratrol impedes the IL-23 receptor/STAT3 axis that governs Th17 polarization, thereby reducing interleukin-17 (IL-17) production—a cytokine intimately linked with neutrophil activation and cartilage erosion in RA. Mitochondrial stabilization, enhanced autophagy, and reduced oxidative phosphorylation stress are additional mechanisms that underlie resveratrol's protective effects in arthritic tissues.^{42,43}

Kaempferol, a dietary flavonoid abundant in leafy greens and tea, modulates the immune response through inhibition of TLR4 expression and its downstream effectors. In activated macrophages and fibroblasts, kaempferol reduces phosphorylation of I κ B α and p65, thereby attenuating NF- κ B-mediated transcription of pro-inflammatory mediators. Additionally, it suppresses MAPK signaling, particularly the p38 and JNK arms, leading to decreased secretion of MMPs and inhibition of osteoclastogenic molecules like RANKL. Kaempferol also directly inhibits transcription factors such as NFATc1 and c-Fos, both essential for osteoclast differentiation, thereby preserving bone integrity in inflammatory settings.^{44,45}

Complementing these phytochemicals, essential trace minerals such as selenium, zinc, and magnesium play critical roles in the regulation of oxidative stress, immune cell differentiation, and inflammatory balance. Selenium is a cofactor for antioxidant enzymes including glutathione peroxidase and thioredoxin reductase, which detoxify peroxides generated during chronic synovitis. Selenium deficiency correlates with heightened disease activity and impaired antioxidant defense in RA patients. Zinc supports thymic T cell maturation and modulates the expression of zinc-finger proteins that influence transcriptional regulation of inflammatory cytokines. It also induces metallothioneins, proteins that bind and neutralize heavy metals and ROS, thereby maintaining intracellular redox equilibrium. Magnesium contributes to the regulation of calcium-dependent signaling in immune and endothelial cells and modulates pain sensitivity and inflammatory gene expression. Hypomagnesemia in RA is often associated with increased levels of C-reactive protein (CRP), interleukin-6, and prostaglandin E2 (PGE2), suggesting a direct link to disease severity.^{46,47}

Combinatorial Therapeutic Strategies in RA

Given the multifactorial pathophysiology of RA, characterized by the simultaneous activation of multiple immune cell types, cytokine networks, and redox imbalances, monotherapy often fails to provide durable remission. The overlapping and compensatory nature of pro-inflammatory signaling cascades—including NF- κ B, JAK/STAT, and MAPK—creates an environment of pharmacologic redundancy, where blockade of a single pathway (e.g., TNF- α) may be insufficient to suppress chronic inflammation long term. Additionally, clinical

resistance to conventional agents such as methotrexate often emerges due to pharmacogenomic variability, drug efflux mechanisms, or compensatory cytokine upregulation.⁴⁸

In this context, combinatorial therapeutic approaches—strategically integrating phytochemicals, mineral cofactors, synthetic DMARDs, and traditional medicinal formulations—offer a promising paradigm shift.^{49,50} These multi-modal regimens aim not merely to suppress inflammation, but to modulate upstream signaling, restore redox balance, and engage in targeted immunologic recalibration.

As demonstrated in Table 3, a prototypical example is the co-administration of curcumin and boswellic acids, both of which exert converging but distinct molecular effects. Curcumin primarily inhibits the NF- κ B and JAK/STAT pathways, reducing IL-6 and IL-1 β transcription in macrophages and synoviocytes, while boswellic acids suppress 5-lipoxygenase activity, thereby decreasing leukotriene B4 production—a key chemoattractant for neutrophils in the synovium. This dual-target inhibition leads to reduced recruitment and activation of both innate and adaptive immune cells and mitigates cartilage matrix breakdown through downregulation of MMP-1 and MMP-15.⁵¹

A further layer of synergy is achieved when such phytochemicals are paired with synthetic DMARDs as observed in Figure 2. For instance, guggulsterone, known to inhibit NF- κ B and downregulate COX-2, enhances the anti-arthritic efficacy of methotrexate by modulating

hepatic CYP450 enzymes and reducing hepatotoxicity, which is a major limitation of long-term methotrexate therapy. Methotrexate suppresses dihydrofolate reductase and purine synthesis, leading to anti-proliferative effects on T and B cells. However, it also increases ROS levels and mitochondrial stress, which may exacerbate synovial damage. Guggulsterone's antioxidant effects counterbalance this, offering a pharmacodynamic buffering effect.⁵³

Combining Ashwagandha (*Withania somnifera*) and selenium is another emerging example of phyto-mineral synergy with immunological consequences. Ashwagandha's withanolides modulate glucocorticoid receptor expression and inhibit iNOS, while selenium replenishes glutathione peroxidase activity and mitigates synovial oxidative injury. Recent data suggest that selenium enhances the nuclear translocation of Nrf2, facilitating the transcription of HO-1 and NQO1—critical enzymes that counteract lipid peroxidation and mitochondrial dysfunction in activated macrophages.⁵⁴

In preclinical studies, combinations such as resveratrol with dexamethasone or curcumin with leflunomide have demonstrated not only additive anti-inflammatory effects, but also attenuation of glucocorticoid-induced osteopenia or hepatotoxicity. For instance, resveratrol downregulates RANKL-mediated NFATc1 activation in osteoclast precursors, countering steroid-induced bone loss while preserving anti-inflammatory efficacy.^{55,56} The net result is an extended therapeutic window and improved long-term safety profile—key criteria for chronic disease management.

Table 3. Synergistic combinatorial strategies in RA management⁵²

Combination therapy	Mechanistic rationale	Observed outcome	Evidence type
Curcumin + Boswellic acid	NF- κ B + 5-LOX inhibition	↓ TNF- α (65%), ↓ joint swelling	In vivo (CIA model)
Guggulsterone + Methotrexate	NF- κ B inhibition + DHFR block	↓ IL-6, ↓ hepatic toxicity	In vivo, Clinical
Resveratrol + Dexamethasone	RANKL + COX-2 inhibition	Preserved bone density, ↓ inflammation	In vivo
Ashwagandha + Selenium	iNOS + Nrf2 activation	↑ IL-10, ↓ oxidative markers	In vivo
Triphala + Leflunomide	MAPK + pyrimidine synthesis inhibition	Delayed arthritis onset	Preclinical

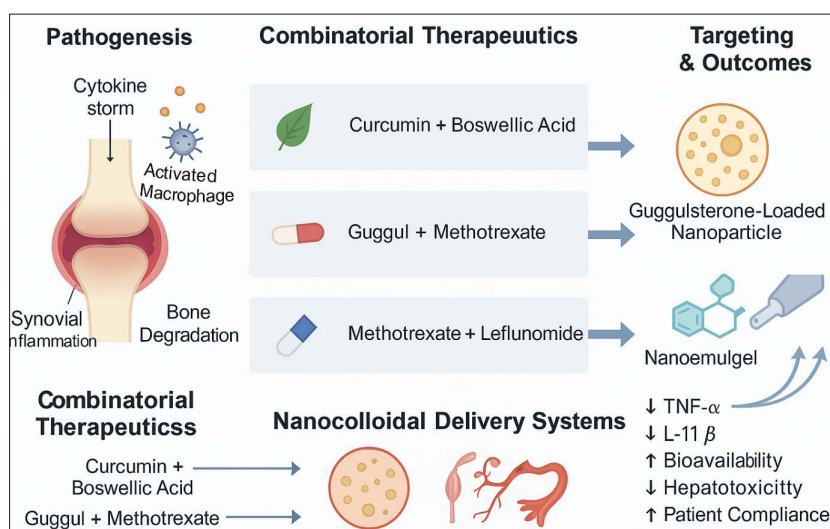


Figure 2. Synergistic targeting by combinatorial therapies

Another layer of combinatorial complexity is introduced by the integration of Ayurvedic polyherbal formulations, such as *Simhanada Guggulu* and *Rasnadi Guggulu*, into modern pharmacological regimens. These formulations contain multiple bioactives—including guggulsterone, castor oil derivatives, *Triphala* components, and mineral salts—that act in concert on immune checkpoints, digestive detoxification pathways, and systemic oxidative stress. While the precise molecular mechanisms of these formulations remain incompletely defined, emerging metabolomics and network pharmacology analyses suggest they regulate the gut–joint axis and modulate cytokine gene expression at both mRNA and protein levels.⁵⁷

