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Novel Insights and Approaches in Rheumatoid Arthritis Management: Pathogenesis, Diagnosis and Therapy

Rahul Punia[1]; Dr. Arun Garg[2]; Neha Bhamboo[3]; Dr. Ashutosh Upadhayay[4]

[2]Professor
[1;2;3;4]MVN University Palwal, Haryana

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Abstract: Rheumatoid arthritis (RA) is a long-term autoimmune condition where the body's immune system unwillingly attacks its own joints, leading to persistent inflammation, swelling (synovitis), and the gradual breakdown of joint tissues. At the heart of RA lies a complex interplay between immune cells especially B cells and T cells which release inflammatory messengers called cytokines. These molecules fuel the ongoing inflammation and contribute to joint damage over time. This review highlights how these immune cells drive the disease process and sustain tissue injury. In addition to conventional therapies, certain nutritional supplements like curcumin, guggul, and glucosamine–chondroitin blends offer mild relief. While not a replacement for standard treatments, they may serve as helpful add-ons in a broader management plan. Excitingly, nanotechnology is opening new frontiers in RA care. Unlike traditional drugs that circulate throughout the body, nanocarriers are engineered to deliver medication directly to inflamed joints. This targeted approach not only boosts treatment precision but also reduces unwanted side effects, offering a glimpse into the future of personalised RA therapy.

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I. INTRODUCTION

➢ *Prevalence and Clinical Features of RA:*

Rheumatoid arthritis (RA) affects approximately 1–3% of the population, with a notable female predominance about 3:1 especially in early adulthood, which tends to diminish with advancing age. Genetic predisposition plays a significant role in susceptibility to the disease. RA is a chronic, progressive autoimmune condition marked by irreversible damage to synovial-lined joints. This leads to loss of joint space, bone erosion, functional impairment, and deformity. A hallmark of RA is the degradation of the extracellular matrix, which contributes to the destruction of cartilage, tendons, ligaments, and bone. Clinically, RA presents as a symmetric polyarthritis, with articular and periarticular manifestations including joint swelling, tenderness on palpation, morning stiffness, and significant limitations in mobility(1). Early diagnosis and prompt initiation of treatment can prevent or substantially slow joint damage in up to 90% of cases, thereby averting permanent disability. The development of standardized tools to assess disease activity and remission has enabled more precise and proactive treatment strategies, aiming to halt disease progression before irreversible joint damage occurs. Outcomes have significantly improved with the recognition of the importance of early diagnosis and early intervention using disease-modifying antirheumatic drugs (DMARDs). The therapeutic goal is to achieve remission or, at minimum, low disease activity ideally within six months of initiating treatment. Methotrexate remains the cornerstone of first-line therapy, typically prescribed at an optimal dose of 25 mg per week, often in combination with glucocorticoids. This regimen helps 40–50% of patients reach remission or low disease activity(2). For those who do not respond adequately, sequential use of targeted biologics such as TNF inhibitors or Janus kinase (JAK) inhibitors alongside methotrexate has enabled up to 75% of these patients to achieve therapeutic targets over time. These biologic therapies have emerged in response to evolving insights into RA pathogenesis(3). While the cost of biologics can be substantial, the introduction of biosimilars drugs that are nearly identical to their reference biologics but more affordable has begun to alleviate the financial burden associated with RA treatment. The immunological landscape of rheumatoid arthritis (RA) is complex and multifactorial. Key contributors include T-cell-mediated antigen-specific responses, T-cell-independent cytokine networks, and the aggressive, tumour-like proliferation of synovial tissue. These mechanisms collectively drive chronic inflammation and joint destruction. In recent years, the role of autoantibodies particularly rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) has regained prominence in understanding RA pathogenesis. These autoantibodies not only serve as diagnostic markers but also actively participate in disease progression by amplifying

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inflammatory cascades and tissue damage. Understanding these pathogenic pathways has paved the way for the development of targeted therapeutic strategies. By focusing on specific immune mechanisms, such as cytokine inhibition, T-cell modulation, and B-cell depletion, modern interventions aim to suppress synovial inflammation and prevent irreversible joint damage. This mechanistic insight has transformed RA management, enabling precision medicine approaches that align treatment with individual immunological profiles(4).

- *Epidemiological Foundations for Arthritis Pathogenesis and Therapy:*

Between 1995 and 2007, a study involving 466 individuals diagnosed with rheumatoid arthritis (RA) revealed key demographic and epidemiological insights. The average age of participants was 55.6 years, with a clear female predominance nearly 69% were women. 66% of the cohort tested positive for rheumatoid factor, reinforcing its diagnostic relevance. The annual incidence of RA during this period was approximately 40.9 cases per 100,000 individuals. Women exhibited a significantly higher incidence rate (53.1 per 100,000) compared to men (27.7 per 100,000). Over time, a moderate increase in RA incidence was observed among women across all age groups, while rates among men remained relatively stable. This trend was also reflected in overall disease prevalence. In 1995, RA affected about 0.62% of the U.S. adult population roughly 1.3 million individuals. By 2005, this figure had risen to 0.72%, equal to approximately 1.5 million adults. These findings underscore a consistent rise in the burden of RA over the decade(5). The annual incidence of new RA cases varies widely from as few as 12 to as many as 1200 per 100,000 individuals depending on several factors, including gender, racial or ethnic background, and the specific time period under study. This variability in incidence shows the multifactorial nature of RA. Both genetic predisposition and environmental exposures contribute to disease onset and progression. For instance, certain HLA-DR alleles have been linked to increased susceptibility, while lifestyle factors such as smoking and infections may act as environmental triggers(6). The prevalence of rheumatoid arthritis (RA) varies among geographical regions, with higher rates observed in industrialized nations and urban populations. These disparities are influenced by a complex interplay of genetic predisposition, environmental exposures, demographic factors, socioeconomic conditions, and the lack of disease reporting systems. While the number of individuals diagnosed with RA has increased over time, encouraging trends show a decline in disease severity, mortality rates, and associated comorbidities. This improvement is largely attributed to advances in early diagnosis, targeted therapies, and comprehensive disease management(7). Emerging research supports the “mucosal origin” hypothesis, which proposes that RA may initiate at mucosal surfaces such as the oral cavity, lungs, or gastrointestinal tract. Genetic susceptibility interacts with environmental triggers such as microbial agents or pollutants to initiate autoimmune responses that eventually manifest in joint pathology.

II. PATHOPHYSIOLOGY OF ARTHRITIS

- *Cellular and Molecular Mechanisms:*

Rheumatoid Arthritis is characterized by the invasion of provocative cells into the joints. The pathogenesis of RA comprise of a complex handle including Pannus arrangement ,synovial fibroblast expansion causing penetration of T-cells, B-cells ,macrophages and plasma cells .Be that as it may, it comprise of arbiters to shape a arrange of forbid framework counting cytokines, tumor corruption calculate, interleukins which fortifies the advancement of pro-inflammatory reaction on the cell .Thus, point of treatment is to avoid joint devastation by progressing useful capacity ,diminishing torment & irritation in arrange to keep up a ordinary way of life(8). The current therapeutic approach to rheumatoid arthritis (RA) involves a strategic combination of medications aimed at both symptom relief and disease control. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to alleviate pain and reduce inflammation, offering patients short-term comfort and improved mobility. However, NSAIDs do not alter the underlying disease process and therefore cannot prevent long-term joint damage. To address disease progression, glucocorticoids are often introduced. These agents possess potent anti-inflammatory properties and can slow the structural deterioration of joints when used appropriately. Their role is particularly valuable in early disease management or during acute flares, although long-term use requires careful monitoring due to potential side effects(9). In addition to these, disease-modifying antirheumatic drugs (DMARDs) both synthetic and biologically derived form the backbone of RA treatment. Natural anti-rheumatic agents are also being explored for their complementary benefits, especially in integrative and phytopharmaceutical approaches.

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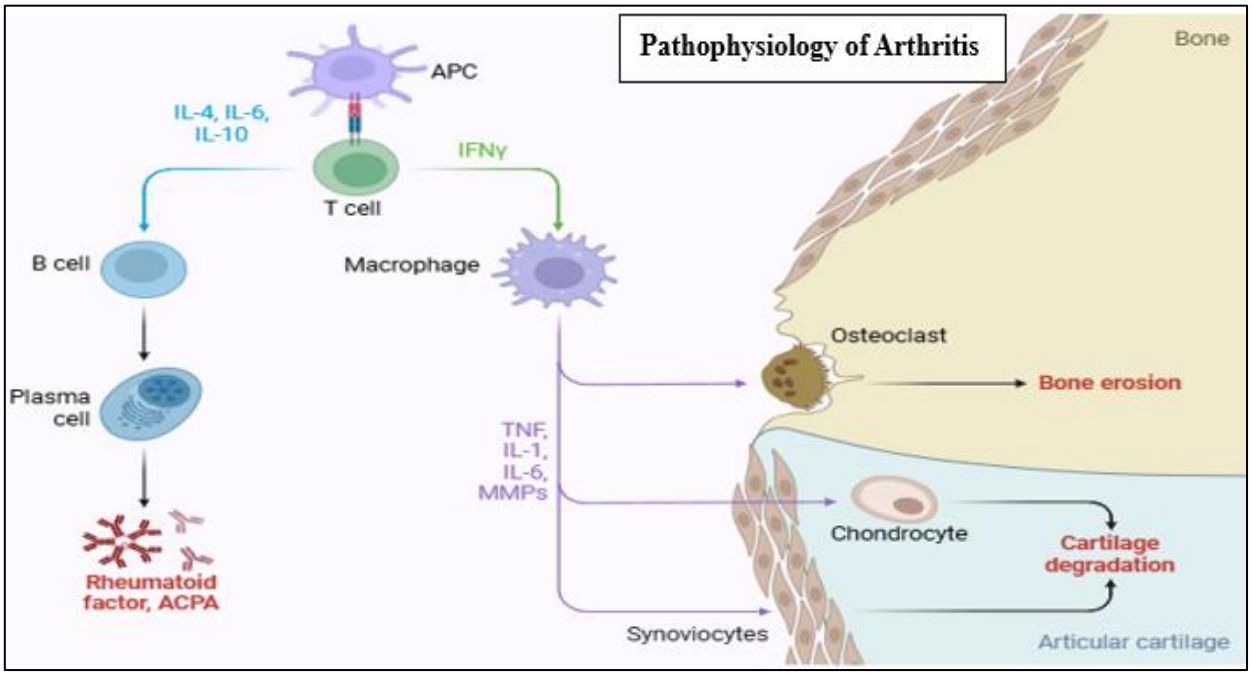

Fig 1 Schematic Overview of Rheumatoid Arthritis Pathophysiology, Illustrating Key Cellular Components, Inflammatory Mediators, and the Cascade Leading to Synovial Inflammation and Joint Destruction.

