Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 20s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Combating Rheumatoid Arthritis with Berberine and Curcumin: A Review of Natural Therapeutics

B Babji Naik[1], A Vamsi Priya[2], G Sowjanya[2], K Indra Sekhar[2], N Sojen Naik[2], Fadul Abdelrahman[2], Bhargav E[2*]

[1]Research Scholar, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India

[2]Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, Anantapur

***Corresponding Author**:

Bhargav Eranti

Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research Campus, Anantapur, India, Email ID: bhargaveranti@yahoo.com

Cite this paper as: B Babji Naik, A Vamsi Priya, G Sowjanya, K Indra Sekhar, N Sojen Naik, Fadul Abdelrahman, Bhargav E, (2025) Combating Rheumatoid Arthritis with Berberine and Curcumin: A Review of Natural Therapeutics. *Journal of Neonatal Surgery*, 14 (20s), 949-965.

ABSTRACT

Rheumatoid arthritis (RA) is a long-term inflammatory disease that causes synovial joint inflammation, which causes pain, stiffness, and gradual joint destruction. In addition to having a major effect on quality of life, the illness may result in systemic problems. The goal of current treatment approaches, which include biologics, corticosteroids, disease-modifying antirheumatic medications (DMARDs), and nonsteroidal anti-inflammatory medicines (NSAIDs), is to manage symptoms and halt the course of the disease. These treatments, however, frequently have problems like poor effectiveness, systemic side effects, and exorbitant expenses. Advanced, tailored medication delivery methods like nanocarriers are necessary because managing RA is made more difficult by poor patient adherence and limited targeting of inflammatory areas.

Berberine and curcumin are bioactive natural compounds with significant therapeutic potential, particularly in managing inflammatory and autoimmune conditions like rheumatoid arthritis (RA). Berberine exhibits potent anti-inflammatory, immunomodulatory, and antioxidant properties, effectively suppressing pro-inflammatory cytokines and oxidative stress Curcumin, a polyphenol derived from turmeric, also demonstrates strong anti-inflammatory and antioxidant effects, inhibiting key molecular pathways involved in RA pathogenesis, such as NF-κB activation. Despite their promising pharmacological profiles, both compounds face challenges like poor water solubility, low bioavailability, and rapid metabolism. Advanced drug delivery systems, such as nanostructured lipid carriers, offer a solution to enhance their therapeutic efficacy and clinical applicability.

Nanostructured lipid carriers (NLCs) are advanced drug delivery systems offering numerous advantages for therapeutic applications. Their unique structure, combining solid and liquid lipids, enhances drug solubility, stability, and bioavailability. NLCs enable controlled and sustained drug release, reducing dosing frequency and improving patient compliance. They can protect sensitive drugs like berberine and curcumin from degradation, extending their shelf life. Additionally, NLCs can be functionalized for targeted delivery, increasing drug accumulation at inflamed joints in conditions like rheumatoid arthritis while minimizing systemic side effects. Their biocompatibility and scalability make NLCs a promising platform for improving the clinical efficacy of challenging therapeutic agents.

Berberine and curcumin exhibit remarkable anti-inflammatory and antioxidant properties, making them promising candidates for managing rheumatoid arthritis (RA). However, their clinical potential is limited by poor solubility and bioavailability. Nanostructured lipid carriers (NLCs) address these limitations by enhancing drug stability, targeted delivery, and controlled release. Preclinical studies demonstrate improved therapeutic efficacy of NLC formulations in RA models, though clinical translation remains limited. Future research should focus on optimizing NLC designs for enhanced targeting, scalability, and regulatory compliance. Combining these carriers with advanced therapeutic strategies offers a pathway to more effective and patient-friendly RA treatments, bridging lab discoveries to clinical practice.

Keywords: *rheumatoid arthritis (RA), . Nanostructured lipid carriers (NLCs)*

1. INTRODUCTION

A chronic autoimmune disease, rheumatoid arthritis (RA) is characterized by ongoing inflammation of the synovial joints, which causes pain, stiffness, and gradual joint destruction. The illness can lead to systemic problems and has a substantial negative influence on quality of life.

Overview of Rheumatoid Arthritis:

Rheumatoid arthritis (RA) is an inflammatory illness characterised by chronic inflammation of the synovial joints, which can lead to systemic effects, bone erosion, and cartilage degeneration. By stimulating immune cells, releasing pro-inflammatory cytokines (such as TNF-α and IL-6), and generating autoantibodies, the pathogenesis results in synovial hyperplasia and joint damage (Fig. 1).The goals of current therapies are to reduce inflammation, alleviate symptoms, and stop the disease from getting worse (1). Nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, traditional synthetic DMARDs such as methotrexate, and biologics that target immune cells or cytokines are among the available options. Despite their effectiveness, these treatments have drawbacks such as side effects, insufficient results, and excessive expenses, which calls for innovative strategies such medication delivery using nanocarriers. There are several drawbacks to traditional treatments for rheumatoid arthritis (RA), such as NSAIDs, corticosteroids, and DMARDs (2).

Although they are good at controlling inflammation and delaying the course of the disease, they frequently have systemic adverse effects include immunosuppression, liver damage, and gastrointestinal problems. Despite being more targeted, biologics are expensive and need to be administered parenterally, which prevents many patients from using them. Furthermore, incomplete remission rates and variations in patient responses draw attention to the unmet therapy needs. Tolerance or decreased effectiveness may result from prolonged use of these treatments (3). To improve efficacy and lessen negative effects, these issues highlight the need for creative solutions, like customized drug delivery systems. But these treatments frequently have drawbacks like less than ideal high expenses, systemic adverse effects, and effectiveness. The management of RA is further complicated by low patient adherence and restricted targeting of inflammatory regions, underscoring the necessity of sophisticated, tailored drug delivery technologies such as nanocarriers (4).