Importantly, the efficacy of combinatorial strategies is not merely additive, but often synergistic, owing to complementary pharmacokinetics and intracellular targeting. For example, while curcumin has poor aqueous solubility and undergoes rapid first-pass metabolism, its co-administration with piperine (from *Piper nigrum*) inhibits hepatic glucuronidation, enhancing curcumin's systemic availability nearly 20-fold.⁵⁸

Similarly, SMEDDS-based delivery systems of guggulsterone improve its absorption and lymphatic transport, aligning its peak plasma concentrations with those of co-administered DMARDs for optimal bioactivity synchrony.

At the molecular level, such synchronization translates to simultaneous blockade of multiple signaling axes: NF- κ B by guggulsterone, STAT3 by curcumin, 5-LOX by boswellic acids, and DHFR by methotrexate. These interactions reduce transcription of IL-1 β , IL-6, TNF- α , and RANKL—thereby suppressing pannus formation, osteoclastogenesis, and angiogenesis in the synovial niche. Moreover, by enhancing antioxidant enzyme levels (SOD, GPx, CAT), these combinations reduce mitochondrial depolarization and ROS-induced chondrocyte apoptosis—key features of progressive joint degradation.

Despite their promise, combinatorial strategies face several mechanistic challenges. One is the differential pharmacodynamics and bio-distribution of natural vs. synthetic agents. Without synchronized release profiles or targeted delivery systems, certain components may exhibit off-target effects or subtherapeutic exposure.⁵⁹ Additionally, herb–drug interactions via CYP450 modulation can alter systemic clearance rates, requiring careful pharmacokinetic modeling. Further, high variability in phytoconstituent content between batches poses risks to reproducibility and regulatory acceptance. These challenges underscore the need for standardized formulations, predictive computational modeling, and rigorous clinical validation.

In conclusion, combinatorial therapeutic regimens represent a mechanistically grounded approach to overcoming the polygenic and redundant nature of RA inflammation. Through the careful selection of synergistic agents and delivery formats, these strategies aim not

only to suppress symptoms, but to restore immunologic tolerance, preserve joint architecture, and reduce long-term toxicity. The next frontier involves integrating these regimens with nanotechnological delivery platforms, which can further optimize pharmacokinetic synchrony and tissue-specific targeting.

Steroidal Approaches in RA: Mechanistic Impact and Therapeutic Optimization

Corticosteroids, particularly glucocorticoids such as prednisolone, dexamethasone, and methylprednisolone, remain a cornerstone of anti-inflammatory therapy in RA. Despite their established efficacy in rapidly suppressing synovial inflammation and providing symptomatic relief, chronic steroid use is fraught with significant adverse effects including metabolic dysregulation, osteoporosis, adrenal suppression, and immunosuppression. Therefore, a mechanistic reevaluation of steroidal actions within the RA microenvironment is essential to optimize their application, minimize systemic toxicity, and guide rational combinatorial use.⁶⁰

At the molecular level, glucocorticoids exert their effects through intracellular glucocorticoid receptors (GRs), members of the nuclear receptor superfamily, which translocate to the nucleus upon ligand binding. Once in the nucleus, GRs bind glucocorticoid response elements (GREs) on DNA, directly inducing the transcription of anti-inflammatory genes such as annexin A1, IL-10, and MAP kinase phosphatase-1 (MKP-1), while simultaneously repressing pro-inflammatory genes by tethering and inhibiting transcription factors like NF- κ B and activator protein-1 (AP-1). This dual transactivation and transrepression mechanism underlies the potent suppression of cytokines such as TNF- α , IL-1 β , and IL-6 in synovial macrophages and FLS.^{61,62}

However, beyond transcriptional modulation, corticosteroids influence cellular phenotypes in a context- and time-dependent manner. In macrophages, GR activation induces a phenotypic shift from M1 (pro-inflammatory) to M2 (anti-inflammatory) polarization, with increased arginase-1 and IL-10 expression. This transition facilitates the resolution of inflammation and supports tissue remodeling. In T lymphocytes, corticosteroids induce apoptosis primarily via the mitochondrial intrinsic pathway, involving Bcl-2 downregulation and cytochrome c release, although long-term use may impair Treg function and promote Th17 resistance—mechanisms implicated in steroid-insensitive RA flares.⁶³

Importantly, glucocorticoids alter the behavior of FLS, which play a central role in pannus formation and cartilage invasion. Dexamethasone suppresses IL-1 β -induced expression of MMP-3 and MMP-13 in FLS by inhibiting p38 MAPK and JNK signaling. It also reduces the secretion of VEGF, thereby attenuating synovial angiogenesis and immune cell infiltration. However, chronic exposure can lead to glucocorticoid receptor

desensitization and decreased GR α isoform expression, reducing cellular responsiveness to steroids over time.⁶⁴

The skeletal system is particularly vulnerable to glucocorticoid-induced adverse effects. Corticosteroids impair osteoblast differentiation by inhibiting Wnt/ β -catenin signaling and increasing expression of Dickkopf-1 (DKK1), an endogenous Wnt antagonist. Simultaneously, they promote osteoclastogenesis via upregulation of RANKL and downregulation of osteoprotegerin (OPG), leading to trabecular bone loss and increased fracture risk in RA patients. These mechanisms collectively contribute to glucocorticoid-induced osteoporosis (GIOP), which remains a major concern in long-term management.⁶⁵

Another emerging concept is the circadian modulation of corticosteroid efficacy and toxicity. In RA, pro-inflammatory cytokines like IL-6 and TNF- α exhibit circadian peaks in the early morning hours, coinciding with symptom exacerbation. Timed corticosteroid delivery—such as delayed-release prednisolone administered at night—aligns the drug's peak action with the cytokine surge, improving symptom control and minimizing systemic exposure. This chronotherapy approach is mechanistically supported by the role of the nuclear receptor REV-ERB α in regulating circadian rhythms of cytokine transcription.⁶⁶

To mitigate long-term toxicity and enhance therapeutic precision, newer strategies are focusing on nanoformulations of corticosteroids. Liposomal and polymeric micelle-based delivery systems encapsulating dexamethasone or prednisolone have shown superior localization to inflamed synovial tissues via the EPR effect, reducing systemic spillover and prolonging intra-articular retention. Folate-conjugated nanoparticles exploit the overexpression of folate receptors on activated macrophages in RA joints, enabling cell-specific drug delivery. In preclinical collagen-induced arthritis models, such approaches have demonstrated not only enhanced anti-arthritic efficacy but also lower systemic glucocorticoid exposure and fewer metabolic side effects.⁶⁷

Combinatorial regimens incorporating low-dose steroids with phytoconstituents offer a compelling strategy to preserve therapeutic efficacy while reducing cumulative steroid burden. Curcumin, for instance, synergizes with dexamethasone by augmenting NF- κ B inhibition and promoting anti-oxidative gene expression. In vitro studies have shown that co-treatment leads to greater suppression of COX-2 and iNOS mRNA than either agent alone.⁶⁸ Moreover, antioxidant-rich phytochemicals such as resveratrol and quercetin protect osteoblasts from dexamethasone-induced apoptosis by restoring mitochondrial membrane potential and inhibiting caspase-9 activation—suggesting a possible role in preventing GIOP.