➢ *Genetic, Environmental, and Infectious Triggers in Rheumatoid Arthritis:*

- *Preclinical rheumatoid arthritis (RA)(10):* Refers to the early, asymptomatic phase of the disease, during which immunological changes begin to emerge before clinical symptoms are evident. This stage is characterized by the presence of specific autoantibodies in the bloodstream, indicating an underlying immune dysregulation. Key autoantibodies associated with preclinical RA include Calpastatin, p68, RA33, perinuclear factor, and IgM rheumatoid factor (RF). These biomarkers reflect early immune activation and are often detectable years before joint inflammation becomes clinically apparent. According to the American Rheumatism Association, the formal diagnosis of RA is strongly supported by the presence of serological markers particularly rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) which serve as critical indicators of disease progression and risk.
- *Genetic Insights and Therapeutic Potential in Arthritis:* The genetic insights of rheumatoid arthritis (RA) have been widely explored through meta-analyses and genome-wide association studies (GWAS), which have identified numerous susceptibility loci linked to disease onset and progression. These studies have deepened our understanding of how inherited variations in immune-regulatory genes contribute to the pathogenesis of RA(11).Gene therapy has emerged as a promising avenue in RA research, offering the potential to deliver therapeutic genes directly to affected joints with high efficiency and minimal tissue disruption. This approach aims to modulate local immune responses and reduce inflammation at the site of disease activity.
- *Environmental and Infectious Triggers in Arthritis:* The development of rheumatoid arthritis (RA) is not solely attributed to genetic predisposition or environmental exposure; rather, it arises from a complex interplay between both, alongside infectious agents. Bacterial and viral infections have been implicated in RA pathogenesis through immunological mechanisms such as molecular mimicry, epitope spreading, and superantigen expression. These processes can mislead the immune system into attacking self-tissues, initiating autoimmunity. A key immunological event involves the activation of citrulline-specific pathogenic T cells and the production of anti-citrullinated protein antibodies (ACPAs) by B cells(12). The interaction between ACPAs and citrullinated proteins within joint tissues promotes localized inflammation, contributing to the chronic nature of RA. In addition to infectious triggers, several modifiable environmental risk factors play a significant role in disease onset and progression. These include: Smoking, Alcohol consumption etc.

III. CONVENTIONAL THERAPEUTIC APPROACHES IN RA

Although a definitive cure for rheumatoid arthritis (RA) remains vacant, current therapeutic strategies aim to reduce pain, reduce inflammation, minimize joint damage, and prevent deformities ultimately helping patients maintain a healthier and more active life. These approaches focus on controlling symptoms and slowing disease progression rather than complexing the condition(13).

➢ *Topical Treatments:*

Recent research shows that when it comes to treating osteoarthritis (OA), both topical and oral NSAIDs (non-steroidal anti-inflammatory drugs) are similarly effective in reducing pain and they outperform paracetamol. Especially promising is that topical NSAIDs come with a lower risk of

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gastrointestinal side effects compared to both oral NSAIDs and paracetamol. This outcome is proved by data from 122 randomized controlled trials, making it a strong case for considering topical options, for those worried about stomach-related issues. Real-world data predicts that topical NSAIDs have better overall safety than oral NSAIDs. They also reduces risks of mortality, CVS disease, and gastrointestinal bleeding than paracetamol in real world(14).A review found that approximately 60% of patients using topical NSAIDs experienced at least a 50% reduction in pain. This level of relief was comparable to that achieved with oral NSAIDs and slightly more effective than the response to topical treatments. These results highlight the impact of topical NSAIDs in managing arthritis pain, offering a non-invasive alternative with similar efficacy(15).

- *Capsaicin (Mechanism and Evolving Understanding):* Capsaicin, the active compound found in chili peppers, has shown promise in pain relief when applied topically. It works by interacting with TRPV1 receptors on pain-sensing neurons, leading to their desensitization over time. This process reduces the transmission of pain signals, offering therapeutic benefits for conditions such as osteoarthritis and neuropathic pain. Capsaicin also depletes substance P-a neuropeptide involved in pain perception, but recent research has questioned whether this depletion is central to its analgesic effects. As our understanding of capsaicin's mechanisms evolves, its role in pain management continues(16). In clinical studies, the intervention typically involved applying topical capsaicin at concentrations of 0.025% or 0.075%, four times a day. This regimen was compared to a placebo over a follow-up period of three to four weeks. Clinical studies have shown that topical capsaicin significantly reduces osteoarthritis pain in the hands, knees, and multiple joints, with outcomes superior to those seen with placebo. However, the integrity of blinding in these trials was compromised due to the characteristic burning sensation caused by capsaicin, which made it easy for participants to identify the active treatment. In a 12-week randomized, multicenter trial involving 113 patients, participants received either 0.025% capsaicin cream or a placebo, applied four times daily. The results showed that capsaicin provided significant pain relief over the 4-12-week treatment period. 81% of patients in the capsaicin group reported improvement, compared to 54% in the placebo group. These findings support the efficacy of low-dose topical capsaicin in managing osteoarthritis-related pain(17).

➢ *Oral Analgesics:*

Pain relief medications, known as analgesics, are grouped into three classes based on their strength, as outlined by the World Health Organization (WHO). First includes mild painkillers like paracetamol and NSAIDs such as ibuprofen and celecoxib. The second involves moderate-strength opioids like codeine, while the Third includes strong opioids such as oxycodone and fentanyl. Managing pain and inflammation is a key part of patient care. Effective pain control not only improves comfort but also helps patients recover faster whether they're in the hospital or at home by minimizing the time they're unable to perform daily activities. It also supports more efficient use of healthcare resources(18).

- *Acetaminophen:* It is widely used as a first-line analgesic for managing a variety of painful conditions. It is often chosen for mild to moderate pain, especially in osteoarthritis; its analgesic efficacy may be limited compared to non-steroidal anti-inflammatory drugs (NSAIDs), particularly in inflammatory pain settings(19). A meta-analysis of 10 randomized trials involving 3,541 patients provided high-quality evidence that acetaminophen offers only modest and clinically insignificant benefits for short-term pain relief in osteoarthritis. These findings were further supported by a network meta-analysis comparing various analgesics for OA pain, which concluded that acetaminophen was no more effective than placebo, regardless of the dose. Specifically, the observed difference was just 4 mm on a 0–100 mm visual analog scale (VAS), a change considered too small to be meaningful in clinical practice(20). The American College of Rheumatology and the Arthritis Foundation (ACR/AF) have issued a conditional recommendation for using acetaminophen. It may not be highly effective when used alone, could still be a reasonable option for short-term relief especially for patients who aren't able to take other pain medications(21). According to the 2019 guidelines from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO), acetaminophen is conditionally recommended. It's suggested only for short-term, occasional pain relief used alongside long-term treatments like chondroitin sulfate or glucosamine(22).
- *Cyclooxygenase Inhibitors (NSAIDs):* Non-steroidal anti-inflammatory drugs, or NSAIDs, are often used to help manage pain in people with osteoarthritis. They work by blocking an enzyme called cyclooxygenase (COX), which helps reduce the production of certain chemicals called prostaglandins that trigger inflammation and pain in the body(23). International guidelines, such as those from the Osteoarthritis Research Society International (OARSI) and the American College of Rheumatology (ACR), recommend using nonsteroidal anti-inflammatory drugs (NSAIDs) as a first-line option for relieving pain in people with arthritis(24).

➢ *Joint-Targeted Injections:*

- *Corticosteroid Injections:* Corticosteroid injections are used to directly target areas of inflammation or pain, such as in tendinitis or joints affected by osteoarthritis. These injections can provide moderate pain relief and may slightly improve joint function. A Cochrane review found that the benefits might be limited. The side effects of these injections were similar to those of a placebo, and the overall quality of the evidence was very low due to inconsistent findings and the small size and poor quality(25).
- *Platelet-Rich Plasma (PRP):* Studies generally supports that PRP can help relieve pain in the short to medium term

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for people with knee osteoarthritis. However, it's still difficult to say how effective it truly is overall. That's because different studies use different methods to prepare and apply PRP, making it hard to compare results(26). A randomized trial involving 288 patients, which was part of a larger meta-analysis, found that intra-articular PRP (platelet-rich plasma) injections didn't offer any noticeable benefits for pain relief or joint structure when compared to a simple saline placebo(27).

- *Botulinum Toxin:* Botulinum toxin is a complex substance produced by certain strains of the bacterium Clostridium botulinum. While it's best known for its cosmetic uses, it has also shown promise as a treatment for osteoarthritis (OA). Research suggests that it may help relieve joint pain by targeting nerve signals involved in pain and inflammation(28). Injecting Botulinum neurotoxin type A directly into the joint may help reduce pain and inflammation linked to osteoarthritis (OA). It works by calming the nerve endings (nociceptors) that release substances responsible for triggering inflammation and pain, potentially easing discomfort and improving joint function. Botulinum toxin (BTX) may also help reduce pain by affecting how nerves communicate(29). Studies including one using a rat model of trigeminal neuralgia suggest that BTX can lower the activity of certain sodium channels involved in pain signaling. It may also reduce the release of pain-related chemicals like substance P, CGRP, and the inflammatory molecule IL-1β, which all play a role in triggering and maintaining pain and inflammation(30). Clinical studies have found that a single injection of botulinum toxin (BTX) directly into the knee joint can help relieve chronic, hard-to-treat pain in some people with osteoarthritis. However, not everyone experiences the same benefit, suggesting that different types of patients may respond differently to this treatment(31).

IV. MICRONUTRIENT THERAPY

➢ *Omega-3 Fatty Acids Supplements:*

A study comparing low and high doses of (omega-3 fatty acids) found that the lower dose (0.45g) actually led to better pain relief and improved joint function over two years than the higher dose (4.5g). Both doses caused similar side effects, mainly stomach upset and acid reflux. While these have shown promising results in treating rheumatoid arthritis, likely because of its anti-inflammatory effects(32).