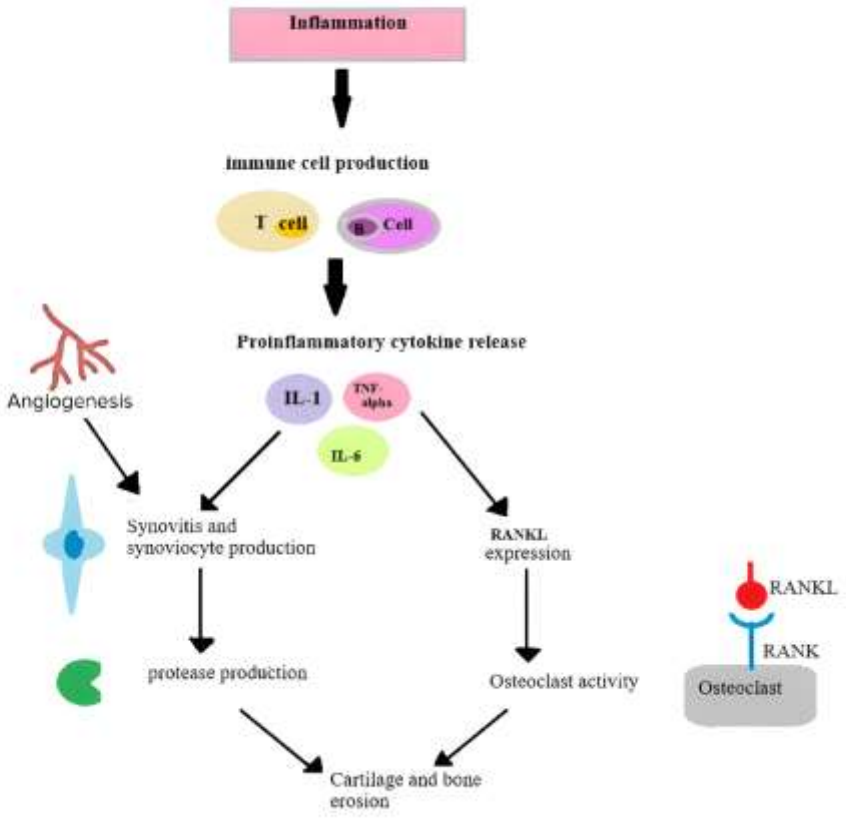

Figure 1 Pathogenesis of Rheumatoid arthritis

Advanced drug delivery systems known as nanostructured lipid carriers (NLCs) have many benefits for therapeutic uses. Their special structure, which combines liquid and solid lipids, improves the stability, solubility, and bioavailability of drugs. By enabling continuous and controlled medication release, NLCs lower dosage frequency and increase patient adherence. They can prolong the shelf life of medications that are susceptible to deterioration, such as curcumin and berberine(5) . NLCs can also be functionalized for targeted administration, which reduces systemic side effects while enhancing medication accumulation at inflammatory joints in diseases like rheumatoid arthritis. NLCs are a promising platform for enhancing the clinical efficacy of difficult medicinal agents because of their scalability and biocompatibility (6).

Emergence of Nanostructured Lipid Carriers

Advanced lipid-based drug delivery methods called nanostructured lipid carriers (NLCs) were created to get around the drawbacks of conventional formulations. Their composition consists of a blend of solid and liquid lipids stabilised by surfactants. This results in a nanostructured matrix that improves the encapsulation and release characteristics of drugs. Improved medication solubility, stability, and bioavailability are among NLCs' salient characteristics. Targeted distribution to inflammatory or sick tissues is made possible by their enhanced permeability and retention (EPR) effect, which is made possible by their small particle size (usually 50–500 nm). NLCs are perfect for therapeutic applications because they provide controlled and prolonged drug release, shield delicate medications from deterioration, and have a high level of biocompatibility (7).

Targeting rheumatoid arthritis (RA) with nanostructured lipid carriers (NLCs) has several benefits. While regulated release guarantees long-term medication administration to inflammatory tissues, their tiny size improves joint penetration. Additionally, NLCs increase the effectiveness of RA therapies by facilitating targeted therapy, lowering systemic adverse effects, and improving drug stability (8).

Nanostructured Lipid Carriers: An Overview

Structure and Composition of NLCs:

A solid lipid phase, a liquid lipid phase, and surfactants make up nanostructured lipid carriers (NLCs), which together provide a reliable drug delivery method. While the liquid lipid phase improves medication solubility and loading capacity, the solid lipid phase maintains structural stability and regulates drug release (9). By forming an incorrect crystal structure, the mixture of liquid and solid lipids improves encapsulation efficiency and decreases drug ejection. By lowering surface tension, surfactants stabilize the lipid matrix and stop particles from aggregating. NLCs are especially successful at encapsulating poorly soluble substances like curcumin and berberine because of their special composition, which enhances medication stability, bioavailability, and targeted delivery (10).

Advantages of NLCs:

1.Better Solubility: NLCs make medications that aren't very soluble in water, such curcumin and berberine, more soluble.

2.Enhanced Bioavailability: By making absorption easier, they raise the bioavailability of active ingredients.
3. Controlled Release: By providing prolonged and regulated medication release, NLCs lower the frequency of dose.
4.Targeted Delivery: They can be designed to specifically target tissues, such rheumatoid arthritis's inflammatory joints.
5.Decreased Toxicity: NLCs lessen toxicity and adverse effects by reducing systemic exposure(11).
6.Stability: NLCs shield medications against deterioration, guaranteeing their stability while being stored.
7. Biocompatibility: NLCs are safe for clinical application since they are often biocompatible.

8.Improved Encapsulation: The lipid matrix increases the effectiveness of medication loading and encapsulation.
9.Sensitive Drug Protection: NLCs protect delicate substances from deterioration in theenvironment.

10. Scalability: NLCs can be easily scaled for commercial manufacturing, making them feasible for large-scale use(12).

2. METHODS OF PREPARATION

1.High-pressure homogenization:When a lipid mixture is forced through a small opening while under high pressure, it creates strong shear forces that reduce the particles to nanoscale sizes, a process known as high-pressure homogenization of nanostructured lipid carriers (NLCs). This method is appropriate for large-scale NLC manufacturing since it guarantees consistent size distribution, promotes drug encapsulation, and increases bioavailability (13).

2.Solvent emulsification-evaporation:A lipid formulation is pushed through a tiny valve at high pressure, producing strong shear forces, in a process known as high-pressure homogenization. By reducing particle size to the nanoscale, this method enhances drug stability, bioavailability, and encapsulation. It is frequently employed to create scalable, homogeneous nanostructured lipid carriers (NLCs)(14).

3.Melt emulsification:Melt emulsification is a process that creates an emulsion by melting solid lipids and combining them with liquid lipids and surfactants. After cooling, the combination solidifies the lipid layer and forms nanoparticles. Nanostructured lipid carriers (NLCs) with improved drug loading can be made using an easy-to-use, solvent-free method

(15).

Formulation Strategies for preparation of NLCs

Selection of Lipids.

Lipid selection criteria, such as medication solubility and biocompatibility.

For rheumatoid arthritis (RA) treatment, choosing the right lipids for nanostructured lipid carriers (NLCs) is essential to guaranteeing the best possible medication delivery. One of the most important requirements is biocompatibility, which guarantees that lipids won't cause toxicity or immunological reactions when taken. For the active ingredients, including curcumin and berberine, to dissolve and increase their bioavailability, lipid solubility is necessary (16). In order to create a durable matrix and preserve the intended solid-liquid phase mixing, the lipids need also have an appropriate melting point. Lipids should also have low cytotoxicity, be simple to process, and allow for regulated release. These characteristics provide long-term, safe, and efficient medication delivery to RA tissues that are inflamed (17).