Despite their widespread use, the application of corticosteroids in RA must remain judicious and informed by emerging insights into GR isoform balance, circadian biology, and tissue-specific delivery. The future

of steroidal therapy likely lies not in their elimination, but in precision modulation—leveraging molecular targeting, nanocarriers, and phytochemical adjuvants to achieve maximal anti-inflammatory benefit with minimal systemic harm.

Advanced Drug Delivery Strategies for RA: Nanotechnology, 3D Systems and Precision Approaches

The complex, polygenic, and compartmentalized pathology of RA demands more than systemic immunosuppression; it requires targeted, site-specific, and patient-adaptable drug delivery strategies. Conventional oral or parenteral drug delivery results in suboptimal biodistribution, systemic toxicity, and diminished efficacy in the synovial microenvironment. Advanced drug delivery systems (DDS) now aim to overcome these barriers using nanotechnology, 3D bioprinting, and patient-specific formulation design, with growing emphasis on personalized rheumatologic care.

Nanocolloidal Systems: Precision Tools for Synovial Targeting

From a pharmaceutical development standpoint, each nanocarrier system described herein is governed by distinct formulation parameters that critically influence performance. For example, SLNs designed for guggulsterone delivery typically employ glyceryl monostearate or Compritol as lipid matrices, stabilized by surfactants such as Poloxamer 188 or Tween 80. The production process necessitates precise control over homogenization pressure and sonication cycles to achieve nanoscale particle sizes (100–200 nm) with narrow polydispersity indices (PDI < 0.3), ensuring uniformity and colloidal stability.⁶⁹

Self-microemulsifying drug delivery systems (SMEDDS) require meticulous optimization of oil, surfactant, and co-surfactant ratios, often guided by ternary phase diagrams to facilitate spontaneous microemulsion formation upon aqueous dilution. Liposomal formulations for phytochemicals are typically characterized by encapsulation efficiency—quantified via high-performance liquid chromatography (HPLC)—alongside zeta potential measurements to predict colloidal stability, and in vitro release kinetics assessed using dialysis membrane models under sink conditions.

Preclinical validation of these nanocarriers generally involves biodistribution profiling, therapeutic efficacy assessment in collagen-induced arthritis (CIA) models, and pharmacokinetic studies demonstrating enhanced systemic exposure (e.g., increased area under the curve [AUC] and peak plasma concentration [C_{max}]) relative to unformulated phytoconstituents.

As summarized in Table 3, nanocolloidal platforms—including SLNs, SMEDDS, nanoemulsions, micelles, liposomes, and polymeric nanoparticles—have markedly expanded the therapeutic utility of lipophilic phytochemicals such as guggulsterone by improving

solubility, chemical stability, and synovial tissue uptake.

Guggulsterone, a hydrophobic compound with limited oral bioavailability and extensive hepatic first-pass metabolism, derives substantial benefit from SLN encapsulation. These lipid-based nanocarriers facilitate lymphatic transport, shield bioactive isomers from oxidative degradation, and exhibit favorable physicochemical attributes—such as particle size (~100–200 nm), tunable surface charge, and extended systemic circulation. Collectively, these features enhance passive targeting via the EPR effect, particularly within inflamed synovial tissues.⁷⁰ This effect, driven by aberrant vasculature and compromised lymphatic clearance in RA, promotes selective accumulation of nanoscale carriers at disease sites, as illustrated in Figure 3.

Surface modification with ligands such as folic acid or hyaluronic acid enables active targeting by binding to overexpressed folate receptors or CD44 on activated macrophages and FLS, respectively. Such ligand–receptor interactions promote receptor-mediated endocytosis, allowing intracellular delivery of guggulsterone and co-encapsulated agents like methotrexate, enhancing therapeutic index while reducing systemic exposure.⁷¹

Emerging nanocarrier platforms such as nanoemulgels and nanocrystals are garnering increasing interest for the delivery of lipophilic phytoconstituents. Nanoemulgels synergistically integrate the solubilization capacity of nanoemulsions with the localized retention properties of gel matrices, thereby enabling transdermal or intra-articular administration of hydrophobic bioactives. In preclinical models of RA, topical application of nanoemulgel formulations containing Guggul extract has demonstrated significant attenuation of paw edema and marked reductions in pro-inflammatory cytokines, including TNF- α and IL-6. These findings support their utility as non-invasive adjuncts to systemic therapy.

Bioengineered nanocarriers encapsulating guggulsterone exhibit a distinct set of pharmaceutical and biopharmaceutical attributes that render them particularly suitable for RA management. Typically sized between 80–200 nm, these carriers—whether formulated as SLNs, polymeric micelles, or liposomes—are optimized to achieve high encapsulation efficiencies (>80%), ensuring maximal payload retention. The lipidic or amphiphilic polymer matrices confer protection against oxidative and enzymatic degradation while enhancing

aqueous dispersibility of the hydrophobic drug.

Surface functionalization with targeting ligands such as folic acid, hyaluronic acid, or mannose enables active targeting of cellular populations implicated in RA pathogenesis, including activated macrophages and FLS. These ligands exploit overexpressed receptors—folate receptors, CD44, and mannose receptors—within inflamed synovial tissues to facilitate receptor-mediated endocytosis and site-specific drug delivery.

Zeta potential modulation within the range of ± 25 –35 mV contributes to colloidal stability, both during storage and systemic circulation, minimizing aggregation and premature clearance. From a pharmacokinetic perspective, these nanocarriers extend the systemic half-life of guggulsterone, enhance lymphatic uptake, and achieve 2–5-fold higher drug concentrations within synovial compartments compared to non-encapsulated formulations. Collectively, these design features enable targeted anti-inflammatory action at the disease site while minimizing off-target exposure and systemic toxicity.⁷²

Stimuli-Responsive and Dual-Release Nanoplatforms

Emerging nanocarriers incorporate stimuli-responsive designs—triggered by environmental cues such as pH, redox potential, or enzyme activity unique to the RA joint microenvironment.

For instance, pH-sensitive polymers (e.g., Eudragit, chitosan derivatives) degrade under acidic pH typical of inflamed synovium (~pH 6.5), releasing encapsulated curcumin, boswellic acid, or guggulsterone specifically at the site of inflammation. Redox-sensitive carriers respond to elevated intracellular glutathione levels in activated immune cells, facilitating cytosolic drug release while sparing healthy tissue.

Dual-release systems are now being engineered to provide sequential delivery of synergistic actives—such as early release of antioxidants (resveratrol) followed by delayed release of immunomodulators (methotrexate)—synchronized with circadian cytokine rhythms. These designs aim to mimic the dynamic nature of RA flares and immune oscillations.⁷³

Integration with 3D Printing and Localized Scaffolds

A transformative advancement in DDS is the use of 3D printing (additive manufacturing) for fabricating customized drug-eluting scaffolds and joint-specific implants. Using biocompatible polymers such as polylactic-co-glycolic acid (PLGA), polycaprolactone (PCL), or gelatin methacryloyl (GelMA), 3D-printed matrices can be loaded with Guggul-based nanoparticles, synthetic DMARDs, or even biologics.⁷⁴

These implants enable localized, sustained drug release directly at inflamed joints, bypassing systemic exposure. Furthermore, the architecture of these scaffolds can be tuned (e.g., porosity, geometry) based on joint size, patient anatomy, and disease stage—making them ideal for personalized intra-articular therapy. In RA animal

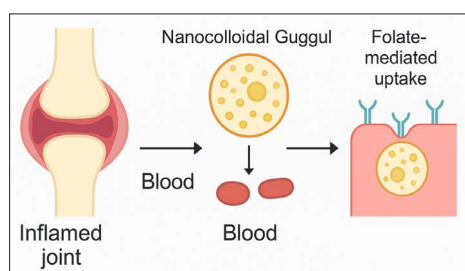


Figure 3. Nanocolloidal drug delivery pathways in inflamed RA joints

models, 3D-printed hydrogels loaded with IL-1Ra nanoparticles significantly reduced cartilage erosion and histologic inflammation scores compared to controls.