➢ *Curcumin (Curcuma longa):*

Curcumin, a bright yellow compound scientifically known as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is widely recognized for its powerful biological effects. It exhibits anti-inflammatory, antioxidant, and anti-tumor properties. Its anti-inflammatory action is considered central to its therapeutic potential, influencing a wide range of disease-modulating activities. This compound is primarily sourced from the root of *Curcuma aromatica Salisb* and the rhizome of *Curcuma longa L.* commonly known as turmeric both belonging to the Zingiberaceae family. In traditional Chinese medicine, these herbs have long been valued for their ability in blood circulation and alleviate blood stasis. They've been used to relieve pain, reduce inflammation, and treat various ailments(33). Curcumin exerts anti-inflammatory effects by modulating key cellular signaling pathways and suppressing the production of inflammatory mediators. It interacts directly with Toll-like receptors (TLRs), which play a crucial role in the body's immune response, and influences several downstream pathways including nuclear factor kappa-B (NF-κB), mitogen-activated protein kinases (MAPK), and activator protein 1 (AP-1)(34). Through these mechanisms, curcumin helps regulate the expression of inflammatory molecules and contributes to the management of various inflammatory conditions. Curcumin can also inhibit NF-κB activity by activating peroxisome proliferator-activated receptor gamma (PPARγ)(35), a nuclear receptor that controls inflammation and metabolic processes. This multi-targeted approach shows curcumin's therapeutic potential in treating chronic inflammatory diseases. Curcumin also exerts its anti-inflammatory effects by modulating the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, a key signaling cascade involved in immune regulation and inflammation. By influencing this pathway, curcumin helps suppress the expression of pro-inflammatory cytokines and contributes to the resolution of inflammatory responses. Another important mechanism involves curcumin's interaction with the NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome a cytosolic multiprotein complex implicated in the pathogenesis of various inflammatory diseases. The NLRP3 inflammasome comprises three core components: a sensor protein, an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and the protease caspase-1. Curcumin can inhibit the assembly of this complex directly or suppress its activation indirectly by downregulating the NF-κB pathway. This dual mode of action highlights curcumin's potential as a therapeutic agent in managing chronic inflammation. Oxidative stress plays a significant role in driving inflammatory processes. It arises from the excessive accumulation of reactive oxygen species (ROS), which in turn activates key transcription factors linked to inflammation. This cascade amplifies the inflammatory response and contributes to the progression of various chronic diseases. Curcumin helps counteract this effect by reducing ROS production. It achieves this through its inhibitory action on nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and by enhancing the activity of endogenous antioxidant enzymes. A central mechanism in this antioxidant response involves the Nrf2-Keap1 signaling pathway, which regulates the expression of protective genes. By mitigating oxidative stress, curcumin indirectly suppresses inflammation, reinforcing its role as a potent anti-inflammatory agent(36).

- *Curcumin's Role in Managing Arthritis:* Several types of arthritis, but the most common ones are osteoarthritis (OA), rheumatoid arthritis (RA), and gouty arthritis. Among these, osteoarthritis is the most widespread. It is a joint disease that causes the cartilage to wear down over time, often leading to pain and swelling. Inflammation also plays a role in its development. Osteoarthritis usually affects people over the age of 50 and is more common in

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women(37). Curcumin helps reduce joint inflammation and relieve pain, mainly through its anti-inflammatory and cartilage-protective actions. In studies using primary cultured chondrocytes (the cells found in cartilage), curcumin was shown to lower the expression of key inflammatory molecules such as IL-1β and TNF-α, as well as cartilage-degrading enzymes like MMP-1, MMP-3, MMP-13, and ADAMTS5. At the same time, it increased the levels of CITED2 a transcriptional regulator known to protect cartilage structure and function. These combined effects highlight curcumin's potential in preserving joint health and managing arthritis symptoms(38). Curcumin helps lower inflammation in arthritis by reducing the production of key inflammatory mediators, including TNF-α, IL-17, IL-1β, TGF-β, and COX-2. These molecules are known to drive joint pain and swelling. In experimental rat models of arthritis induced by agents like lipopolysaccharide (LPS), Collagen II, and Monoiodoacetic acid curcumin has been shown to reduce both cartilage damage and synovial inflammation. This highlights its potential as a natural compound for managing arthritis symptoms and protecting joint tissues(39). Gouty arthritis, commonly known as gout, is a metabolic condition marked by repeated episodes of joint inflammation. It is caused by high levels of uric acid in the blood (hyperuricemia), which leads to the buildup of monosodium urate (MSU) crystals in the joints and surrounding tissues. This condition typically affects adults over the age of 40(40). Curcumin has shown potential in easing gout-related inflammation. It works by blocking the TLR4/NF-κB signaling pathway and suppressing the activity of the NLRP3 inflammasome both of which play key roles in triggering the inflammatory response caused by MSU crystals(41).

➢ *Guggul (Commiphora mukul):*

The guggul tree (*Commiphora mukul*), part of the Burseraceae family, grows mainly in the dry regions of India, Pakistan, and Bangladesh. During the winter season, a yellowish resin known as oleogum is tapped from the tree. On average, each tree yields about 700 to 900 grams of this resin, which is traditionally used for its medicinal properties. Guggul, also known as balsam or oleo gum resin, is found in balsam canals located in the phloem of the leaf veins and stem base of the *Commiphora mukul* tree(42). This resin is a complex blend of minerals, gums, terpenes, essential oils, sterols (such as Guggulsterol I–V), sterones (including Z-, E-, M-guggulsterone and dehydroguggulsterone-M), ferrulates, lignans, and flavanones. The ethyl acetate soluble portion of the resin, known as guggulipid, contains several bioactive compounds like diterpenoids, triterpenoids, steroids, lignans, and fatty tetrol esters. When fractionated based on pH, guggulipid yields approximately 95% neutral, 4% acidic, and 1% basic fractions. Further separation of the neutral fraction gives 88% non-ketonic and 12% ketonic components. The ketonic fraction is rich in steroids, including the two isomers E-(cis-) and Z-(trans-) guggulsterone(43). Phenolic compounds are naturally found in many plants and are known for their strong antioxidant and anti-inflammatory properties. Common types include hydroxybenzoic acid derivatives like gallic acid, protocatechuic acid, gentisic acid, vanillic acid, p-hydroxybenzoic acid, syringic acid, and ellagic acid. There are also cinnamic acid derivatives such as caffeic acid, chlorogenic acid, ferulic acid, sinapic acid, and p-coumaric acid(44).

- *Guggul's Role in managing Arthritis:* Guggulsterone helps fight arthritis by blocking NF-κB activation, a key inflammatory pathway, it reduces the production of inflammatory molecules like COX-2 and MMP-9, which are known to do joint damage and inflammation in arthritis(45). By targeting these mediators, the sterol supports joint health and may slow the progression of the disease. The anti-arthritic and anti-inflammatory effects of gum guggul were first reported by Gujral and colleagues in 1960. Later studies compared the activity of Commiphora mukul (guggul) with common non-steroidal anti-inflammatory drugs (NSAIDs) like phenylbutazone and ibuprofen(46). In one such study, researchers induced an arthritis-like condition in albino rabbits by injecting a mycobacterial adjuvant mixed with liquid paraffin into the right hock joint mimicking rheumatoid arthritis in humans. The progression of this condition was monitored over five months, both with and without treatment. During the study, phenylbutazone and ibuprofen were given orally at 100 mg/kg per day, while fraction 'A' of gum guggul was administered at 500 mg/kg per day. All treatments lasted for five months, allowing researchers to evaluate and compare their anti-inflammatory effects. All the three drugs used reduced the joint swelling(47).

➢ *Glucosamine and Chondroitin: Joint Health Support Agents :*

Glucosamine and chondroitin for treating knee osteoarthritis (OA) have shown mixed results(48). While some studies found little benefit, especially with glucosamine hydrochloride, others reported modest improvements when higher-quality forms were used. Mainly, glucosamine sulfate at a dose of 1,500 mg per day and chondroitin at 800 mg per day showed significant, limited relief in knee pain compared to placebo(49). These findings suggest that the type and dosage of these supplements may influence their effectiveness(50). The placebo effect has played a significant role in studies on glucosamine and chondroitin. A clear example is the Glucosamine/Chondroitin Intervention Trial (GAIT), where about 60% of participants reported at least a 20% reduction in pain regardless of whether they received the actual supplement or a placebo. This highlights the strong psychological and subjective influence in pain perception during arthritis treatment(51).

V. NEW HORIZONS IN RHEUMATOID ARTHRITIS THERAPY

➢ *Nanomedicine:*

Nanomedicine represents a dynamic intersection of nanotechnology, pharmaceutical sciences, and biomedical research. Over recent years, it has evolved rapidly, driven by the development of innovative nano-formulations designed for therapeutic delivery, diagnostic imaging, and integrated applications. According to the U.S. Food and Drug Administration (FDA), nano-formulations are defined as

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products that incorporate nanoparticles typically within the size range of 1–100 nano-meters (nm)(52). This definition also extends to formulations outside this range, provided they exhibit dimension-dependent properties that influence their biological behaviour, efficacy, or safety profile. These nano-formulations offer several advantages over conventional free drug molecules, including enhanced solubility, improved pharmacokinetic profiles, greater therapeutic efficacy, and reduced systemic toxicity. To date, over 50 nano-pharmaceuticals have reached the market, encompassing a wide array of nano-formulation platforms. Among these, lipid-based nanoparticles have emerged as the most prominent. These are typically multicomponent systems composed of a phospholipid, an ionizable lipid, cholesterol, and a PEGylated lipid, each contributing to the carrier's stability and functionality(53). The most traditional and well-studied form of lipid nanoparticles is the liposome. First described in 1961 by British haematologist Alec D. Bangham, liposomes were visualized under an electron microscope when negatively stained dry phospholipids spontaneously assembled into spherical vesicles with a bilayer structure. This discovery laid the foundation for decades of liposomal research. By 1980, the development of actively targeted liposomes engineered with surface-bound ligands marked a significant advancement. These targeted systems demonstrated improved site-specific drug delivery by enhancing accumulation at diseased tissues, organs, or cells, while minimizing off-target distribution. As a result, the therapeutic performance of these advanced liposomes is markedly superior to that of conventional formulations. Although liposomes have been extensively studied for over three decades as versatile carriers for a wide range of drug molecules, it was not until the 1990s that the first liposomal drug received approval from the U.S. Food and Drug Administration (FDA). This landmark approval was granted to Doxil®, a stealth liposomal formulation encapsulating the chemotherapeutic agent doxorubicin. Doxil® is clinically employed in the treatment of ovarian cancer, metastatic breast cancer, and various forms of myeloma. The encapsulation of doxorubicin within PEGylated liposomes significantly reduced the cardiotoxic side effects commonly associated with the free drug, such as chronic cardiomyopathy and congestive heart failure(54). PEGylation, the process of coating liposomes with polyethylene glycol (PEG), plays a crucial role in extending the circulation time of the formulation by evading rapid clearance by the mononuclear phagocyte system. This prolonged systemic presence facilitates passive targeting of tumors via the enhanced permeability and retention (EPR) effect, allowing the drug to accumulate preferentially at the tumor site. Consequently, Doxil® demonstrates both reduced cardiotoxicity and enhanced anticancer efficacy compared to free doxorubicin. Building on the clinical success of lipid-based formulations such as Doxil®, Onpattro®, and several other lipid nanoparticles (LNPs), extensive research efforts have been directed toward translating laboratory innovations into commercially viable nanomedicine products. It aims to explore the landscape of FDA-approved lipid-based nanoparticles, offering insights into both the opportunities and the challenges that shape future developments in this field(55). We begin by presenting a comprehensive overview of lipid-based nanoparticles, emphasizing the relationship between their structural components and functional properties. This foundational understanding sets the stage for examining their application in cancer drug delivery, where LNPs have demonstrated remarkable efficacy and safety enhancements. We then delve into the more complex domain of genetic material delivery, highlighting the formulation strategies and biological barriers involved. Finally, we address the expanding role of lipid nanoparticles in vaccine development, including their use in preventative vaccines against viral infections and therapeutic vaccines for cancer, particularly in the context of immunotherapy.