Illustrations of the liquid and solid lipids utilized in curcumin and berberine.

Based on their compatibility, solubility, and biocompatibility, a range of solid and liquid lipids can be employed for nanostructured lipid carriers (NLCs) that carry curcumin and berberine (18).

Solid Lipids:

Stearic acid: stearic acid is a solid lipid that is frequently utilized because it is biocompatible and can encapsulate hydrophobic medications like berberine and curcumin.

Another solid lipid that contributes to the formation of stable NLCs with enhanced drug loading capability is palmitic acid. Glyceryl monostearate (GMS): A popular solid lipid with regulated release and stability(19).

Lipids in liquid form:

Caprylic/capric triglyceride: This medium-chain triglyceride helps with medication encapsulation by giving lipophilic substances enhanced solubility.

Oleic acid: A liquid lipid that helps stabilize NLC formulations and increase the solubility of berberine and curcumin. Castor oil: A liquid lipid that improves the encapsulated medications' release characteristics.

The combination of these lipids maximizes the NLC formulations' stability, bioavailability, and therapeutic effectiveness(20).

Optimization of Formulation Parameters

The ratio of drugs to fats. For berberine and curcumin, the drug-lipid ratio is a crucial factor in the optimization of nanostructured lipid carrier (NLC) formulations. The stability, release profile, and efficiency of drug encapsulation are all directly impacted by this ratio. Although a larger drug-lipid ratio can increase loading capacity, it may also decrease NLC stability, which could result in aggregation or early drug release. On the other hand, a lower drug-lipid ratio might lead to improved stability and regulated release but less drug loading (21). Maximum drug incorporation is guaranteed by the ideal drug-lipid ratio without sacrificing the NLCs' physical stability. Usually, rigorous optimization studies are utilized to strike a balance, taking into account variables including the drug's lipophilicity, the kind of lipids used, and the intended therapeutic results. For rheumatoid arthritis, this equilibrium guarantees focused delivery, prolonged release, and successful treatment (22).

The polydispersity index (PDI) and particle size. Key factors in the optimization of nanostructured lipid carriers (NLCs) for the delivery of curcumin and berberine in rheumatoid arthritis (RA) therapy include particle size and polydispersity index (PDI)(23).

Particle Size:

When it comes to medication release, stability, and bioavailability, NLC particle size is vital. Because of their increased surface area, smaller nanoparticles (usually between 50 and 200 nm) are more effective in encapsulating drugs and can more easily penetrate inflammatory tissues thanks to the enhanced permeability and retention (EPR) effect. By focusing on particular receptors on the inflammatory cells, small particle sizes also encourage greater cellular absorption. Larger particles may have lower drug release rates and bioavailability, while particles that are too tiny may aggregate or become unstable (24).

Polydispersity Index (PDI):

The homogeneity of the particle size distribution is measured by PDI. For steady medication release and persistent therapeutic benefits, a restricted size distribution is indicated by a PDI value around 0.1. A wide dispersion is indicated by a high PDI (>0.3), which may result in uneven medication administration and compromise the repeatability of treatment results. By avoiding quick clearance, ensuring uniform distribution inside inflammatory joints, and optimizing PDI, the NLC

formulation offers consistent therapeutic responses, enhancingoverall efficacy in the treatment of RA.Therefore, to achieve targeted, controlled drug administration and improved therapeutic outcomes, it is imperative to optimize both particle size and PDI (25).

Entrapment efficiency:

The percentage of the drug that is successfully incorporated into the nanostructured lipid carriers (NLCs) in relation to the total amount of drug employed during formulation is known as entrapment efficiency (EE). A high EE guarantees that a significant amount of the active ingredient, like curcumin or berberine, is encapsulated, which aids in sustained release and efficient medication administration (26). The lipid composition, the drug-lipid ratio, the preparation technique, and the drug's solubility in the lipid phase are all factors that affect EE. When treating rheumatoid arthritis, a high EE increases the drug's stability within the carrier, preventing premature release and improving overall bioavailability and therapeutic efficacy (27).

Characterization Techniques.

Analysis of particle size (dynamic light scattering, for example).

Characterizing nanostructured lipid carriers (NLCs) and assessing their potential for medication delivery require particle size analysis. Dynamic Light Scattering (DLS) is one of the most often used methods for this. The intensity variations in scattered light brought on by the Brownian motion of suspended particles are measured by DLS. The hydrodynamic diameter of the particles, which yields data on the particle size distribution, is computed using these fluctuations. When detecting particle sizes in the nanometer range, which is usually between 10 nm and 1 µm, DLS is quite effective (28). The method involves little sample preparation, is quick, and is non-invasive. By examining the polydispersity index (PDI), which shows how uniform the particle size distribution is, it also sheds light on particle stability. The therapeutic success of NLC formulations in conditions like rheumatoid arthritis depends on continuous drug release, enhanced cellular uptake, and targeted distribution, all of which are ensured by optimizing particle size and PDI(29).

Zeta potential

For evaluating the stability and dispersibility of nanoparticles in suspension, such as nanostructured lipid carriers (NLCs), zeta potential—a measurement of the surface charge of the particles—is essential. Electrophoretic mobility is the measurement of the velocity at which particles move in a colloidal solution when an electric field is applied. Higher values (positive or negative) indicate more stability because of electrostatic repulsion, which prevents aggregation. The zeta potential is a reflection of the repulsive forces between particles. For NLCs to be stable, avoid clumping, and guarantee consistent drug delivery, their zeta potential should be at least ±30 mV(30).

Morphology (e.g., TEM, SEM).

Understanding the size, shape, and surface properties of nanostructured lipid carriers (NLCs), which have a direct bearing on the effectiveness of drug delivery, requires morphological study. Two important methods for this are scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (31).

Transmission Electron Microscopy (TEM):

TEM offers high-resolution imaging of NLCs, making it possible to view interior features and nanoscale particle shape. When it comes to examining the internal organization of lipids and guaranteeing consistent drug encapsulation, TEM is especially helpful. It displays minute characteristics including particle form and the architecture of the lipid matrix(32).

Scanning Electron Microscopy (SEM):

SEM is useful for evaluating the surface morphology and general particle form of NLCs, even though it has a lower resolution than TEM. Drug release profiles and biodistribution depend on the smoothness, aggregation, and surface roughness of particle coatings, all of which are revealed by SEM images. In order to ensure optimal drug encapsulation, stability, and targeted distribution in therapeutic applications, both approaches allow for comprehensive analysis of particle size, shape, and surface characteristics (33).