Beyond local scaffolds, 3D bioprinting is being explored to model synovial tissue in vitro using RA patient-derived cells. These ex vivo models serve both as drug screening platforms and as a basis for personalized formulation design.

Personalized Delivery Systems and AI-Driven Formulation

The shift toward personalized medicine in RA is now influencing DDS design. Using patient-specific inflammatory profiles (cytokine expression, immune cell phenotypes, pharmacogenomics), formulations can be tailored to optimize response.

Artificial intelligence (AI) and machine learning (ML) algorithms are being employed to simulate nanocarrier behavior under individual patient conditions, predicting drug loading, release kinetics, biodistribution, and therapeutic response. Integration with electronic health records and cytokine monitoring allows real-time adjustment of dosing regimens—laying the groundwork for adaptive nanomedicine in RA.

Furthermore, wearable microfluidic devices coupled with transdermal nanopatches are being prototyped to deliver drugs based on circadian biomarker fluctuations, offering chronotherapy-aligned, closed-loop delivery systems.

Contemporary drug delivery strategies for RA have evolved well beyond conventional passive carriers, embracing mechanistically driven platforms that align with the dynamic pathophysiology of joint inflammation. Nanocolloidal systems incorporating Guggul-derived phytoconstituents offer improved site-specific targeting, enhanced therapeutic efficacy, and reduced systemic toxicity. Moreover, the advent of stimuli-responsive and dual-release nanocarriers enables spatiotemporal synchronization of drug release with inflammatory flares, thereby optimizing pharmacodynamic outcomes.

The convergence of advanced fabrication technologies—such as 3D printing—and AI-driven personalization is further transforming RA therapeutics. These innovations facilitate precise drug placement and individualized formulation design, tailored to patient-specific disease profiles and pharmacokinetic needs. Although currently in translational phases, such integrative approaches signal

a paradigm shift toward personalized, mechanistically precise RA therapy, particularly when combined with hybrid phytochemical–synthetic regimens.

Recent applications of AI in RA nanomedicine underscore its potential to accelerate formulation development and therapeutic optimization. Machine learning algorithms trained on nanoparticle composition–response datasets have been employed to predict optimal drug-to-excipient ratios for SLNs and SMEDDS. Convolutional neural networks (CNNs) have been utilized to analyze confocal microscopy images, enabling quantitative assessment of cellular uptake efficiency. Reinforcement learning models are being explored to refine chronotherapeutic dosing schedules based on real-time cytokine fluctuations, thereby aligning drug administration with inflammatory cycles.

For instance, a 2024 study demonstrated the use of gradient-boosted decision trees to predict release kinetics of methotrexate–guggulsterone SLNs with over 90% accuracy, effectively halving the number of required experimental iterations. Such AI-guided methodologies not only streamline formulation workflows but also enhance the precision and adaptability of RA nanotherapeutics.⁷⁵

Regulatory and Commercial Challenges: Bridging Traditional Wisdom with Modern Standards

The therapeutic resurgence of phytochemicals such as Guggul in RA—especially when formulated in novel nanocarriers—poses both regulatory promise and paradox. On one hand, these agents align with the principles of personalized, multi-targeted, and low-toxicity treatment. On the other, they face a fragmented and evolving global regulatory landscape, especially when derived from traditional systems such as Ayurveda. The path to clinical adoption and market entry thus requires overcoming significant hurdles related to standardization, safety validation, intellectual property rights, and harmonization across regulatory jurisdictions.⁷⁶

Regulatory Landscape for Herbal and Nanoformulated Phytopharmaceuticals

Globally, the US FDA and EMA (European Medicines Agency) have introduced specific pathways for botanical drugs as illustrated in Table 4. The FDA's CDER Botanical Guidance (2016) defines phytopharmaceuticals

Table 4. Comparison of global and Indian regulatory frameworks for herbal and nanoformulated therapies⁷⁷

Agency	Traditional claims accepted?	Nanoformulations permitted?	Clinical trial required?	Examples
FDA (USA)	No (must follow botanical drug pathway)	Yes, under NDA with full tox/PK	Yes (Phase I–III)	Veregen®, Fulyzaq®
EMA (Europe)	Yes (if >30 years use)	Yes (with herbal monographs)	Sometimes waived (for traditional use)	HMPC-registered teas, tinctures
CDSCO (India)	Yes (AYUSH classical only)	Yes (under Rule 158B as phytopharmaceuticals)	Yes (unless Ayurvedic classical)	Guggul extract (phytopharma)
AYUSH (India)	Yes (lineage documentation)	No clear nano policy	Not mandatory if classical	Simhanada Guggulu
FSSAI (India)	Yes (as nutraceuticals)	Yes (only GRAS components)	Not applicable	Guggul-based capsules

as complex plant-derived products requiring rigorous control over identity, purity, bioactive markers, and stability. However, such frameworks still struggle to accommodate complex mixtures or synergistic multi-herb formulations typical of Ayurveda. The EMA's Committee on Herbal Medicinal Products (HMPC) allows traditional use registration if safety is established over at least 30 years (15 in Europe), but demands evidence of plausibility and quality control.

In India, the regulatory divide is even more distinct. Conventional new drugs fall under the Drugs and Cosmetics Act (1940), while classical Ayurvedic medicines are governed by AYUSH, which allows traditional documentation in lieu of clinical trials. However, the 2015 amendment to Schedule Y of the Drugs and Cosmetics Rules now formally recognizes “phytopharmaceuticals” as a new category—defined as purified, fractionated plant extracts with at least four defined bioactives, subjected to full non-clinical and clinical testing like modern drugs. This applies to drugs like guggulsterone, curcumin, and boswellic acids when used in isolation or enriched nanoformulations.

The Central Drugs Standard Control Organization (CDSCO) oversees phytopharmaceuticals under Rule 158B, mandating preclinical safety, human pharmacokinetics, and Phase I–III trials. For Guggul-based nanomedicine, this places it outside the traditional Ayurvedic category and within modern drug regulation—requiring advanced toxicology, stability, and PK/PD modeling. Formulations with nanocarriers such as SLNs or SMEDDS must also comply with biosafety and nanotoxicology standards, including zeta potential, particle size distribution, and polymer degradation profiles.

Quality Control, Reproducibility, and Intellectual Property Challenges

A major barrier in translating Guggul and other botanicals into nanoformulated RA therapies is the lack of standardization. Plant-derived compounds are highly susceptible to batch variability due to differences in soil, climate, harvesting time, and extraction methods. Even small deviations can alter the concentration of key bioactives like guggulsterone-E/Z isomers, impacting reproducibility and therapeutic outcomes.⁷⁶ Current pharmacopeial standards (e.g., API, USP) provide monographs for crude guggul resin, but not for nanoencapsulated forms or combination therapies with DMARDs.