- *Transport Hurdles for Nanomedicines:*

Despite the numerous advantages offered by nanoparticles, their clinical performance can be significantly compromised when they lack effective targeting mechanisms. Non-targeted nanoparticles are readily recognized and cleared by the mononuclear phagocyte system (MPS), which is active in the bloodstream, bone marrow, and organs such as the spleen, lungs, and liver. This rapid clearance is often exacerbated by the hydrophobic nature of many nanoparticles, which promotes the adsorption of plasma proteins and other blood constituents onto their surface a phenomenon known as opsonization(56). To achieve successful in vivo drug delivery, nanoparticles must exhibit prolonged circulation time, allowing them to reach the intended site of action before being eliminated. However, even with extended systemic presence, drug targeting remains a challenge. Structural abnormalities in tumor vasculature or atypical cellular architecture can hinder the enhanced permeability and retention (EPR) effect, thereby reducing the efficiency of nanoparticle accumulation and internalization at the target site. Nanomedicines face a multitude of biological barriers that can hinder their therapeutic efficacy. These include the formation of a protein corona, rapid elimination by the mononuclear phagocyte system (MPS), complex fluid dynamics, interactions with the endothelial surface of blood vessels, penetration through the extracellular matrix, traversal across the cellular membrane, lysosomal degradation, and efflux pump activity(57). Each of these hurdles must be strategically addressed to ensure successful drug delivery. To overcome these challenges, nanoparticles are often functionalized with molecular targeting ligands, enhancing their specificity and minimizing off-target effects. One notable strategy to evade clearance by the reticuloendothelial system (RES) is known as inverse targeting. This approach involves temporarily suppressing the RES's natural uptake mechanisms by administering a high dose of blank delivery systems or immunomodulatory agents such as dextran sulphate. This overloads the RES, reducing its capacity to eliminate therapeutic nanoparticles and thereby prolonging their circulation time. Various colloidal transport systems including micelles, fluid crystals, vesicles, and nanoparticle dispersions containing small molecules have demonstrated promising potential for target-specific drug delivery. These systems aim to optimize drug encapsulation, control release kinetics, and extend the shelf life of the formulation, all while minimizing adverse effects. Colloidal drug formulations often exhibit liquid crystalline structures or amphiphilic characteristics, which can significantly influence their

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molecular interactions within biological systems. These structural features affect how the drug behaves in vivo, including its solubility, stability, and cellular uptake. One effective strategy to reduce premature clearance is the surface modification of hydrophobic nanoparticles with hydrophilic materials, which minimizes recognition by the reticuloendothelial system (RES) and allows the carriers to reach diverse target sites more efficiently. Upon exposure to biological fluids, nanoparticles rapidly adsorb proteins and other biomolecules onto their surface, forming what is known as the protein corona. This dynamic layer confers a unique biological identity to the nanoparticle, shaping its perception by cells and influencing internalization, biodistribution, and overall therapeutic performance. The activated macrophages of the RES play a central role in clearing aged blood cells and circulating foreign substances, including nanoparticles, by directing them to RES organs such as the liver, spleen, and lungs. A major limitation of nanotherapeutic systems is their rapid phagocytosis and RES-mediated clearance, which significantly reduces their bioavailability and therapeutic window. Overcoming this challenge requires strategic design of nanoparticle surfaces and delivery mechanisms to evade immune detection and prolong systemic circulation(58).

Table 1 Herbal Drug-Loaded Nanocarriers and Their Formulation Strategies in Rheumatoid Arthritis Management.

Sr. No.	Nanocarrier Type	Herbal Drug Incorporated	Formulation Type	Therapeutic Role	References
1.	Liposomes	Curcumin	Topical gel	Anti-inflammatory, Antioxidant	(59)
2.	Niosomes	Boswellic Acid	Transdermal Gel	Inhibits leukotriene synthesis, reduces joint swelling	(60)
3.	Solid Lipid Nanoparticles (SLNs)	Quercetin	Oral capsule, gel	Antioxidant, reduces TNF-α and IL-1β	(61)
4.	Nanostructured Lipid Carriers (NLCs)	Resveratrol	Topical cream	Modulates NF-κB pathway, antioxidant	(62)
5.	Polymeric Nanoparticles (PLGA)	Withaferin A (from *Withania somnifera*)	Injectable, oral suspension	Immunomodulatory, anti-arthritic	(63)
6.	Cubosomes	Gingerol (from *Zingiber officinale*)	Topical emulgel	Reduces inflammation and pain	(64)
7.	Micelles	Berberine	Oral solution	Suppresses pro-inflammatory cytokines	(65)
8.	Gold Nanoparticles (AuNPs)	Piperine (from *Piper nigrum*)	Injectable, oral suspension	Enhances bioavailability, anti-inflammatory	(66)
9.	Chitosan Nanoparticles	Diosgenin (from *Dioscorea spp.*)	Oral capsule	Reduces oxidative stress and joint damage	(67)
10.	Nanoemulsions	Eucalyptol (from *Eucalyptus globulus*)	Topical spray	Analgesic, anti-inflammatory	(68)

VI. TYPES OF NANOCARRIER SYSTEMS

➢ *Nano-Emulsions:*

These are colloidal dispersions composed of nanometric droplets of one liquid phase dispersed within another immiscible continuous phase. These systems exhibit kinetic stability meaning they remain stable over time but lack thermodynamic stability, which differentiates them from true solutions(69). Typically, nano-emulsions consist of droplets smaller than 200 nm, forming stable liquid-in-liquid mixtures that offer several advantages due to their unique physicochemical properties. Their small droplet size results in a high surface area-to-volume ratio, which facilitates efficient encapsulation and delivery of active pharmaceutical ingredients. The robust stability of nano-emulsions is largely attributed to the use of appropriate surfactants, which prevent droplet coalescence and maintain dispersion integrity. This stability, combined with their optically transparent appearance and controlled flow properties, makes nano-emulsions highly versatile for pharmaceutical applications. One of their key strengths lies in formulation flexibility(70). Depending on the solubility characteristics of the surfactants used, nano-emulsions can be tailored into oil-in-water (O/W) or water-in-oil (W/O) systems. Additionally, double emulsions typically water-in-oil-in-water (W/O/W) can be engineered to simultaneously encapsulate both hydrophilic and hydrophobic drugs, expanding their utility in complex drug delivery scenarios.

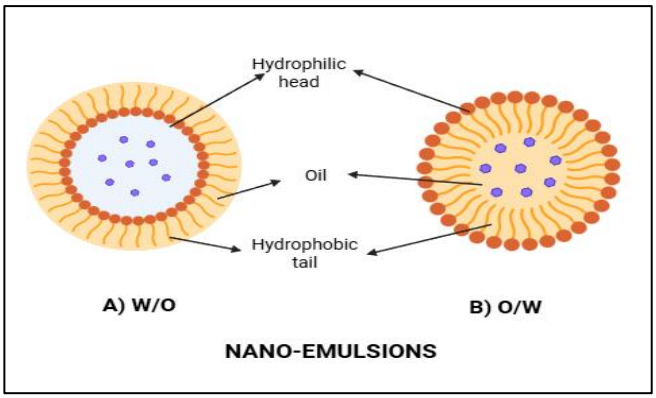

Fig 2 Schematic Representation of Nano-Emulsion Types: (A) Water-in-Oil (W/O) and (B) Oil-in-Water (O/W) Systems.

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Emulsifying agents, including surfactants, hydrophilic colloids, and particulate solids, play a critical role in stabilizing nano-emulsions by forming protective films around droplets and preventing aggregation. Moreover, formulations exhibiting an absolute zeta potential greater than 30 mV benefit from enhanced electrostatic repulsion between droplets, further improving colloidal stability(71). Achieving high encapsulation efficiency is essential for ensuring the effective retention and delivery of active pharmaceutical compounds. Equally important is storage stability, which is typically evaluated through physical parameters such as droplet size distribution, phase separation, and zeta potential(72). The emulsification techniques used to prepare nano-emulsions whether high-energy (e.g., ultrasonication, high-pressure homogenization) or low-energy (e.g., phase inversion, spontaneous emulsification) offer flexibility in formulation. High-energy methods provide superior control over droplet dispersion and can operate with lower surfactant concentrations, while low-energy methods are more cost-effective and efficient, often yielding uniform droplet sizes. Historically, the concept of using lipid nanoparticles (LNPs) for drug delivery was first explored in the 19th century by Müller and Gascon. Among these, solid lipid nanoparticles (SLNs) have gained prominence due to their solid lipid core, typically ranging from 50 to 1000 nm. SLNs offer numerous advantages for pharmaceutical applications: they are biocompatible, biodegradable, and non-toxic, making them safe for therapeutic use. Importantly, their synthesis does not require organic solvents, addressing both environmental and safety concerns. SLNs exhibit excellent physical stability, which contributes to prolonged shelf life and consistent performance. They enable controlled drug release and targeted delivery, thereby enhancing therapeutic selectivity. Furthermore, SLNs effectively protect encapsulated drugs whether lipophilic or hydrophilic from degradation, improving bioavailability and efficacy. Their scalability and compatibility with large-scale manufacturing further reinforce their potential as robust drug delivery platforms. Numerous formulation strategies have been reported for solid lipid nanoparticles (SLNs), offering diverse avenues to tailor their physicochemical properties for specific drug delivery applications(73). Among these, High Pressure Homogenization (HPH) has emerged as one of the most effective and scalable techniques. By applying intense pressure gradients and mechanical shear forces, HPH facilitates the formation of uniform, stable, spherical nanoparticles, optimizing SLN production for targeted drug loading and delivery. This method enables the generation of smaller particles with increased surface area, which enhances drug loading efficiency and improves bioavailability(74). However, SLNs are not without limitations. Prolonged storage can lead to changes in particle size, which may alter drug release kinetics. Additionally, polymorphic transitions within the lipid matrix and gelation phenomena can compromise formulation stability over time. Despite these challenges, SLNs continue to hold significant promise in pharmaceutical research. Their ability to protect encapsulated drugs from biochemical and physicochemical degradation, coupled with their biocompatibility, non-toxicity, and environmentally friendly production, underscores their value as a robust platform for controlled and targeted drug delivery(75).