Drug release studies:

When assessing how well nanostructured lipid carriers (NLCs) function in applications involving regulated and sustained drug delivery, drug release experiments are essential. In order to optimize formulation characteristics like as drug encapsulation, particle size, and lipid content, these studies evaluate the pace and amount of drug release from NLCs. In order to promote therapeutic efficacy, reduce side effects, and enhance bioavailability, the main goal is to make sure the medicine is released at the appropriate pace throughout time (34).

Techniques like dialysis membrane diffusion or basket or paddle procedures are commonly used in in vitro drug release research. The dialysis membrane approach involves placing the NLCs in a donor compartment and allowing the drug to diffuse into a receiver compartment with a buffer through a semipermeable membrane. To monitor the release rate, the drug's concentration in the receiver solution is monitored on a regular basis(35). The paddle or basket approach involves agitating

NLCs in a medium at a steady temperature and measuring the amount of medication released over time using high-performance liquid chromatography (HPLC) or spectrophotometric analysis (36).Parameters like continuous release, which is best for therapeutic consistency, and initial burst release, which can be reduced by formulation optimization, can be used to assess release profiles. In order to predict the drug's behaviour in vivo and optimize treatment regimens, the release kinetics are frequently model using mathematical equations such as zero-order, first-order, or Higuchi models (37).

Mechanistic Insights: Delivery of NLCs in Rheumatoid Arthritis

Enhancing permeability and retention effects in RA

When it comes to rheumatoid arthritis (RA) medication distribution, the Enhanced Permeability and Retention (EPR) impact is crucial. Because RA involves angiogenesis and pro-inflammatory cytokines, inflammatory joints have higher vascular permeability. Nanocarriers, such as nanostructured lipid carriers (NLCs), might passively accumulate in the inflammatory tissues due to this vascular anomaly. The absence of efficient lymphatic drainage in the afflicted areas lends more credence to the preservation of these nanocarriers. By utilizing the EPR effect, NLCs containing therapeutic drugs like curcumin and berberine can improve therapeutic efficacy in the therapy of RA, decrease systemic adverse effects, and improve drug localization (38).

Role of NLCs in overcoming biological barriers

In rheumatoid arthritis (RA), biological barriers that restrict the therapeutic potential of medications like curcumin and berberine are successfully overcome by nanostructured lipid carriers (NLCs). These obstacles include difficulties in targeting inflammatory joints, low bioavailability, and poor solubility. By encasing hydrophobic molecules in a lipid matrix and shielding them from oxidation and enzymatic degradation, NLCs improve medication stability (39). NLCs can accumulate in inflammatory tissues with leaky vasculature because of their small particle size and surface characteristics, which allow passive targeting through the enhanced permeability and retention (EPR) effect. Additionally, NLCs enhance lymphatic uptake and facilitate transport across the gastrointestinal barrier, which improves medication absorption. Additionally, the lipid composition encourages regulated medication release and extended circulation time, which lowers the frequency of dose and systemic side effects. Furthermore, NLCs' surface modifications—such as the addition of targeting ligands—improve their interaction with particular cell receptors and guarantee accurate delivery to inflammatory joint tissues, which increases the effectiveness of treatment for RA(40).

Anti-Inflammatory Mechanisms of Berberine and Curcumin Delivered via NLCs.

TNF-α and IL-6, two pro-inflammatory cytokines, are downregulated.Berberine and curcumin-loaded nanostructured lipid carriers (NLCs) are crucial for inhibiting pro-inflammatory cytokines including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), which play a significant role in the pathogenesis of rheumatoid arthritis (RA). These cytokines cause joint damage, increase inflammation, and encourage synovial hyperplasia (41). Known for their anti-inflammatory qualities, berberine and curcumin block signaling pathways like NF-κB and JAK/STAT, which control the release of TNF-α and IL-6. NLCs ensure focused activity and prolonged release by improving these phytochemicals' delivery and absorption at inflammatory joint sites. This reduces joint discomfort, inhibits cytokine-mediated inflammation, and delays the course of RA (42).

A decrease in indicators of oxidative stress. Berberine and curcumin-loaded nanostructured lipid carriers (NLCs) effectively reduce oxidative stress markers, a key contributor to the onset of rheumatoid arthritis (RA). Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) and antioxidant defences, leads to cartilage deterioration, joint damage, and synovial inflammation (43). Curcumin and berberine have strong antioxidant properties that scavenge reactive oxygen species (ROS) and increase the activity of endogenous antioxidants including superoxide dismutase (SOD) and glutathione peroxidase (GPx). NLCs ensure effective ROS neutralization by enhancing their stability, bioavailability, and targeted transport to inflammatory tissues. This offers substantial therapeutic benefits in the management of RA by lowering oxidative stress indicators, safeguarding joint structures, and reducing inflammation (44).

Preclinical and Clinical Evidence.

Preclinical Studies

In vitro research showing that NLC formulations are more effective.

Studies conducted in vitro have shown that nanostructured lipid carriers (NLCs) are more effective in delivering curcumin and berberine during rheumatoid arthritis (RA) treatment. These investigations demonstrate the encapsulated drug's improved solubility, stability, and controlled release. When NLC formulations are applied to cultured macrophages and synovial fibroblasts, they dramatically lower inflammatory indicators such prostaglandins, IL-6, and TNF-α. When compared to free medications, the nanoparticles show more cellular absorption, guaranteeing targeted delivery and extended retention in inflammatory cells. Furthermore, by reducing reactive oxygen species (ROS) levels, NLCs lessen oxidative stress. These results demonstrate how NLCs may improve therapeutic efficacy in the treatment of RA (45).

In-vivo studies in RA animal models.

The therapeutic potential of nanostructured lipid carriers (NLCs) loaded with curcumin and berberine has been demonstrated in in vivo investigations employing animal models of rheumatoid arthritis (RA)(46). With their improved anti-inflammatory and antioxidant properties, these formulations considerably lessen cartilage degeneration, synovial hyperplasia, and joint edema. The NLCs have improved bioavailability, prolonged circulation, and targeted accumulation in inflammatory joints due to the enhanced permeability and retention (EPR) action. Furthermore, they effectively reduce pro-inflammatory cytokines like TNF-α and IL-6 as well as oxidative stress markers like reactive oxygen species (ROS). These findings demonstrate the effectiveness of NLCs in lowering RA symptoms and maintaining joint integrity (47).

Potential Role of Phytochemicals

Potent natural compounds like curcumin and berberine have significant therapeutic applications, particularly in the management of inflammatory and autoimmune diseases like rheumatoid arthritis (RA). Berberine has anti-inflammatory qualities by altering immune responses and blocking pro-inflammatory cytokines (such TNF-α and IL-6). It also possesses antioxidant properties that protect tissue from damage and reduce oxidative stress (48). Turmeric contains curcumin, which protects joint structures by neutralizing free radicals and blocking important inflammatory processes, such as NF-κB activation. Both substances show promise in reducing RA symptoms and delaying the course of the illness. Despite issues with stability and bioavailability, their safety and multitargeted effects make them appealing substitutes or supplements to traditional therapy (49).