Quality assurance protocols for nanoparticle-encapsulated phytoconstituents must include characterization by HPLC, FTIR, DSC, and TEM, along with in vitro release studies and long-term ICH stability trials. Moreover, phytochemical-based therapies often fall into a “gray zone” with respect to intellectual property protection—where natural compounds cannot be patented, but their delivery systems or synergistic combinations might be. This complicates global commercialization, especially for academic and

small-industry developers.

ICMR and National Initiatives: Validating Phytomedicine and Traditional Practitioners

India's ICMR (Indian Council of Medical Research) has increasingly supported scientific validation of traditional systems and phytoconstituents. In 2020, ICMR, in collaboration with AYUSH and CSIR, initiated cross-disciplinary clinical trials for botanicals such as Ashwagandha, Guduchi, and Turmeric in inflammatory diseases. For RA, efforts have focused on generating GLP-compliant toxicology, dose–response data, and translational biomarkers for plant-derived agents like guggulsterone.

Importantly, ICMR has also taken a policy-level initiative to integrate “traditional healers” and divine practitioners into national healthcare delivery through Documentation and Knowledge Validation Programmes (DKVPs). Under this scheme, grassroots therapeutic knowledge—often transmitted orally through tribal or Vedic channels—is recorded, evaluated, and curated through scientific lenses. Recognizing that many rural RA patients consult such healers before formal diagnosis, ICMR proposes evidence-based training, community trials, and inclusion of successful formulations into official AYUSH pharmacopoeia. This approach ensures that ethnomedical wisdom is not marginalized, but validated and harmonized with modern care.

In parallel, the National Medicinal Plants Board (NMPB) has initiated the Phytopharmaceutical Mission to support cultivation, processing, and GMP-certified manufacturing of RA-relevant botanicals, including *Commiphora wightii* (guggul). Meanwhile, FSSAI regulates botanical nutraceuticals under functional food guidelines—offering a non-pharmaceutical route to market for Guggul-based supplements.⁷⁷

Commercial Scalability and Clinical Translation

Even with regulatory approval, commercial scalability remains a formidable challenge, particularly for nanocolloidal systems requiring sterile production, high-pressure homogenization, or lyophilization. Many herbal industries lack infrastructure for nano-manufacturing or do not meet WHO-GMP standards. Additionally, clinical trial costs for phytopharmaceuticals remain prohibitive due to the need for full toxicological profiling and large-scale efficacy data. Collaborations between academia, AYUSH-research units, and biotech startups are increasingly seen as a pathway forward.

Moreover, there is a need for regulatory harmonization between modern and traditional sectors. While AYUSH emphasizes lineage and historical use, CDSCO demands empirical pharmacology—creating friction in the approval of hybrid formulations. Consensus guidelines co-published by ICMR and AYUSH (2023) now propose a “dual validation model”, allowing traditional claims to be retained if pharmacodynamic congruence is scientifically

demonstrated.

The journey of Guggul-based nanoformulations from traditional Ayurvedic texts to modern rheumatologic clinics is shaped by a rapidly evolving regulatory ecosystem. While international agencies demand rigor in pharmacokinetics, toxicity, and quality control, Indian frameworks are gradually converging with this evidence-based ethos through ICMR and AYUSH collaborations. Importantly, initiatives recognizing the value of divine and traditional practitioners represent a bold move toward inclusive translational science. By blending ancestral wisdom with nanotechnology and regulatory science, India stands poised to lead in the global phytopharmaceutical revolution—particularly in the domain of personalized, immune-modulating RA therapies.

Outlook

RA, as a paradigm of immune-mediated inflammatory disease, continues to demand therapeutic strategies that go beyond symptom suppression to address its immunological complexity, oxidative imbalance, and degenerative trajectory. This review elucidated the emerging potential of combinatorial phytochemical–mineral–synthetic regimens, particularly those anchored in nanotechnological delivery systems, to disrupt the multifactorial pathways underlying RA pathogenesis. Guggulsterone and allied phytoconstituents, when bioenhanced through SLNs, emulsomes, or folate-conjugated micelles, demonstrate significant improvements in joint-specific drug delivery, intracellular uptake, and cytokine attenuation.

Integration of 3D-printed scaffolds, stimuli-responsive nanocarriers, and chronotherapy-aligned release platforms further refines the personalization of treatment. These innovations not only augment therapeutic efficacy but also mitigate systemic toxicity, bone loss, and drug resistance—offering a multidimensional upgrade over conventional monotherapies. Moreover, initiatives by ICMR and AYUSH to scientifically validate traditional knowledge and involve divine practitioners within a regulated, evidence-based framework, represent a transformative step in harmonizing cultural wisdom with modern pharmacology.

Yet, despite these promising advances, the translation of Guggul-based nanomedicine into standardized, globally acceptable therapeutic regimens remains incomplete. Two critical scientific challenges remain open:

1. Immunological precision vs biological variability: While combinatorial approaches modulate key pathways like NF- κ B, JAK/STAT, and MAPK, there remains insufficient clarity on how these agents behave across heterogeneous RA phenotypes, including seronegative vs seropositive variants, or early- vs late-stage disease. Future research must decode the immune–phytochemical interactome across patient subpopulations using transcriptomic

and immunophenotyping tools.

2. Regulatory dualism and evidence harmonization: The evolving Indian framework, though commendable in recognizing phytopharmaceuticals, still grapples with the dual standards between modern drug approval and classical AYUSH acceptance. The absence of harmonized validation protocols for hybrid therapies (e.g., Guggul-loaded methotrexate liposomes) complicates their adoption in mainstream rheumatology. Bridging this evidence gap demands not just reforms in policy, but cross-disciplinary translational models co-authored by regulators, clinicians, and traditional healers.

Conclusion

In summary, this review integrates molecular, pharmaceutical, and regulatory perspectives to highlight how phytochemical–mineral–synthetic combinations, particularly when delivered via nanocarriers, can address RA's multifactorial pathology. From targeting NF- κ B, JAK/STAT, and MAPK pathways to restoring glycosaminoglycan integrity and reducing oxidative stress, these strategies show promise in joint preservation and immune recalibration. Pharmaceutical advancements such as SLNs, SMEDDS, and stimuli-responsive carriers enhance bioavailability and site-specific delivery, while regulatory initiatives by CDSCO, AYUSH, and ICMR create a framework for clinical translation. Future research should focus on harmonizing quality control, validating clinical efficacy across RA phenotypes, and bridging traditional knowledge with cutting-edge delivery science for patient-specific care.

Authors' Contribution

Conceptualization: Nagaraju Ravouru.

Data curation: Nagaraju Ravouru.

Formal analysis: Arun Rasheed.

Investigation: Prasanna R. Yalavarthi.

Methodology: Arun Rasheed.

Project administration: Jyothi Basini.

Resources: Nagaraju Ravouru, Arun Rasheed, Jyothi Basini, Aruna K. Dommaraju, Rekha D. Allagadda, Prasanna R. Yalavarthi.

Software: Aruna K. Dommaraju.

Supervision: Aruna K. Dommaraju.

Validation: Rekha D. Allagadda.

Visualization: Jyothi Basini.

Writing—original draft: Rekha D. Allagadda.

Writing—review & editing: Prasanna R. Yalavarthi.

Competing Interests

The authors declare that they have no competing interests related to this publication.

Consent to Participate

Not applicable.

Consent to Publish

Not applicable.