- *As a Promise in Treating Arthritis:* Nano-emulsions are tiny droplets that act as carriers for medicines which normally do not dissolve well in water. In rheumatoid arthritis (RA), they are especially helpful because inflamed joints develop leaky blood vessels and poor drainage, making it easier for these nano-sized droplets to slip through and stay in the joint tissue. Once inside, they release the medicine gradually, ensuring a steady effect that reduces inflammation and pain. Their small size, usually between 50–200 nano meters, allows them to concentrate more in diseased joints than in healthy ones, which means the drug works exactly where it is needed most. In simple terms, nano-emulsions function like smart delivery vehicles bringing medicine directly to swollen joints, keeping it there longer, and releasing it slowly to maximize relief(76).

➢ *Niosomes:*

These are specialized vesicular drug delivery systems formed through the self-assembly of non-ionic surfactants in aqueous environments. Unlike ionic surfactants, non-ionic surfactants carry no net electrical charge, which facilitates their organization into stable bilayer structures.

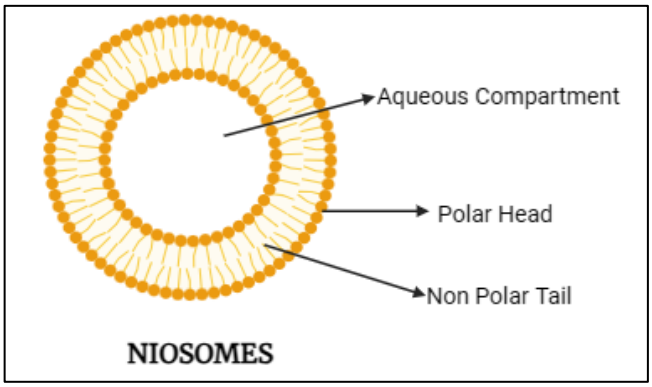

Fig 3 Schematic Representation of Niosomes.

This architecture enables niosomes to encapsulate both hydrophilic and hydrophobic drugs, making them highly versatile for pharmaceutical and cosmetic applications. Their ability to accommodate poorly water-soluble active compounds makes niosomes particularly valuable in topical formulations, where enhanced skin penetration and localized delivery are desired. Moreover, niosomes offer flexibility in modifying size, surface characteristics, and lipid composition, allowing researchers to fine-tune drug loading efficiency and release kinetics(77). The physicochemical properties of niosomes are influenced by several formulation parameters, including the type and concentration of surfactant, alkyl chain length, and the Critical Packing Parameter (CPP) a key determinant of the preferred aggregate morphology. By adjusting these variables, niosomes can be engineered to achieve optimal stability, encapsulation efficiency, and targeted delivery performance. The physical state of niosomal bilayers, whether in a liquid-crystalline or gel phase, is influenced by several formulation parameters,

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including temperature, type of lipid or surfactant, and the presence of stabilizing agents such as cholesterol. These variables offer additional control over the structural and functional properties of niosomes, making them highly adaptable for drug delivery applications. Niosome formation typically involves the hydration of a surfactant-lipid mixture, followed by techniques such as ether injection, manual agitation, sonication, or microfluidization(78). These methods provide flexibility in tailoring vesicle size, lamellarity, and encapsulation efficiency, depending on the therapeutic requirements. One of the key advantages of niosomes over liposomes is their superior chemical stability. Niosomes exhibit greater resistance to oxidation and chemical degradation, which translates into extended shelf life and improved formulation robustness. The nonionic surfactants used in niosomal systems are generally biodegradable, biocompatible, and non-immunogenic, making them suitable for a wide range of pharmaceutical and cosmetic applications. Moreover, the ease of handling and storage of these surfactants, combined with the ability to precisely control composition, size, lamellarity, surface charge, and stability, further enhances the appeal of niosomes as versatile and efficient drug delivery platforms(79). Despite their many advantages, niosomes face several formulation challenges, including vesicle aggregation, fusion, drug leakage, and hydrolysis of encapsulated compounds over time. These stability issues can compromise therapeutic efficacy and shelf life. To address contamination concerns, gamma sterilization has emerged as a promising technique for niosome decontamination, offering rapid and effective sterilization without compromising vesicle integrity. In contrast, liposomes particularly distinguish themselves through their exceptional deformability, which allows them to traverse pores significantly smaller than their own diameter.

- *As a Promise in Treating Arthritis:* Niosomes are tiny, bubble-like carriers that help deliver medicine right where it's needed in rheumatoid arthritis. They naturally gather in inflamed joints because the blood vessels there are leaky, and they can also pass more easily through the skin when used in creams or gels. Once inside the joint, they're taken up by the inflammatory cells themselves, which makes the treatment even more effective(80).

➢ *Transferosomes:*

They are composed of phospholipids, edge activators (typically surfactants), and water, forming a bilayer structure capable of encapsulating both hydrophilic and hydrophobic drugs. Hydrophilic drugs are housed within or adsorbed to the aqueous core, while hydrophobic drugs are embedded within the lipid bilayer. Key formulation components such as phosphatidylcholine C18, known for its skin-friendly and non-toxic properties, and surfactants like sodium cholate, sodium deoxycholate, Polysorbate 80, Span 80, and dipotassium glycyrrhizinate contribute to the stability, flexibility, and skin permeability of transferosomes. These attributes make transferosomes highly suitable for topical and transdermal drug delivery, especially in conditions like rheumatoid arthritis, where deep tissue penetration is crucial. Transferosomes are recognized for their biocompatibility and biodegradability, ensuring safety for both the human body and the environment. One of their standout features is their high entrapment efficiency, often reaching up to 90%, which allows them to effectively encapsulate lipophilic drugs across a wide range of molecular weights. Their unique deformability enables them to adapt their shape during transit, enhancing their ability to penetrate deep into tissues and deliver drugs more efficiently. Despite these advantages, transferosomes are not without limitations. Natural phospholipids, commonly used in their formulation, may contain impurities that affect consistency and safety. Additionally, the cost of production can be relatively high, and encapsulating hydrophobic drugs may present formulation challenges. Nevertheless, their capacity for controlled and sustained drug release, combined with their ability to navigate biological barriers, makes transferosomes a promising advancement in modern drug delivery systems.

- *As a Promise in Treating Arthritis:* Transferosomes are ultra-flexible carriers that can deliver medicine deep into the skin and directly to inflamed joints in rheumatoid arthritis. Thanks to their deformable structure, they can squeeze through the tiny pores of the skin far more effectively often 5 to 10 times better than regular, rigid liposomes. Their size (about 70–300 nano-meters) allows them to travel intact across the skin, guided by natural hydration gradients(81).

➢ *Liposomes:*

Liposomes are among the most widely studied nanocarriers in the field of targeted drug delivery. Typically ranging in diameter from 50 to 500 nanometers, these spherical lipid vesicles are formed by emulsifying natural or synthetic lipids in an aqueous medium. Their ability to encapsulate both hydrophilic and hydrophobic drugs makes them highly versatile for delivering therapeutic agents to specific sites within the body(82). Liposomes are structurally classified based on their size and the number of lipid bilayers they contain.

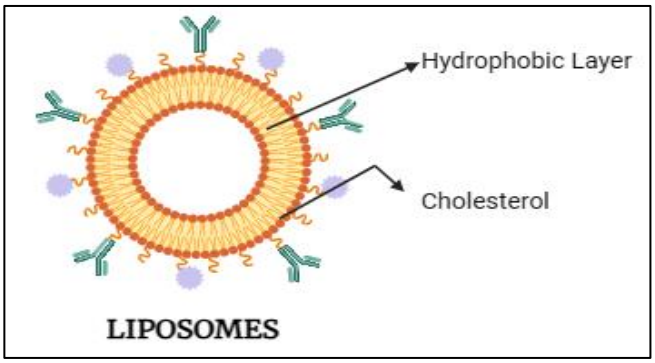

Fig 4 Schmetic Representation of Liposomes.

- *These Include:*

✓ Small Unilamellar Vesicles (SUVs): Single bilayer vesicles with diameters around 20–100 nm
✓ Large Unilamellar Vesicles (LUVs): Larger single bilayer vesicles typically above 100 nm
✓ Multilamellar Vesicles (MLVs): Multiple concentric bilayers resembling an onion-like structure

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- ✓ Multivesicular Vesicles (MVVs): Vesicles containing multiple non-concentric internal compartments.

This structural diversity allows liposomes to be tailored for a wide range of drug delivery applications, including systemic, topical, and localized therapies(83). Larger liposomes with fewer bilayers tend to exhibit higher encapsulation efficiency for hydrophilic compounds, which directly influences drug loading capacity and release kinetics in liposomal drug delivery systems. The lipid composition of liposomes typically involves the self-assembly of diacyl-chain phospholipids in aqueous environments, forming bilayer structures that mimic biological membranes(84). These lipids primarily glycerophospholipids and sphingomyelins possess hydrophilic head groups and hydrophobic tails, resulting in an amphiphilic architecture that stabilizes the vesicle through electrostatic repulsion(85). Sphingomyelin, a phospholipid that replaces glycerol in its backbone. It is used in formulations such as Marqibo® (vincristine sulfate liposome injection) to enhance liposome stability in acidic environments, thereby improving pharmacokinetic properties and targeted drug delivery(86). Cholesterol is another key component, commonly added to increase membrane flexibility, reinforce bilayer integrity, and reduce the permeability of water-soluble substances across the lipid membrane. Liposome fabrication employs various techniques, including thin-film hydration, ethanol injection, and double emulsion methods. These processes typically involve the formation of multilamellar vesicles (MLVs) or unilamellar vesicles (ULVs), followed by size reduction, drug loading, buffer exchange, sterilization, and if required lyophilization to enhance shelf stability. In Gene Delivery, liposomes offer distinct advantages(87). They can bind effectively with charged genetic materials, protect them from enzymatic degradation, and facilitate the transport of large genetic fragments. Surface modifications, such as the attachment of targeting ligands or antibodies, further enhance their specificity and therapeutic potential(88). Liposomes also face several challenges. These include high production costs, susceptibility to leakage and fusion, chemical instability over time, short systemic half-life, and limited long-term stability. Ongoing research continues to address these limitations, aiming to optimize liposomal formulations for broader and more effective clinical applications(89).