Although curcumin and berberine have medicinal promise, there are many obstacles in the way of their effective delivery. Due to their low water solubility, these substances have limited intestinal absorption. They have a short half-life and low systemic bioavailability due to their quick metabolism and excretion. Furthermore, under physiological settings, their stability is weakened, with berberine being vulnerable to first-pass metabolism and curcumin being prone to degradation. These elements reduce their clinical effectiveness and raise the possibility of adverse consequences by requiring high dosages for therapeutic benefits. By improving solubility, stability, and targeted distribution to disease areas, advanced delivery technologies such nanostructured lipid carriers (NLCs) overcome these drawbacks (50).

Berberine and Curcumin: Pharmacological Profile and Challenges

Berberine

A naturally occurring isoquinoline alkaloid, berberine has a fused tetracyclic ring system and a planar quaternary ammonium structure. Its structure contains methylenedioxy and hydroxyl functional groups, which contribute to its bioactivity. Its molecular formula is $C_{20}H_{18}NO_4$. Numerous pharmacological characteristics, including as anti-inflammatory, antioxidant, antibacterial, and immunomodulatory activities, are displayed by berberine (51). By neutralizing free radicals, it lowers oxidative stress, suppresses pro-inflammatory cytokines like TNF-α and IL-6, and modifies signaling pathways like AMPK and NF-κB. Because of these characteristics, berberine has promise as a treatment for metabolic disorders and chronic inflammatory diseases such rheumatoid arthritis (52).

Curcumin and berberine are prospective treatments for rheumatoid arthritis (RA) because of their strong immunomodulatory and anti-inflammatory properties. By blocking pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 as well as important pathways like NF-κB and MAPK, berberine lowers inflammation. Additionally, it reduces joint injury caused by T-cells and macrophages by modifying immune cell activity. Curcumin also inhibits the enzymes NF-κB, COX-2, and LOX, which lowers oxidative stress and cytokine production. Curcumin also restores immunological homeostasis by encouraging regulatory T-cell responses. By focusing on several molecular pathways implicated in the pathophysiology of RA, these substances work together to reduce joint inflammation and discomfort while also delaying the course of the disease (53).

Curcumin

Turmeric (Curcuma longa) contains a polyphenol called curcumin, which has a unique diarylheptanoid structure. It is made up of two aromatic rings with hydroxyl and methoxy groups joined by a seven-carbon chain that has keto-enol tautomerism and conjugated double bonds. By chelating metal ions and scavenging reactive oxygen species, this structure adds to its bioactive qualities, which include strong antioxidant activity (54). By blocking cyclooxygenase-2 (COX-2) and nuclear factor-kappa B (NF-κB), curcumin also has potent anti-inflammatory properties. Despite its low bioavailability, it is useful against chronic inflammatory illnesses like rheumatoid arthritis because of its capacity to control signaling pathways, lower oxidative stress, and regulate immunological responses (55). By blocking NF-κB, COX-2, and pro-inflammatory cytokines like TNF-α and IL-6, curcumin reduces inflammation. Its antioxidant processes include lowering lipid peroxidation, increasing glutathione levels, and scavenging reactive oxygen species. Curcumin is useful in the treatment of rheumatoid arthritis because of its ability to control inflammatory pathways and shield tissues from oxidative damage (56).

Limitations of Berberine and Curcumin for Rheumatoid Arthritis:

1.PoorSolubility: The low water solubility of both substances restricts their uptake in biological systems.

2. Poor Bioavailability: Low plasma concentrations are caused by rapid metabolism and systemic clearance.

3. Short Half-Life: Both have brief therapeutic effects since they are rapidly metabolized.

4. Instability: Berberine experiences a great deal of first-pass metabolism, but curcumin is chemically unstable in physiological or alkaline environments.

5. Limited Targeting: These chemicals are not specifically delivered to inflammatory RA joints by conventional formulations (57).

Bioactive natural substances like curcumin and berberine have great therapeutic promise, especially for the treatment of autoimmune and inflammatory diseases like rheumatoid arthritis (RA). With its strong anti-inflammatory, immunomodulatory, and antioxidant qualities, berberine efficiently reduces oxidative stress and pro-inflammatory cytokines. Turmeric contains a polyphenol called curcumin, which has potent anti-inflammatory and antioxidant properties. It also inhibits several molecular processes that contribute to the pathophysiology of RA, including NF-κB activation. Both compounds have issues such as low bioavailability, fast metabolism, and poor water solubility, despite their encouraging pharmacological characteristics. Nanostructured lipid carriers are one example of an advanced drug delivery technology that can improve a medicine's therapeutic efficacy and clinical applicability (58).

Because of its exceptional anti-inflammatory and antioxidant qualities, berberine and curcumin are potential options for the treatment of rheumatoid arthritis (RA). However, their low solubility and bioavailability limit their clinical potential (59). These restrictions are overcome by nanostructured lipid carriers (NLCs), which improve controlled release, targeted distribution, and drug stability. Although there is yet no clinical translation, preclinical research shows that NLC formulations are more therapeutically effective in RA models. The optimization of NLC designs for improved targeting, scalability, and regulatory compliance should be the main emphasis of future research. By connecting laboratory findings to clinical practice, the combination of these carriers with cutting-edge therapeutic approaches provides a route to more efficient and patient-friendly RA treatments (60).

3. CURCUMIN AND BERBERINE INCLUDE THE DELIVERY SYSTEMS

S.NO.	AUTHORS	DELIVERY SYSTEMS	BRIEF DESCRIPTION
1.	Ieva Rinkunaite1*	curcumin-loaded solid lipid nanoparticles (curcumin)	Complete Freund's adjuvant was used to cause arthritis in Wistar rats, and the arthritis score system was used every day to gauge the severity of the condition. Beginning on the sixth day following the induction of arthritis, animals were administered curcumin formulations orally every day for 20 days in a row. The ELISA test was used to measure pro-inflammatory cytokines in order to ascertain the inflammatory background. Haematologic tests, weight changes, and limb swelling were also monitored.
2.	Maria Letizia Mancaa,1	curcumin loaded hyalurosomes (curcumin)	Hyalurosomes infused with curcumin were suggested as novel rheumatoid arthritis therapeutic methods. An eco-friendly, one-step process was used to prepare the vesicles. Thorough pre-formulation research was conducted utilizing several types and amounts of phospholipids in order to determine the best formulation in terms of size, surface charge, and stability during storage.
3.	Bhupinder Kapoor,	Liposomes (curcumin)	The intrasynovial distribution of these medications for the treatment of RA has been accomplished via a variety of techniques, including microemulsions, microspheres, liposomes, microballoons, cocrystals, nanoemulsions, dendrimers, microsponges, and so on. Because of their size and chemical makeup, liposomes have been shown to be particularly successful in keeping the medication in the synovial cavity. Liposomes can be used to counteract the rapid