Data Availability Statement

No new data were created or analyzed during the study. Data sharing is not applicable to this article.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the author(s) used ChatGPT in order to rephrase to reduce plagiarism, improve the language and grammar. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Ethical Approval

Not applicable.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

References

- Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023-38. doi: [10.1016/s0140-6736\(16\)30173-8](#).
- Jahid M, Khan KU, Rehan UI H, Ahmed RS. Overview of Rheumatoid Arthritis and Scientific Understanding of the Disease. *Mediterr J Rheumatol*. 2023;34(3):284-91. doi: [10.31138/mjr.20230801.oo](#).
- Zou Y, Cheung PP, Teoh LK, Chen C, Lahiri M. Sociodemographic factors as determinants of disease, disability and quality of life trajectories in early rheumatoid arthritis: a multi-ethnic inception cohort study. *Int J Rheum Dis*. 2020;23(1):55-64. doi: [10.1111/1756-185x.13747](#).
- Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25. doi: [10.1002/acr.22783](#).
- Smolen JS, Landewé RBM, Bijlsma JW, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685-99. doi: [10.1136/annrheumdis-2019-216655](#).
- Garhwal A, Kendya P, Soni S, Kori S, Soni V, Kashaw SK. Drug delivery system approaches for rheumatoid arthritis treatment: a review. *Mini Rev Med Chem*. 2024;24(7):704-20. doi: [10.2174/1389557523666230913105803](#).
- El Zorkany B, Alwahshi HA, Hammoudeh M, Al Emadi S, Benitha R, Al Awadhi A, et al. Suboptimal management of rheumatoid arthritis in the Middle East and Africa: could the EULAR recommendations be the start of a solution? *Clin Rheumatol*. 2013;32(2):151-9. doi: [10.1007/s10067-012-2153-7](#).
- Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int J Biochem Cell Biol*. 2009;41(1):40-59. doi: [10.1016/j.biocel.2008.06.010](#).
- Alarcon JF, Karusan NR, Presciutti C, Miras J, Magana JR, Guerra-Rebollo M, et al. Revolutionizing rheumatoid arthritis therapy: the potential of lipid nanocarriers. *RSC Adv*. 2025;15(33):27388-402. doi: [10.1039/d5ra04258e](#).
- Kumar D, Pandey S, Shivhare B, Bala M, Kumar M, Kumar P, et al. Natural polysaccharide-based nanodrug delivery systems for targeted treatment of rheumatoid arthritis: a review. *Int J Biol Macromol*. 2025;310(Pt 3):143408. doi: [10.1016/j.ijbiomac.2025.143408](#).
- Ammon HP. Boswellic acids in chronic inflammatory diseases. *Planta Med*. 2006;72(12):1100-16. doi: [10.1055/s-2006-947227](#).
- Shishodia S, Aggarwal BB. Guggulsterone inhibits NF- κ B and I κ B α kinase activation, suppresses expression of anti-apoptotic gene products, and enhances apoptosis. *J Biol Chem*. 2004;279(45):47148-58. doi: [10.1074/jbc.M408093200](#).
- Meineri G, Martello E, Radice E, Bruni N, Saettone V, Atuahene D, et al. Chronic intestinal disorders in humans and pets: current management and the potential of nutraceutical antioxidants as alternatives. *Animals (Basel)*. 2022;12(7):812. doi: [10.3390/ani12070812](#).
- Maares M, Haase H. Zinc and immunity: an essential interrelation. *Arch Biochem Biophys*. 2016;611:58-65. doi: [10.1016/j.abb.2016.03.022](#).
- Basisht GK, Singh RH, Chandola H. Management of rheumatoid arthritis (Aamavata) using symbiohealth healthcare system. *Ayu*. 2012;33(4):466-74. doi: [10.4103/0974-8520.110513](#).
- Gogtay NJ, Bhatt HA, Dalvi SS, Kshirsagar NA. The use and safety of non-allopathic Indian medicines. *Drug Saf*. 2002;25(14):1005-19. doi: [10.2165/00002018-200225140-00003](#).
- Gaur PK, Mishra S, Purohit S. Solid lipid nanoparticles of guggul lipid as drug carrier for transdermal drug delivery. *Biomed Res Int*. 2013;2013:750690. doi: [10.1155/2013/750690](#).
- Gaur PK, Mishra S, Aeri V. Formulation and evaluation of guggul lipid nanovesicles for transdermal delivery of aceclofenac. *ScientificWorldJournal*. 2014;2014:534210. doi: [10.1155/2014/534210](#).
- Zhang R, Zhang Z, McClements DJ. Nanoemulsions: an emerging platform for increasing the efficacy of nutraceuticals in foods. *Colloids Surf B Biointerfaces*. 2020;194:111202. doi: [10.1016/j.colsurfb.2020.111202](#).
- Meka RR, Venkatesha SH, Acharya B, Moudgil KD. Peptide-targeted liposomal delivery of dexamethasone for arthritis therapy. *Nanomedicine (Lond)*. 2019;14(11):1455-69. doi: [10.2217/nnm-2018-0501](#).
- Shishodia S, Sethi G, Ahn KS, Aggarwal BB. Guggulsterone inhibits tumor cell proliferation, induces S-phase arrest, and promotes apoptosis through activation of c-Jun N-terminal kinase, suppression of Akt pathway, and downregulation of antiapoptotic gene products. *Biochem Pharmacol*. 2007;74(1):118-30. doi: [10.1016/j.bcp.2007.03.026](#).
- Obrzut O, Gostyrńska-Stawna A, Kustrzyńska K, Stawny M, Krajka-Kuźniak V. Curcumin: a natural warrior against inflammatory liver diseases. *Nutrients*. 2025;17(8):1373. doi: [10.3390/nu17081373](#).
- Alivernini S, Firestein GS, McInnes IB. The pathogenesis of rheumatoid arthritis. *Immunity*. 2022;55(12):2255-70. doi: [10.1016/j.immuni.2022.11.009](#).
- Meier FM, Frerix M, Hermann W, Müller-Ladner U. Current immunotherapy in rheumatoid arthritis. *Immunotherapy*. 2013;5(9):955-74. doi: [10.2217/imt.13.94](#).
- Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum*. 1987;30(11):1205-13. doi: [10.1002/art.1780301102](#).
- Begovich AB, Carlton VE, Honigberg LA, Schrodi SJ, Chokkalingam AP, Alexander HC, et al. A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. *Am J Hum Genet*. 2004;75(2):330-7. doi: [10.1086/422827](#).
- Plenge RM, Seielstad M, Padyukov L, Lee AT, Remmers EF, Ding B, et al. TRAF1-C5 as a risk locus for rheumatoid arthritis—a genome-wide study. *N Engl J Med*. 2007;357(12):1199-209. doi: [10.1056/NEJMoa073491](#).
- Karouzakis E, Gay RE, Gay S, Neidhart M. Increased recycling of polyamines is associated with global DNA hypomethylation in rheumatoid arthritis synovial fibroblasts. *Arthritis Rheum*. 2012;64(6):1809-17. doi: [10.1002/art.34340](#).
- Rani L, Mathur P, Verma R, Kumar V, Mishra AK, Sahoo PK. Translation research in therapeutic approaches from conventional to novel nano-therapeutics for rheumatoid arthritis treatment. *Curr Rheumatol Rev*. 2025;21(1):37-53. doi: [10.2174/0115733971288433240408062359](#).

30. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum.* 2006;54(1):38-46. doi: [10.1002/art.21575](https://doi.org/10.1002/art.21575).
31. Sakkas LI, Daoussis D, Liossis SN, Bogdanos DP. The infectious basis of ACPA-positive rheumatoid arthritis. *Front Microbiol.* 2017;8:1853. doi: [10.3389/fmicb.2017.01853](https://doi.org/10.3389/fmicb.2017.01853).
32. Prabha J, Kumar M, Kumar D, Chopra S, Bhatia A. Nano-platform strategies of herbal components for the management of rheumatoid arthritis: a review on the battle for next-generation formulations. *Curr Drug Deliv.* 2024;21(8):1082-105. doi: [10.2174/1567201821666230825102748](https://doi.org/10.2174/1567201821666230825102748).
33. Nikolaeva TI, Laurinavichus KS, Molchanov MV, Kuznetsova SM, Emelyanenko VI, Shekhovtsov PV. Complex of collagen peptides and glycosaminoglycans: prevention and treatment of diseases of the musculoskeletal system. *Biol Bull Rev.* 2024;14(3):S219-32. doi: [10.1134/s2079086424600449](https://doi.org/10.1134/s2079086424600449).
34. Elango J, Zamora-Ledezma C, Ge B, Hou C, Pan Z, Bao B, et al. Paradoxical dual role of collagen in rheumatoid arthritis: cause of inflammation and treatment. *Bioengineering (Basel).* 2022;9(7):321. doi: [10.3390/bioengineering9070321](https://doi.org/10.3390/bioengineering9070321).
35. Richter J, Capková K, Hříbalová V, Vannucci L, Danyi I, Malý M, et al. Collagen-induced arthritis: severity and immune response attenuation using multivalent N-acetyl glucosamine. *Clin Exp Immunol.* 2014;177(1):121-33. doi: [10.1111/cei.12313](https://doi.org/10.1111/cei.12313).
36. Shukla V, Tripathi D, Sharma S, Purohit A, Singh P. Phytomedicine meets nanotechnology: a cellular approach to rheumatoid arthritis treatment. *Nano TransMed.* 2024;3:100051. doi: [10.1016/j.ntm.2024.100051](https://doi.org/10.1016/j.ntm.2024.100051).
37. Jia X, He L, Chang Y, Li J, Wang J, Zhang X, et al. Research trends and developments in nanomaterials for rheumatoid arthritis: a comprehensive bibliometric analysis. *Drug Des Devel Ther.* 2025;19:4355-71. doi: [10.2147/dddt.S514898](https://doi.org/10.2147/dddt.S514898).
38. Zewail MB, Doghish AS, El-Husseiny HM, Mady EA, Mohammed OA, Elbadry AMM, et al. Lipid-based nanocarriers: an attractive approach for rheumatoid arthritis management. *Biomater Sci.* 2024;12(24):6163-95. doi: [10.1039/d4bm01058b](https://doi.org/10.1039/d4bm01058b).
39. Schinocca C, Rizzo C, Fasano S, Grasso G, La Barbera L, Ciccia F, et al. Role of the IL-23/IL-17 pathway in rheumatic diseases: an overview. *Front Immunol.* 2021;12:637829. doi: [10.3389/fimmu.2021.637829](https://doi.org/10.3389/fimmu.2021.637829).
40. Sharma S, Ghosh R, Marianesan AB, Hussain S, Pandey JD, Kumar M. Nanostructured lipid carriers in rheumatoid arthritis: treatment, advancements and applications. *Inflammopharmacology.* 2025;33(3):941-58. doi: [10.1007/s10787-025-01669-2](https://doi.org/10.1007/s10787-025-01669-2).
41. Langdon K, Haleagrahara N. Regulatory T-cell dynamics with abatacept treatment in rheumatoid arthritis. *Int Rev Immunol.* 2018;37(4):206-14. doi: [10.1080/08830185.2018.1465943](https://doi.org/10.1080/08830185.2018.1465943).
42. Wu F, Gao J, Kang J, Wang X, Niu Q, Liu J, et al. B cells in rheumatoid arthritis: pathogenic mechanisms and treatment prospects. *Front Immunol.* 2021;12:750753. doi: [10.3389/fimmu.2021.750753](https://doi.org/10.3389/fimmu.2021.750753).
43. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. *Immunol Rev.* 2010;233(1):233-55. doi: [10.1111/j.0105-2896.2009.00859.x](https://doi.org/10.1111/j.0105-2896.2009.00859.x).
44. Khan H, Yadav N, Sharma S, Rawat R. Management of rheumatoid arthritis by development of nanocarriers and their significance over conventional dosage forms. *Recent Adv Drug Deliv Formul.* 2025;19(1):2-15. doi: [10.2174/0126673878324613240805065651](https://doi.org/10.2174/0126673878324613240805065651).
45. Ali A, Rahul, Jori C, Kumar J, Kumar A, Kanika, et al. Sinapic acid-pullulan based inflammation responsive nanomicelles for the local treatment of experimental inflammatory arthritis. *Int J Biol Macromol.* 2024;278(Pt 3):134903. doi: [10.1016/j.ijbiomac.2024.134903](https://doi.org/10.1016/j.ijbiomac.2024.134903).
46. Li S, Lin J, Wang C, Liu J, Wang Y, Chen Y, et al. Synergistic metabolic modulation of fibroblast-like synoviocytes via targeted dual prodrug nanoparticles to mitigate rheumatoid arthritis. *Acta Pharm Sin B.* 2025;15(1):542-56. doi: [10.1016/j.apsb.2024.11.007](https://doi.org/10.1016/j.apsb.2024.11.007).
47. Pinto AJ, Peçanha T, Meireles K, Benatti FB, Bonfiglioli K, de Sá Pinto AL, et al. A randomized controlled trial to reduce sedentary time in rheumatoid arthritis: protocol and rationale of the Take a STAND for Health study. *Trials.* 2020;21(1):171. doi: [10.1186/s13063-020-4104-y](https://doi.org/10.1186/s13063-020-4104-y).
48. He J, Chu Y, Li J, Meng Q, Liu Y, Jin J, et al. Intestinal butyrate-metabolizing species contribute to autoantibody production and bone erosion in rheumatoid arthritis. *Sci Adv.* 2022;8(6):eabm1511. doi: [10.1126/sciadv.abm1511](https://doi.org/10.1126/sciadv.abm1511).
49. Singh S, Tiwary N, Sharma N, Behl T, Antil A, Anwer MK, et al. Integrating nanotechnological advancements of disease-modifying anti-rheumatic drugs into rheumatoid arthritis management. *Pharmaceuticals (Basel).* 2024;17(2):248. doi: [10.3390/ph17020248](https://doi.org/10.3390/ph17020248).
50. Walsh NC, Crotti TN, Goldring SR, Gravallese EM. Rheumatic diseases: the effects of inflammation on bone. *Immunol Rev.* 2005;208:228-51. doi: [10.1111/j.0105-2896.2005.00338.x](https://doi.org/10.1111/j.0105-2896.2005.00338.x).
51. Alonso N, Monczor F, Echeverría E, Davio C, Shayo C, Fernández N. Signal transduction mechanism of biased ligands at histamine H2 receptors. *Biochem J.* 2014;459(1):117-26. doi: [10.1042/bj20131226](https://doi.org/10.1042/bj20131226).
52. Monczor F, Fernandez N. Current knowledge and perspectives on histamine H1 and H2 receptor pharmacology: functional selectivity, receptor crosstalk, and repositioning of classic histaminergic ligands. *Mol Pharmacol.* 2016;90(5):640-8. doi: [10.1124/mol.116.105981](https://doi.org/10.1124/mol.116.105981).
53. Bakker RA, Schoonus SB, Smit MJ, Timmerman H, Leurs R. Histamine H1-receptor activation of nuclear factor-kappa B: roles for Gβγ- and Gα(q/11)-subunits in constitutive and agonist-mediated signaling. *Mol Pharmacol.* 2001;60(5):1133-42. doi: [10.1124/mol.60.5.1133](https://doi.org/10.1124/mol.60.5.1133).
54. Nautiyal G, Sharma SK, Kaushik D, Pandey P. Nano-based therapeutic strategies in management of rheumatoid arthritis. *Recent Pat Nanotechnol.* 2024;18(4):433-56. doi: [10.2174/1872210517666230822100324](https://doi.org/10.2174/1872210517666230822100324).
55. Figus FA, Piga M, Azzolin I, McConnell R, Iagnocco A. Rheumatoid arthritis: extra-articular manifestations and comorbidities. *Autoimmun Rev.* 2021;20(4):102776. doi: [10.1016/j.autrev.2021.102776](https://doi.org/10.1016/j.autrev.2021.102776).
56. Sanghavi N, Ingrassia JP, Korem S, Ash J, Pan S, Wasserman A. Cardiovascular manifestations in rheumatoid arthritis. *Cardiol Rev.* 2024;32(2):146-52. doi: [10.1097/crd.0000000000000486](https://doi.org/10.1097/crd.0000000000000486).
57. Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. *Pharmacol Rev.* 2005;57(2):163-72. doi: [10.1124/pr.57.2.3](https://doi.org/10.1124/pr.57.2.3).
58. Chan ES, Cronstein BN. Methotrexate--how does it really work? *Nat Rev Rheumatol.* 2010;6(3):175-8. doi: [10.1038/nrrheum.2010.5](https://doi.org/10.1038/nrrheum.2010.5).
59. Prasad P, Verma S, Surbhi, Ganguly NK, Chaturvedi V, Mittal SA. Rheumatoid arthritis: advances in treatment strategies. *Mol Cell Biochem.* 2023;478(1):69-88. doi: [10.1007/s11010-022-04492-3](https://doi.org/10.1007/s11010-022-04492-3).
60. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis.* 2013;72 Suppl 2:ii111-5. doi: [10.1136/annrheumdis-2012-202576](https://doi.org/10.1136/annrheumdis-2012-202576).
61. Szekanecz Z, Buch MH, Charles-Schoeman C, Galloway J, Karpouzas GA, Kristensen LE, et al. Efficacy and safety of JAK inhibitors in rheumatoid arthritis: update for the practising clinician. *Nat Rev Rheumatol.* 2024;20(2):101-15. doi: [10.1038/s41584-023-01062-9](https://doi.org/10.1038/s41584-023-01062-9).