- *As a Promise in Treating Arthritis:* Liposomes are tiny, bubble-like carriers that can deliver drugs directly to inflamed joints in rheumatoid arthritis. Their effectiveness depends a lot on their size. Larger liposomes (over 200 nano-meters), when injected straight into the joint, tend to stay there longer because they are taken up by the synovial lining cells. This prolongs drug exposure and results in two to five times higher local drug levels compared to free drugs. Smaller liposomes (under 200 nano-meters), especially when coated with PEG, circulate in the bloodstream for longer after intravenous administration. They take advantage of the leaky blood vessels in RA joints, slipping through and accumulating in the synovium while avoiding rapid clearance by the body's defense system. Liposomes help block harmful pathways such as NF-κB, TNF-α, and MMPs, ultimately reducing inflammation, protecting cartilage, and slowing down joint damage(90).

➢ *Ethosomes:*

Ethosomes, first introduced by Touitou in 1997, represent a novel class of lipid-based nanocarriers specifically designed to enhance transdermal and topical drug delivery. Composed of phospholipids, ethanol, and water, ethosomes are distinguished by their high ethanol content, which plays a critical role in disrupting the skin's lipid barrier(91). This unique feature allows ethosomes to penetrate deeply into the skin layers or even reach systemic circulation, making them highly effective for delivering a wide range of therapeutic agents. Their size versatility, ranging from nanometers to microns, allows for precise control over drug transport and release, enhancing their adaptability across various pharmaceutical applications. Ethosomes are broadly categorized into three types: Classical Ethosomes, which are structurally similar to traditional liposomes but with added ethanol; Binary Ethosomes, which include an additional alcohol to fine-tune vesicle properties; Transethosomes, the next-generation systems that combine ethanol with edge activators to further improve flexibility, penetration, and drug retention(92). These features make ethosomes particularly valuable for overcoming the limitations of conventional topical formulations, offering enhanced drug permeation, improved bioavailability, and targeted delivery with minimal systemic side effects. Despite their complex and time-intensive synthesis and limited stability particularly due to sensitivity to temperature and humidity ethosomes offer significant advantages as transdermal drug delivery systems(93). Their unique composition enables the effective delivery of a wide range of therapeutic agents, including peptides and macromolecules, through the skin. This is largely attributed to their ability to fuse with the skin's lipid bilayers, facilitating deep transcutaneous penetration(94). Ethosomes can be customized into various formulations, enhancing patient compliance and opening new avenues for therapeutic and cosmetic applications(95). These include the complexity of preparation, which can hinder production scalability, limited long-term stability, and the potential for skin irritation or incompatibility with certain drugs. The potential of ethosomes, it is essential to optimize their composition and manufacturing processes, ensuring both stability and efficacy(96). Moreover, comprehensive in vivo studies are needed to better understand their pharmacokinetics, safety profile, and therapeutic performance across different clinical contexts(97).

- *As a Promise in Treating Arthritis:* Ethosomes are soft, phospholipid vesicles enriched with a high amount of ethanol that make them excellent carriers for delivering drugs through the skin. In rheumatoid arthritis, their unique design allows them to penetrate deeply into the skin and reach the tissues around inflamed joints. Because of this, ethosomes can pass through the skin much more effectively often two to four times better than regular liposomes(98).

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VII. DRAWBACKS AND CHALLENGES OF LIPID-BASED NANOCARRIERS

Nanomedicine holds immense promise for the clinical management of rheumatoid arthritis (RA), offering innovative strategies for targeted and sustained drug delivery. However, several critical limitations must be addressed to fully translate these technologies into effective patient therapies. Although nanoparticles (NPs) can be engineered to target specific organs, tissues, or cellular environments, achieving precise localization within inflamed joints remains a significant challenge. This is primarily due to the dense synovial tissue architecture and limited vascularization in arthritic joints, which restricts the effectiveness of systemic administration. Moreover, once in circulation, nanoparticles are prone to opsonization a process where plasma proteins bind to their surface, marking them for clearance by the mononuclear phagocyte system (MPS). This immune recognition leads to rapid phagocytic removal of the particles by macrophages in organs such as the liver and spleen, thereby reducing their bioavailability and therapeutic potential. Once administered systemically, nanoparticles (NPs) often face rapid clearance from the bloodstream due to opsonization, a process in which plasma proteins coat the particle surface, flagging them for removal by the reticuloendothelial system (RES). This leads to their accumulation in organs such as the spleen, liver (particularly Kupffer cells), bone marrow, lymph nodes, and lungs (via alveolar macrophages). While this biological response is natural, it poses a major challenge to achieving targeted delivery to inflamed joints in rheumatoid arthritis (RA), where limited vascularization and dense synovial tissue restrict nanoparticle access. Another concern is the long-term impact of nanomaterials on the human body. Their accumulation in RES organs raises questions about potential toxicity, especially if the particles are not biodegradable or cannot be safely eliminated. It is therefore essential to demonstrate that NPs can be degraded upon specific stimuli or safely cleared from the body to avoid chronic complications. Beyond biological barriers, clinical translation of nanomedicine faces its own hurdles. The manufacturing process must be scalable and reproducible, ensuring consistency in size, shape, and physicochemical properties. To meet regulatory and therapeutic standards, rigorous clinical trials are required to evaluate the efficacy and safety of nanomedicines in RA patients. Moreover, developers must navigate evolving regulatory frameworks, which demand continuous adaptation and validation of nanoparticle-based therapies.

- *Multidimensional Perspectives: Safety, Regulatory, and Consumer Considerations:*

Nanotechnology is revolutionizing arthritis care by enabling targeted drug delivery and reducing side effects(99). Tiny particles like nanogels or liposomes can carry anti-inflammatory drugs directly to affected joints, offering faster and more effective relief. However, safety is a major concern. Because these particles are so small, they can interact with cells in unpredictable ways, potentially triggering immune responses or accumulating in organs over time. From a regulatory standpoint, agencies like the FDA and EMA are still developing clear guidelines for nanomedicine. Unlike traditional drugs, nanotech-based therapies require rigorous testing to ensure they're safe, stable, and effective. Regulatory bodies are pushing for transparency in manufacturing processes and long-term safety data before approving these treatments(100). Consumers are cautiously optimistic. Many arthritis patients are eager for alternatives to conventional drugs, especially those with fewer side effects. But they also want assurance that these new therapies are thoroughly tested. Public awareness campaigns and clear labelling can help build trust. Ultimately, while nanotechnology holds great promise, its success depends on balancing innovation with safety and transparency.

VIII. FUTURE OUTLOOK AND CLINICAL TRANSLATION

Nanotechnology offers exciting possibilities for treating arthritis, but it's not without hurdles. One major concern is safety because nanoparticles are so small, they can travel to unexpected parts of the body and may cause side effects we don't fully understand yet. Another challenge is regulation. Health authorities like the FDA are still figuring out how to evaluate and approve these advanced therapies, which can slow down their availability. Manufacturing is also tricky; producing nanoparticles consistently and at scale is expensive and technically demanding(101). Lastly, public trust is a factor. Many patients are unfamiliar with nanotechnology and may be hesitant to try something new without clear evidence of its safety and benefits. Despite these challenges, the future looks promising. Researchers are developing smart nanoparticles that can release drugs only when they reach inflamed joints, reducing side effects(102). There's also growing interest in personalized nanomedicine, where treatments are tailored to each person's biology. As more clinical trials are completed and regulations become clearer, we can expect wider adoption of nanotech-based arthritis treatments. With better education and transparent communication, patients are likely to become more open to these innovations.

IX. CONCLUSION

Topical NSAIDs and capsaicin are often recommended as first-line treatments for rheumatoid arthritis (RA) because they offer a good balance of safety and effectiveness. For more persistent pain, oral analgesics like acetaminophen and opioids, as well as intra-articular injections such as corticosteroids and hyaluronic acid, can provide relief though their use is often limited by potential side effects. While targeted therapies are typically discussed in terms of molecular mechanisms, they can also be designed to act on specific immune cell populations by modifying how drugs are transported within the body. In this context, nanocarrier systems have gained attention for their ability to deliver drugs directly to inflamed tissues. Moreover, priming strategies techniques that prepare the body or the carrier for more efficient drug uptake are emerging as promising tools to enhance delivery outcomes. Despite the benefits of targeted medications in RA management, many nanocarrier-based systems still face challenges, particularly related to safety.

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Issues such as immunogenicity, off-target effects, and formulation complexity continue to limit their widespread clinical use.

REFERENCES

[1]. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. Eur J Radiol. 1998 May;27:S18–24.

[2]. Kalal B. "RHEUMATOID ARTHRITIS: CURRENT INSIGHT INTO PATHOGENESIS, DIAGNOSIS AND THERAPEUTIC ADVANCES." J Popul Ther Clin Pharmacol. 2023 Apr 11;1–10.

[3]. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. JAMA. 2018 Oct 2;320(13):1360.

[4]. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: Results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheum. 2010 June;62(6):1576–82.

[5]. Gabriel SE. THE EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS. Rheum Dis Clin N Am. 2001 May;27(2):269–81.

[6]. Finckh A, Gilbert B, Hodkinson B, Bae SC, Thomas R, Deane KD, et al. Global epidemiology of rheumatoid arthritis. Nat Rev Rheumatol [Internet]. 2022 Sept 6 [cited 2025 Oct 30]; Available from: https://www.nature.com/articles/s41584-022-00827-y

[7]. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology. 2012 July 1;51(suppl 5):v3–11.

[8]. Derksen VFAM, Huizinga TWJ, Van Der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Semin Immunopathol. 2017 June;39(4):437–46.

[9]. Mohanty S, Panda S, Bhanja A, Pal A, Chandra SS. Novel Drug Delivery Systems for Rheumatoid Arthritis: An Approach to Better Patient Compliance. Biomed Pharmacol J. 2019 Mar 28;12(1):157–70.

[10]. Kourilovitch M, Galarza-Maldonado C, Ortiz-Prado E. Diagnosis and classification of rheumatoid arthritis. J Autoimmun. 2014 Feb;48–49:26–30.

[11]. Dolati S, Sadreddini S, Rostamzadeh D, Ahmadi M, Jadidi-Niaragh F, Yousefi M. Utilization of nanoparticle technology in rheumatoid arthritis treatment. Biomed Pharmacother. 2016 May;80:30–41.

[12]. Liao KP, Alfredsson L, Karlson EW. Environmental influences on risk for rheumatoid arthritis. Curr Opin Rheumatol. 2009 May;21(3):279–83.

[13]. Paglia MDG, Silva MT, Lopes LC, Barberato-Filho S, Mazzei LG, Abe FC, et al. Use of corticoids and non-steroidal anti-inflammatories in the treatment of rheumatoid arthritis: Systematic review and network meta-analysis. Florez ID, editor. PLOS ONE. 2021 Apr 7;16(4):e0248866.

[14]. Shtroblia V, Petakh P, Kamyshna I, Halabitska I, Kamyshnyi O. Recent advances in the management of knee osteoarthritis: a narrative review. Front Med. 2025 Jan 21;12:1523027.