			clearance of intra-synovially given medicines, increasing drug uptake by the target synovial cells.
4.	Neelu Singh,	NLCs (nanostructured lipid carriers) (berberine)	This assesses the therapeutic potential and medication delivery of a nanoformulation loaded with berberine (Br) in an animal model of rheumatoid arthritis (RA). The melt-emulsification method was used to create the Br-loaded NLCs (nanostructured lipid carriers), which were then optimised using the Box-Behnken design.
5.	Mohammed H. Elkomy [1]	Surface-Modified Bilosomes (berberine)	In order to improve the management of RA inflammation, we sought to enhance the transdermal distribution of a natural substance, berberine, by encapsulating it in chitosan and surface-modified bilosome nanogel. The thin-film hydration method was used to manufacture the chitosan-coated bilosomes loaded with berberine (BER-CTS-BLS), which were then optimised for a number of causative factors.
6.	Fei Sun	Exosomes (berberine)	To assess how exosomes released by bone marrow-derived mesenchymal stem cells (BMSCs) treated with berberine affect synovial inflammation in a model of collagen-induced arthritis (CIA). Exosomes were separated from both untreated (BMSC-EXs) and berberine-treated (Ber BMSC-EXs) BMSCs. Ber-BMSC-EXs or BMSC-EXs were created and administered to CIA rats. The clinical arthritis index was calculated..

4. HIGHLIGHT THE IMPORTANCE OF NATURAL INGREDIENTS WHEN COMPARED TO SYNTHETIC FORMULATIONS.

Compared to synthetic formulations, natural components have several advantages, especially in terms of efficacy, environmental impact, and health. This is why they are important:

1. Health Advantages: Gentler on the Body: Natural components frequently have a lower risk of causing allergic reactions, inflammation, or long-term health issues. Better Absorption: Natural chemicals are recognized and processed by the body more effectively than manufactured ones (61). No Dangerous Additives: Preservatives, artificial perfumes, and other compounds that may become hazardous over time are present in many synthetic formulations (62).

Sustainability of the Environment Biodegradable: Natural materials decompose quickly, lowering pollution. Eco-Friendly Production: Their manufacturing uses less hazardous chemicals, which lowers their carbon footprint. Sustainable Sourcing: Unlike synthetic substitutes that depend on petroleum-based components, a large number of natural products originate from renewable resources (63).Purity & Effectiveness Nutrient-Rich: Vital vitamins, minerals, and antioxidants that are frequently lost during synthetic processing are retained in natural components. • Less Processing: They retain their original advantages due to minimal chemical changes (64).Verified by Tradition: The effectiveness of numerous natural components has been demonstrated for years in traditional medicine, skincare, and wellness (65).

Reduced Adverse Reactions

No Harsh Chemicals: Natural substances function in harmony with the body, in contrast to synthetic ones that may result in rashes, dryness, or long-term health hazards. Minimal Toxins: Toxins included in many synthetic formulations build up in the body over time and may cause health problems (66). The present state of clinical trials employing curcumin and berberine NLCs is discussed in 6.2 Clinical Trials and Translational Potential. With few studies specifically concentrating on these formulations, the clinical assessment of nanostructured lipid carriers (NLCs) loaded with curcumin and berberine for

rheumatoid arthritis (RA) is still in its early phases. Clinical trials on traditional forms of curcumin and berberine, however, have shown anti-inflammatory and antioxidant effects in RA patients, confirming their promise as therapeutics. NLCs provide better medication delivery by resolving drawbacks such high metabolism and low bioavailability. In order to ensure safety, scalability, and regulatory compliance, translational efforts are concentrated on improving NLC formulations for clinical usage. To verify their effectiveness, safety, and long-term advantages in the treatment of RA,more research is required (67).Clinical translation challenges.
There are various obstacles in the way of the therapeutic application of berberine and curcumin-loaded nanostructured lipid carriers (NLCs) for rheumatoid arthritis (RA). First, the scalability of NLC production is complicated because large-scale manufacturing makes it challenging to maintain the precision needed in drug encapsulation efficiency, nanoparticle size, and composition. Second, there are regulatory obstacles since NLCs are sophisticated drug delivery systems that need to undergo thorough safety, effectiveness, and stability assessments in accordance with strict regulations (68). Third, there are further issues regarding clinical application due to the potential immunogenicity of nanocarriers and the variation in individual patient reactions. It is also necessary to guarantee the lipid carriers' stability during prolonged storage. Additionally, pharmacokinetics, the best dosage, and long-term safety characteristics unique to RA patients must be covered in clinical trials. Cost-effectiveness is still a crucial factor to take into account because large-scale production and regulatory compliance can raise costs. To overcome these obstacles and enable successful clinical application, interdisciplinary initiatives involving regulatory science, pharmacology, and nanotechnology are needed (69).

Future Perspectives and Challenges.

Advancements in NLC technology (e.g., surface modifications for active targeting).

The potential of nanostructured lipid carriers (NLCs) for active targeting in rheumatoid arthritis (RA) treatment has been greatly increased by developments in NLC technology, especially in surface changes. Receptor-mediated targeting of inflammatory joint tissues is made possible by functionalizing NLC surfaces with ligands such folic acid, peptides, or antibodies. To ensure precise drug delivery to afflicted areas, RA-specific ligands, for example, can bind to overexpressed receptors, such as integrins or folate receptors (70). Additionally, by decreasing opsonization and immune system clearance, polyethylene glycol (PEG) coating lengthens circulation duration. Other developments include stimuli-responsive NLCs, which release medications in reaction to temperature or pH variations in inflammatory areas. These developments enhance RA treatment, decrease systemic side effects, and increase therapeutic efficacy (71).

The possibility of combined treatments.

Given the complex nature of rheumatoid arthritis (RA), combination therapy using nanostructured lipid carriers (NLCs) hold great promise. Co-loading synergistic substances, like curcumin and berberine, improves their immunomodulatory, antioxidant, and anti-inflammatory properties. NLCs make it possible to precisely regulate medication ratios, which maximizes therapeutic benefits and reduces adverse effects. Furthermore, NLCs can combine phytochemicals with traditional medications (such methotrexate) to offer the advantages of both targeted administration and decreased systemic toxicity. By addressing several RA pathways at once, including cytokine suppression, oxidative stress reduction, and immunological modulation, this strategy improves therapeutic efficacy. Personalized RA therapy is made possible by combination-loaded NLCs, which also enhance patient adherence and clinical results (72).