62. Rahman I, Kode A, Biswas SK. Assay for quantitative determination of glutathione and glutathione disulfide levels using enzymatic recycling method. *Nat Protoc.* 2006;1(6):3159-65. doi: [10.1038/nprot.2006.378](https://doi.org/10.1038/nprot.2006.378).
63. Brigelius-Flohé R, Maiorino M. Glutathione peroxidases. *Biochim Biophys Acta.* 2013;1830(5):3289-303. doi: [10.1016/j.bbagen.2012.11.020](https://doi.org/10.1016/j.bbagen.2012.11.020).
64. Ursini F, Maiorino M, Forman HJ. Redox homeostasis: the golden mean of healthy living. *Redox Biol.* 2016;8:205-15. doi: [10.1016/j.redox.2016.01.010](https://doi.org/10.1016/j.redox.2016.01.010).
65. Rajak P, Karmakar A, Sarma S, Bhuyan B. Topical administration of nanostructured lipid carriers as a viable approach to reduce inflammation: a review. *Antiinflamm Antiallergy Agents Med Chem.* 2025;24(1):26-42. doi: [10.2174/0118715230311633240708075738](https://doi.org/10.2174/0118715230311633240708075738).
66. Sriram A, Ithape H, Singh PK. Deep-insights: nanoengineered gel-based localized drug delivery for arthritis management. *Asian J Pharm Sci.* 2025;20(1):101012. doi: [10.1016/j.ajps.2024.101012](https://doi.org/10.1016/j.ajps.2024.101012).
67. Thabet NM, Abdel-Rafei MK, Amin MM. Fractionated whole body γ -irradiation aggravates arthritic severity via boosting NLRP3 and RANKL expression in adjuvant-induced arthritis model: the mitigative potential of ebselen. *Inflammopharmacology.* 2023;31(4):1929-49. doi: [10.1007/s10787-023-01238-5](https://doi.org/10.1007/s10787-023-01238-5).
68. Turrubiates-Hernández FJ, Márquez-Sandoval YF, González-Estevez G, Reyes-Castillo Z, Muñoz-Valle JF. The relevance of selenium status in rheumatoid arthritis. *Nutrients.* 2020;12(10):3007. doi: [10.3390/nu12103007](https://doi.org/10.3390/nu12103007).
69. Shishodia S, Azu N, Rosenzweig JA, Jackson DA. Guggulsterone for chemoprevention of cancer. *Curr Pharm Des.* 2016;22(3):294-306. doi: [10.2174/138161282266615112153117](https://doi.org/10.2174/138161282266615112153117).
70. Ijaz S, Iqbal J, Abbasi BA, Tufail A, Yaseen T, Uddin S, et al. Current stage of preclinical and clinical development of guggulsterone in cancers: Challenges and promises. *Cell Biol Int.* 2024;48(2):128-42. doi: [10.1002/cbin.12112](https://doi.org/10.1002/cbin.12112).
71. Xu HB, Chen XZ, Yu ZL, Xue F. Guggulsterone from *Commiphora mukul* potentiates anti-glioblastoma efficacy of temozolomide in vitro and in vivo via down-regulating EGFR/PI3K/Akt signaling and NF- κ B activation. *J Ethnopharmacol.* 2023;301:115855. doi: [10.1016/j.jep.2022.115855](https://doi.org/10.1016/j.jep.2022.115855).
72. Xu A, Yang R, Zhang M, Wang X, Di Y, Jiang B, et al. Macrophage targeted triptolide micelles capable of cGAS-STING pathway inhibition for rheumatoid arthritis treatment. *J Drug Target.* 2022;30(9):961-72. doi: [10.1080/1061186x.2022.2070173](https://doi.org/10.1080/1061186x.2022.2070173).
73. Teja PK, Mithiya J, Kate AS, Bairwa K, Chauthe SK. Herbal nanomedicines: recent advancements, challenges, opportunities and regulatory overview. *Phytomedicine.* 2022;96:153890. doi: [10.1016/j.phymed.2021.153890](https://doi.org/10.1016/j.phymed.2021.153890).
74. Wahi A, Bishnoi M, Raina N, Singh MA, Verma P, Gupta PK, et al. Recent updates on nano-phyto-formulations based therapeutic intervention for cancer treatment. *Oncol Res.* 2023;32(1):19-47. doi: [10.32604/or.2023.042228](https://doi.org/10.32604/or.2023.042228).
75. Adarsh Krishna TP, Ajeesh Krishna TP, Edachery B, Antony Ceasar S. Guggulsterone - a potent bioactive phytosteroid: synthesis, structural modification, and its improved bioactivities. *RSC Med Chem.* 2024;15(1):55-69. doi: [10.1039/d3md00432e](https://doi.org/10.1039/d3md00432e).
76. Malve H, Bhalerao P. Past, present, and likely future of nutraceuticals in India: evolving role of pharmaceutical physicians. *J Pharm Bioallied Sci.* 2023;15(2):68-74. doi: [10.4103/jpbs.jpbs_96_23](https://doi.org/10.4103/jpbs.jpbs_96_23).
77. Gatt AR, Vella Bonanno P, Zammit R. Ethical considerations in the regulation and use of herbal medicines in the European Union. *Front Med Technol.* 2024;6:1358956. doi: [10.3389/fmedt.2024.1358956](https://doi.org/10.3389/fmedt.2024.1358956).