[15]. Derry S, Conaghan P, Da Silva JAP, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2016 Apr 22 [cited 2025 Nov 1];2020(2). Available from: http://doi.wiley.com/10.1002/14651858.CD007400.pub3

[16]. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth. 2011 Oct;107(4):490–502.

[17]. Altman RD, Aven A, Holmburg CE, Pfeifer LM, Sack M, Young GT. Capsaicin cream 0.025% as Monotherapy for Osteoarthritis: A double-blind study. Semin Arthritis Rheum. 1994 June;23(6):25–33.

[18]. Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2011 [cited 2025 Nov 5]. p. CD008659.pub2. Available from: https://doi.wiley.com/10.1002/14651858.CD008659.pub2

[19]. Machado GC, Maher CG, Ferreira PH, Pinheiro MB, Lin CWC, Day RO, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015 Mar 31;350(mar31 2):h1225–h1225.

[20]. Da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, et al. RETRACTED: Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. The Lancet. 2016 May;387(10033):2093–105.

[21]. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res. 2020 Feb;72(2):149–62.

[22]. Bruyère O, Honvo G, Veronese N, Arden NK, Branco J, Curtis EM, et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum. 2019 Dec;49(3):337–50.

[23]. Sohail R, Mathew M, Patel KK, Reddy SA, Haider Z, Naria M, et al. Effects of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Gastroprotective NSAIDs on the Gastrointestinal Tract: A Narrative Review. Cureus [Internet]. 2023 Apr 3 [cited 2025 Nov 3]; Available from: https://www.cureus.com/articles/146797-effects-of-non-steroidal-anti-inflammatory-drugs-nsaids-and-gastroprotective-nsaids-on-the-gastrointestinal-tract-a-narrative-review

[24]. Sabha M, Hochberg MC. Non-surgical management of hip and knee osteoarthritis; comparison of ACR/AF

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26apr015

and OARSI 2019 and VA/DoD 2020 guidelines. Osteoarthr Cartil Open. 2022 Mar;4(1):100232.

[25]. Jüni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Musculoskeletal Group, editor. Cochrane Database Syst Rev [Internet]. 2015 Oct 22 [cited 2025 Nov 3];2015(11). Available from: http://doi.wiley.com/10.1002/14651858.CD005328.pub3

[26]. Gato-Calvo L, Magalhaes J, Ruiz-Romero C, Blanco FJ, Burguera EF. Platelet-rich plasma in osteoarthritis treatment: review of current evidence. Ther Adv Chronic Dis. 2019 Jan;10:2040622319825567.

[27]. Bennell KL, Paterson KL, Metcalf BR, Duong V, Eyles J, Kasza J, et al. Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis: The RESTORE Randomized Clinical Trial. JAMA. 2021 Nov 23;326(20):2021.

[28]. Sconza C, Leonardi G, Carfì C, Kon E, Respizzi S, Scaturro D, et al. Intra-Articular Injection of Botulinum Toxin for the Treatment of Knee Osteoarthritis: A Systematic Review of Randomized Controlled Trials. Int J Mol Sci. 2023 Jan 12;24(2):1486.

[29]. Mendes JG, Natour J, Nunes-Tamashiro JC, Toffolo SR, Rosenfeld A, Furtado RNV. Comparison between intra-articular Botulinum toxin type A, corticosteroid, and saline in knee osteoarthritis: a randomized controlled trial. Clin Rehabil. 2019 June;33(6):1015–26.

[30]. Singh JA, Mahowald ML, Noorbaloochi S. Intraarticular Botulinum Toxin A for Refractory Painful Total Knee Arthroplasty: A Randomized Controlled Trial. J Rheumatol. 2010 Nov;37(11):2377–86.

[31]. Arendt-Nielsen L, Jiang GL, DeGryse R, Turkel C. Intra-articular onabotulinumtoxinA in osteoarthritis knee pain: effect on human mechanistic pain biomarkers and clinical pain. Scand J Rheumatol. 2017 July 4;46(4):303–16.

[32]. Hill CL, March LM, Aitken D, Lester SE, Battersby R, Hynes K, et al. Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. Ann Rheum Dis. 2016 Jan;75(1):23–9.

[33]. Ammon H, Wahl M. Pharmacology of Curcuma longa. Planta Med. 1991 Feb;57(01):1–7.

[34]. Gao Y, Zhuang Z, Lu Y, Tao T, Zhou Y, Liu G, et al. Curcumin Mitigates Neuro-Inflammation by Modulating Microglia Polarization Through Inhibiting TLR4 Axis Signaling Pathway Following Experimental Subarachnoid Hemorrhage. Front Neurosci. 2019 Nov 15;13:1223.

[35]. Kahkhaie KR, Mirhosseini A, Aliabadi A, Mohammadi A, Mousavi MJ, Haftcheshmeh SM, et al. Curcumin: a modulator of inflammatory signaling pathways in the immune system. Inflammopharmacology. 2019 Oct;27(5):885–900.

[36]. Yousefian M, Shakour N, Hosseinzadeh H, Hayes AW, Hadizadeh F, Karimi G. The natural phenolic compounds as modulators of NADPH oxidases in hypertension. Phytomedicine. 2019 Mar;55:200–13.

[37]. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. The Lancet. 2011 June;377(9783):2115–26.

[38]. Zhang Z, Leong DJ, Xu L, He Z, Wang A, Navati M, et al. Curcumin slows osteoarthritis progression and relieves osteoarthritis-associated pain symptoms in a post-traumatic osteoarthritis mouse model. Arthritis Res Ther. 2016 Dec;18(1):128.

[39]. Yan D, He B, Guo J, Li S, Wang J. Involvement of TLR4 in the protective effect of intra-articular administration of curcumin on rat experimental osteoarthritis. Acta Cir Bras. 2019;34(6):e201900604.

[40]. Chen B, Li H, Ou G, Ren L, Yang X, Zeng M. Curcumin attenuates MSU crystal-induced inflammation by inhibiting the degradation of IκBα and blocking mitochondrial damage. Arthritis Res Ther. 2019 Dec;21(1):193.

[41]. Li X, Xu D, Sun D, Zhang T, He X, Xiao D. Curcumin ameliorates monosodium urate-induced gouty arthritis through Nod-like receptor 3 inflammasome mediation via inhibiting nuclear factor-kappa B signaling. J Cell Biochem. 2019 Apr;120(4):6718–28.

[42]. Deng R. Therapeutic Effects of Guggul and Its Constituent Guggulsterone: Cardiovascular Benefits. Cardiovasc Drug Rev. 2007 Dec;25(4):375–90.

[43]. 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 June;74(1):118–30.

[44]. Hazra AK, Sur TK, Chakraborty B, Seal T. HPLC ANALYSIS OF PHENOLIC ACIDS AND ANTIOXIDANT ACTIVITY OF SOME CLASSICAL AYURVEDIC GUGGULU FORMULATIONS. Int J Res Ayurved Pharm. 2018 Jan 21;9(1):112–7.

[45]. Shishodia S, Aggarwal BB. Guggulsterone Inhibits NF-κB and IκBα Kinase Activation, Suppresses Expression of Anti-apoptotic Gene Products, and Enhances Apoptosis. J Biol Chem. 2004 Nov;279(45):47148–58.

[46]. Gujral ML, Sareen K, Tangri KK, Amma MK, Roy AK. Antiarthritic and anti-inflammatory activity of gum guggul (Balsamodendron mukul Hook). Indian J Physiol Pharmacol. 1960 Oct;4:267–73.

[47]. Sharma JN, Sharma JN. Comparison of the anti-inflammatory activity of Commiphora mukul (an indigenous drug) with those of phenylbutazone and ibuprofen in experimental arthritis induced by mycobacterial adjuvant. Arzneimittelforschung. 1977 July;27(7):1455–7.

[48]. Eriksen P, Bartels EM, Altman RD, Bliddal H, Juhl C, Christensen R. Risk of Bias and Brand Explain the Observed Inconsistency in Trials on Glucosamine for Symptomatic Relief of Osteoarthritis: A Meta-Analysis of Placebo-Controlled Trials. Arthritis Care Res. 2014 Dec;66(12):1844–55.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26apr015