Resolving issues with scalability and regulations.

Two major obstacles to implementing nanostructured lipid carriers (NLCs) in clinical settings for rheumatoid arthritis (RA) are scalability and regulatory issues. Particle size, drug encapsulation, and formulation stability must all be precisely controlled for scaling up NLC manufacturing, which can be difficult and resource-intensive. To achieve quality standards, batch-to-batch repeatability must be guaranteed (73). Comprehensive preclinical and clinical tests to prove safety, efficacy, and long-term stability are among the regulatory obstacles. The strict requirements for innovative drug delivery systems, which include thorough characterisation and toxicity investigations, must also be met by NLCs. Innovations in scalable production methods, standardization procedures, and interdisciplinary cooperation for regulatory compliance are necessary to meet these problems (74).

Patent

S.NO	Application Number	Invention Title	BRIEF DESCRIPTION
1	202541005740	Topical gel formulation of cissus quadrangularis for the management of arthritis-related bone pain	Abstract The present invention relates to a topical gel formulation derived from Cissus quadrangularis (Pirandai), a medicinal plant known for its anti-inflammatory and bone-healing properties, designed for the management of arthritis-related bone pain. The gel is formulated using bioactive compounds such as

			flavonoids, triterpenoids, and ascorbic acid extracted from Cissus quadrangu/aris. These compounds work synergistically to reduce inflammation, alleviate pain, and support bone regeneration. The invention offers a localized, non-invasive treatment with reduced systemic absorption compared to traditional oral medications. A randomized controlled trial demonstrated the gel's efficacy in providing significant pain relief and improved joint function. The formulation provides a natural, safe, and effective alternative for managing arthritis-related bone pain, addressing the gaps in existing treatments and offering a promising solution in herbal therapeutics for musculoskeletal disorders.
2	202541002351	AI-Driven Multi-Modal Framework for Enhanced Diagnosis and Personalized Treatment of Rheumatoid Arthritis	An AI-driven multimodal framework for improved rheumatoid arthritis diagnosis and individualized treatment is shown in the invention. By integrating imaging, genomic, and clinical data, the system improves diagnostic accuracy, predicts disease progression, and tailors treatment plans using advanced deep learning techniques. Key innovations include the use of GANs for data augmentation, RNNs for time-series analysis, and DRL for personalized therapeutic optimization. Explainable AI tools ensure transparency and foster clinical trust. Scalable and accessible, this framework bridges the gap between advanced AI research and real-world clinical applications, revolutionizing RA management.
3	202441016325	Phytochemical-loaded exosomes for attenuating pannus formation in rheumatoid arthritis	The present invention relates to a novel drug delivery system for the treatment of rheumatoid arthritis (RA). Rheumatoid arthritis is a chronic inflammatory autoimmune disorder affecting the joints, characterized by pain, swelling, and eventual joint destruction. Exosomes, extracellular vesicles secreted by cells, have emerged as promising therapeutic agents due to their ability to deliver bioactive molecules to target cells. More specifically, the invention encompasses the encapsulation of phytochemical compounds within exosomes to target and alleviate symptoms associated with RA. The phytochemical-encapsulated exosomes will have enhanced therapeutic efficacy, target specificity, and improved bioavailability than the conventional drug delivery methods. The invention provides a promising approach to the management of RA, addressing the limitations of current treatment modalities.
4	202321082704	Biosynthesis of nanoparticulate hydrogel from plectranthusamboinicuslour. spreng for rheumatoid arthritis	The present invention provides a process for preparing herbal nanoparticulate hydrogel for its anti-inflammatory property. Said hydrogel constitutes Plectranthusamboinicus leaves, Poly(lactic-co-glycolic acid) (PLGA), Gelatin,

		treatment.	Poly vinyl alcohol (PVA), Carboxy methyl cellulose (CMC), Glycerol. The method of preparing comprises of collecting raw materials and extraction, synthesis of herbal nanoparticles and formulation of herbal nanoparticulate hydrogel with anti-inflammatory and anti-proliferative property for the potential use in treatment of rheumatoid arthritis.
5	202341055065	Fabrication of berberine loaded ethosomal gel for arthritis	The ethosomal gel could be considered as a promising carrier for treating arthritis compromising of Berberine administered topically. The present invention demonstrated enhanced bio distribution of Berliner through chromosomal gel formulation.
6	202331064448	Extraction and purification of anti-inflammatory compounds from natural sources for use in managing rheumatoid arthritis	The present invention relates to developing pharmaceutical and therapeutic solutions for Rheumatoid Arthritis (RA) through the extraction and purification of anti-inflammatory compounds from natural sources. The anti-inflammatory and analgesic properties of natural extracts from turmeric, ginger, and grapes. The extraction methods yield high-purity curcumin from turmeric, essential oils from ginger, and resveratrol from grape skins. These bioactive compounds are then skillfully combined into a gel formulation. This gel, rich in curcumin, gingerol, and resveratrol, offers targeted relief for Rheumatoid Arthritis sufferers. Emollients ensure skin hydration, penetration enhancers facilitate deep absorption, and preservatives maintain product safety. The formulation addresses not only joint inflammation and pain but also sensitive skin associated with Rheumatoid Arthritis.
7	202347049507	Novel arthritis emulgel composition and its preparation process	The new topical formulation of arthritic emulgel is the subject of the current innovation. In particular, the current invention pertains to a new topical formulation of arthritic emulgel that combines pharmaceutically acceptable excipients with active components. More precisely, the current invention pertains to a new formulation of arthritic emulgel that combines methyl salicylate, menthol, boswellia serrata extract, curcumin (using Force C3TM increased absorption technology), and other pharmaceutically approved excipients as active components. More precisely, the present invention pertains to a unique composition that may contain one or more of the following: chondroitin sulphate, glucosamine sulphate, and ginger extract. The procedure for creating a new topical formulation of arthritic emulgel, which includes the steps of dissolving, mixing, adding, sonicating, regulating the pH, and stirring, is also related to the current invention.
8	493/CHE/2006	Composition for relief	The chemical composition of the present