[49]. Reginster JY, Dudler J, Blicharski T, Pavelka K. Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT). Ann Rheum Dis. 2017 Sept;76(9):1537–43.
[50]. Reichenbach S, Sterchi R, Scherer M, Trelle S, Bürgi E, Bürgi U, et al. Meta-analysis: Chondroitin for Osteoarthritis of the Knee or Hip. Ann Intern Med. 2007 Apr 17;146(8):580–90.
[51]. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, et al. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795–808.
[52]. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date. Pharm Res. 2016 Oct;33(10):2373–87.
[53]. Lu W, Yao J, Zhu X, Qi Y. Nanomedicines: Redefining traditional medicine. Biomed Pharmacother. 2021 Feb;134:111103.
[54]. Soininen SK, Repo JK, Karttunen V, Auriola S, Vähäkangas KH, Ruponen M. Human placental cell and tissue uptake of doxorubicin and its liposomal formulations. Toxicol Lett. 2015 Dec;239(2):108–14.
[55]. Barenholz Y (Chezy). Doxil® — The first FDA-approved nano-drug: Lessons learned. J Controlled Release. 2012 June;160(2):117–34.
[56]. Komano Y, Yagi N, Onoue I, Kaneko K, Miyasaka N, Nanki T. Arthritic Joint-Targeting Small Interfering RNA-Encapsulated Liposome: Implication for Treatment Strategy for Rheumatoid Arthritis. J Pharmacol Exp Ther. 2012 Jan;340(1):109–13.
[57]. Kofoed Andersen C, Khatri S, Hansen J, Slott S, Pavan Parvathaneni R, Mendes AC, et al. Carbon Nanotubes—Potent Carriers for Targeted Drug Delivery in Rheumatoid Arthritis. Pharmaceutics. 2021 Mar 27;13(4):453.
[58]. Lee MJ, Lee MH, Shim CK. Inverse targeting of drugs to reticuloendothelial system-rich organs by lipid microemulsion emulsified with poloxamer 338. Int J Pharm. 1995 Jan;113(2):175–87.
[59]. Sun H, Zhan M, Mignani S, Shcharbin D, Majoral JP, Rodrigues J, et al. Modulation of Macrophages Using Nanoformulations with Curcumin to Treat Inflammatory Diseases: A Concise Review. Pharmaceutics. 2022 Oct 20;14(10):2239.
[60]. Kajal, Sharma DR, Pandit V, Ashawat M. Formulation and Evaluation of Niosomal Loaded Transdermal Patches for the Treatment of Osteoarthritis. Drug Deliv Lett. 2024 Sept;14(4):290–307.
[61]. Alotaibi BS, Waqas MK, Saleem S, Yasin H, Kharaba Z, Murtaza G. Rheumatoid Arthritis Treatment Potential of Stearic Acid Nanoparticles of Quercetin in Rats. ACS Omega. 2024 Feb 13;9(6):7003–11.
[62]. Sahu A, Rathee S, Saraf S, Raikwar S, Das Bidla P, Pawar RS, et al. Development and Characterization of Leflunomide and Resveratrol Loaded Nanostructured Lipid Carrier Based In-situ Hydrogel System for Effective Management of Rheumatoid Arthritis. J Pharm Innov. 2025 June;20(3):107.
[63]. Alenazi F, Moursi S, Mahmoud MR, Shahid SMA, Khatoon F, Shahid Khan M, et al. Withaferin A alleviates inflammation in animal models of arthritis by inhibiting the NF-κB pathway and cytokine release. Chem Biol Interact. 2024 Aug;398:111114.
[64]. Chando A, Basudkar V, Gharat S, Momin M, Khan T. Development and preclinical assessment of nanoemulgel loaded with phytoconstituents for the management of rheumatoid arthritis. Drug Deliv Transl Res. 2024 Feb;14(2):524–41.
[65]. Gad HA, Abbas H, El Sayed NS, Khattab MA, El Hassab MA, Mansour M. Berberine loaded thermosensitive lipid nanoparticles: in vitro characterization, in silico study, and in vivo anti-arthritic effect. J Liposome Res. 2024 Apr 2;34(2):303–15.
[66]. Bawazeer S, Khan I, Rauf A, Aljohani ASM, Alhumaydhi FA, Khalil AA, et al. Black pepper (Piper nigrum) fruit-based gold nanoparticles (BP-AuNPs): Synthesis, characterization, biological activities, and catalytic applications – A green approach. Green Process Synth. 2022 Jan 4;11(1):11–28.
[67]. Nabizadeh Z, Nasrollahzadeh M, Kruppke B, Nasrabadi D. A combination of chitosan nanoparticles loaded with celecoxib and kartogenin has anti-inflammatory and chondroprotective effects: Results from an in vitro model of osteoarthritis. Heliyon. 2024 May;10(10):e31058.
[68]. Nahata A, Seng LS. Terpenes and Terpene Based Nanoformulations: A New Prospect for Arthritis Management. Int J Med Pharm Health Sci. 2024 Dec 30;1(4):196–207.
[69]. Dhule KD, Nandgude TD. Lipid Nano-System Based Topical Drug Delivery for Management of Rheumatoid Arthritis: An Overview. Adv Pharm Bull. 2023 Nov 1;13(4):663–77.
[70]. Mohd Nordin UU, Ahmad N, Salim N, Mohd Yusof NS. Lipid-based nanoparticles for psoriasis treatment: a review on conventional treatments, recent works, and future prospects. RSC Adv. 2021;11(46):29080–101.
[71]. Tayeb HH, Felimban R, Almaghrabi S, Hasaballah N. Nanoemulsions: Formulation, characterization, biological fate, and potential role against COVID-19 and other viral outbreaks. Colloid Interface Sci Commun. 2021 Nov;45:100533.
[72]. Chuo SC, Mohd Setapar SH. Application of nanotechnology for development of cosmetics. In: Nanotechnology for the Preparation of Cosmetics Using Plant-Based Extracts [Internet]. Elsevier; 2022 [cited 2025 Nov 10]. p. 327–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128229675000047
[73]. MÃ¼ller R. Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. Eur J Pharm Biopharm. 2000 July 3;50(1):161–77.
[74]. Mohammed HA, Khan RA, Singh V, Yusuf M, Akhtar N, Sulaiman GM, et al. Solid lipid nanoparticles for targeted natural and synthetic drugs delivery in high-

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26apr015

incidence cancers, and other diseases: Roles of preparation methods, lipid composition, transitional stability, and release profiles in nanocarriers' development. Nanotechnol Rev. 2023 Feb 18;12(1):20220517.

[75]. Avasarala H, Dinakaran S, Boddeda B, Dasari SP, Jayanthi VR, Swaroopa P. Ethosomal gel: a novel choice for topical delivery of the antipsychotic drug Ziprasidone Hydrochloride. Braz J Pharm Sci. 2022;58:e19317.

[76]. Suresh P, Salem-Bekhit MM, Veedu HP, Alshehri S, Nair SC, Bukhari SI, et al. Development of a Novel Methotrexate-Loaded Nanoemulsion for Rheumatoid Arthritis Treatment with Site-Specific Targeting Subcutaneous Delivery. Nanomaterials. 2022 Apr 11;12(8):1299.

[77]. Srinivasan M, Rajabi M, A. Mousa S. Nanobiomaterials in cancer therapy. In: Nanobiomaterials in Cancer Therapy [Internet]. Elsevier; 2016 [cited 2025 Nov 10]. p. 57–89. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323428637000037

[78]. Karim K, Mandal A, Biswas N, Guha A, Chatterjee S, Behera M, et al. Niosome: A future of targeted drug delivery systems. J Adv Pharm Technol Res. 2010;1(4):374.

[79]. Waddad AY, Abbad S, Yu F, Munyendo WLL, Wang J, Lv H, et al. Formulation, characterization and pharmacokinetics of Morin hydrate niosomes prepared from various non-ionic surfactants. Int J Pharm. 2013 Nov;456(2):446–58.

[80]. Fadaei MS, Fadaei MR, Kheirieh AE, Rahmanian-Devin P, Dabbaghi MM, Nazari Tavallaei K, et al. Niosome as a promising tool for increasing the effectiveness of anti-inflammatory compounds. EXCLI J 23Doc212 ISSN 1611-2156 [Internet]. 2024 [cited 2026 Jan 18]; Available from: https://www.excli.de/index.php/excli/article/view/6868

[81]. Mahmoud A, Rady M, Abdel-Halim M, El-Shenawy BM, Mansour S. Transdermal Delivery of Tofacitinib Citrate via Mannose-Decorated Transferosomes Loaded with Tofacitinib Citrate in Arthritic Joints. Mol Pharm. 2024 Dec 2;21(12):6458–72.

[82]. Jha S, K. Sharma P, Malviya R. Liposomal Drug Delivery System for Cancer Therapy: Advancement and Patents. Recent Pat Drug Deliv Formul. 2016 Dec 7;10(3):177–83.

[83]. Maja L, Željko K, Mateja P. Sustainable technologies for liposome preparation. J Supercrit Fluids. 2020 Nov;165:104984.

[84]. Temml V, Kutil Z. Structure-based molecular modeling in SAR analysis and lead optimization. Comput Struct Biotechnol J. 2021;19:1431–44.

[85]. Large DE, Abdelmessih RG, Fink EA, Auguste DT. Liposome composition in drug delivery design, synthesis, characterization, and clinical application. Adv Drug Deliv Rev. 2021 Sept;176:113851.

[86]. Pajewski R, Djedovič N, Harder E, Ferdani R, Schlesinger PH, Gokel GW. Pore formation in and enlargement of phospholipid liposomes by synthetic models of ceramides and sphingomyelin. Bioorg Med Chem. 2005 Jan;13(1):29–37.

[87]. Liu P, Chen G, Zhang J. A Review of Liposomes as a Drug Delivery System: Current Status of Approved Products, Regulatory Environments, and Future Perspectives. Molecules. 2022 Feb 17;27(4):1372.

[88]. Daraee H, Etemadi A, Kouhi M, Alimirzalu S, Akbarzadeh A. Application of liposomes in medicine and drug delivery. Artif Cells Nanomedicine Biotechnol. 2016 Jan 2;44(1):381–91.

[89]. Cevc G, Gebauer D. Hydration-Driven Transport of Deformable Lipid Vesicles through Fine Pores and the Skin Barrier. Biophys J. 2003 Feb;84(2):1010–24.

[90]. Zheng X, Yang H, Zhang Z, Liang X, Liu Y, Wang C, et al. pH-responsive size-adjustable liposomes induce apoptosis of fibroblasts and macrophages for rheumatoid arthritis treatment. Acta Biomater. 2024 Apr;179:256–71.

[91]. Bendas ER, Tadros MI. Enhanced transdermal delivery of salbutamol sulfate via ethosomes. AAPS PharmSciTech. 2007 Oct;8(4):213.

[92]. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: An overview. J Adv Pharm Technol Res. 2010;1(3):274.

[93]. M. Abdulbaqi I, Darwis Y, Abdul Karim Khan N, Abou Assi R, Ali Khan A. Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials. Int J Nanomedicine. 2016 May;2279.

[94]. Shinde P, Page A, Bhattacharya S. Ethosomes and their monotonous effects on Skin cancer disruption. Front Nanotechnol. 2023 Jan 12;5:1087413.

[95]. Esposito E, Calderan L, Galvan A, Cappellozza E, Drechsler M, Mariani P, et al. Ex Vivo Evaluation of Ethosomes and Transethosomes Applied on Human Skin: A Comparative Study. Int J Mol Sci. 2022 Dec 1;23(23):15112.

[96]. Avasarala H, Dinakaran S, Boddeda B, Dasari SP, Jayanthi VR, Swaroopa P. Ethosomal gel: a novel choice for topical delivery of the antipsychotic drug Ziprasidone Hydrochloride. Braz J Pharm Sci. 2022;58:e19317.

[97]. Sguizzato M, Mariani P, Spinozzi F, Benedusi M, Cervellati F, Cortesi R, et al. Ethosomes for Coenzyme Q10 Cutaneous Administration: From Design to 3D Skin Tissue Evaluation. Antioxidants. 2020 June 3;9(6):485.

[98]. Fan C, Li X, Zhou Y, Zhao Y, Ma S, Li W, et al. Enhanced Topical Delivery of Tetrandrine by Ethosomes for Treatment of Arthritis. BioMed Res Int. 2013;2013:1–13.

[99]. Narkhede MR, Bhamare SN. Nanotechnology-Driven Drug Delivery in Rheumatoid Arthritis: Current Trends, Key Challenges, and Future Perspectives. Biosci Biotechnol Res Asia. 2025 Mar 25;22(1):1–21.

[100]. Gupta N, Shaik AR, Chettupalli AK, Bukke SPN, Goruntla N. Nanomedicine for the management of rheumatoid arthritis: current status and prospective therapeutic approaches. Discov Med. 2025 Apr 28;2(1):111.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26apr015

[101]. Ren S, Xu Y, Dong X, Mu Q, Chen X, Yu Y, et al. Nanotechnology-empowered combination therapy for rheumatoid arthritis: principles, strategies, and challenges. J Nanobiotechnology. 2024 July 22;22(1):431.
[102]. Priya S, Jain KK, Daryani J, Desai VM, Kathuria H, Singhvi G. Revolutionizing rheumatoid arthritis treatment with emerging cutaneous drug delivery systems: overcoming the challenges and paving the way forward. Nanoscale. 2025;17(1):65–87.