		osteoarthritis, rheumatoid arthritis, cervical spondylosis, polyarthritis, and ankylosing spondylosis and method of use thereof	invention, which includes glucosamine sulphate, shallaki extract, ginger extract, and curcumin, is intended to be taken as capsules to alleviate the symptoms of osteoarthritis, rheumatoid arthritis, cervical spondylosis, polyarthritis, and ankylosing spondylosis.
9	202021028699	Solid lipid nanoparticles of plant extract for the treatment of rheumatoid arthritis	The present invention relates to a solid lipid nanoparticles composition comprising effective amount of at least one plant extract for treatment of rheumatoid arthritis. The present invention more particularly relates to a solid lipid nanoparticles consisting of gingerol obtained from ginger extract, chlorogenic acid obtained from coffee bean extract or 3-acetyl-11-keto-beta-boswellic acid obtained from boswellia extract with atleast one lipid selected from the group of fatty acids or glycerides and at least one surfactant for treatment of rheumatoid arthritis suitable for lymphatic uptake on oral administration. The invention also relates to method of treatment of rheumatoid arthritis by oral administration of solid lipid nanoparticles of Coffee bean extract, Ginger extract, Bowellia extract suitable for Lymphatic uptake. The invention relates to a process of preparation of the solid lipid nanoparticles of at least one plant extract by melt emulsification homogenisation method.
10	202341088582	A novel composition for enhancing the targeting efficacy in the treatment of rheumatoid arthritis	A NOVEL COMPOSITION FOR ENHANCING THE TARGETING EFFICACY OF THE SELECTED DRUGS A novel composition for enhancing the targeting efficacy in the treatment of selected drugs relates to a composition of lipid, Saquinavir, Surfactant and hyaluronic acid% and the process of preparing the same. SQV-loaded nanoparticles and those coated with HA exhibited a reduction in peak intensity for SQV and GMS compared to their individual crystalline states. This reduction suggests successful interactions between drug and lipid components facilitated by the less-ordered lipid crystal lattices within the nanoparticles. This structural arrangement enhances drug encapsulation and stability by inhibiting rapid drug expulsion, due to GMS, an essential lipid component, contributing to this effect with its amorphous structure, creating additional space within the nanoparticles for drug accommodation. This expanded capacity limits drug expulsion and enhances drug- loading efficiency, underscoring the pivotal role of lipid composition and structure in optimizing nanoparticle formulations for improved drug delivery.

5. CONCLUSION

Summary of the potential of berberine and curcumin-loaded NLCs for RA treatment.Berberine and curcumin-loaded nanostructured lipid carriers (NLCs) hold immense potential as innovative therapeutic approaches for rheumatoid arthritis (RA). These natural phytochemicals exhibit potent anti-inflammatory, antioxidant, and immunomodulatory properties, targeting key pathways involved in RA pathogenesis, such as cytokine overexpression, oxidative stress, and immune dysregulation. However, their clinical application is limited by poor solubility, low bioavailability, and rapid metabolism.

NLCs address these challenges by encapsulating berberine and curcumin within lipid matrices, significantly enhancing their solubility, stability, and bioavailability. These carriers provide sustained and controlled drug release, ensuring prolonged therapeutic effects while reducing dosing frequency and systemic side effects. The small particle size of NLCs and their surface properties enable targeted delivery to inflamed joints via the enhanced permeability and retention (EPR) effect. Additionally, surface modifications, such as ligand functionalization, further enhance active targeting, improving therapeutic precision.

Preclinical studies demonstrate the efficacy of berberine and curcumin-loaded NLCs in reducing inflammation, suppressing pro-inflammatory cytokines (e.g., TNF-α, IL-6), and alleviating oxidative stress markers in RA models. These findings highlight their potential to mitigate disease progression, protect joint structures, and improve patient outcomes. Future advancements in scalability, regulatory compliance, and clinical trials will be pivotal in translating these promising formulations into clinical practice.

Emphasis on the need for further research to ensure clinical success.

Further research is essential to ensure the clinical success of berberine and curcumin-loaded nanostructured lipid carriers (NLCs) for rheumatoid arthritis (RA). Key areas of focus include optimizing NLC formulations for enhanced stability, drug loading efficiency, and controlled release. Comprehensive preclinical studies are needed to evaluate long-term safety, pharmacokinetics, and biodistribution in relevant RA models. Clinical trials must establish efficacy, safety, and dosing regimens in diverse patient populations. Addressing challenges like large-scale manufacturing, regulatory compliance, and cost-effectiveness is crucial. Additionally, exploring combination therapies and advanced targeting strategies will further enhance therapeutic potential, paving the way for successful clinical translation.

Acknowledgements

We sincerely express our gratitude to our esteemed Principal, Dr. Y. Padmanabha Reddy, Raghavendra Institute of Pharmaceutical Education and Research (RIPER), for his invaluable support and encouragement throughout this work.

Conflicts of interest

None

REFERENCES

[1] Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone research. 2018;*6*(1):15.

[2] Lin Y-J, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020;*9*(4):880.

[3] Esfahani K, Elkrief A, Calabrese C, Lapointe R, Hudson M, Routy B, et al. Moving towards personalized treatments of immune-related adverse events. Nature reviews Clinical oncology. 2020;*17*(8):504-15.

[4] Alshawwa SZ, Kassem AA, Farid RM, Mostafa SK, Labib GS. Nanocarrier drug delivery systems: characterization, limitations, future perspectives and implementation of artificial intelligence. Pharmaceutics. 2022;*14*(4):883.

[5] Teixeira M, Carbone C, Souto E. Beyond liposomes: Recent advances on lipid based nanostructures for poorly soluble/poorly permeable drug delivery. Progress in lipid research. 2017;*68*:1-11.

[6] Domingues C, Santos A, Alvarez-Lorenzo C, Concheiro A, Jarak I, Veiga F, et al. Where is nano today and where is it headed? A review of nanomedicine and the dilemma of nanotoxicology. ACS nano. 2022;*16*(7):9994-10041.

[7] Haider M, Abdin SM, Kamal L, Orive G. Nanostructured lipid carriers for delivery of chemotherapeutics: A review. Pharmaceutics. 2020;*12*(3):288.

[8] Garg NK, Tyagi RK, Singh B, Sharma G, Nirbhavane P, Kushwah V, et al. Nanostructured lipid carrier mediates effective delivery of methotrexate to induce apoptosis of rheumatoid arthritis via NF-κB and FOXO1. International journal of pharmaceutics. 2016;*499*(1-2):301-20.

[9] Gordillo-Galeano A, Mora-Huertas CE. Solid lipid nanoparticles and nanostructured lipid carriers: A review

emphasizing on particle structure and drug release. European Journal of Pharmaceutics and Biopharmaceutics. 2018;*133*:285-308.

[10] Rizwanullah M, Ahmad J, Amin S. Nanostructured lipid carriers: a novel platform for chemotherapeutics. Current drug delivery. 2016;*13*(1):4-26.

[11] Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines. 2022;*10*(9):2055.

[12] Mehta M, Bui TA, Yang X, Aksoy Y, Goldys EM, Deng W. Lipid-based nanoparticles for drug/gene delivery: an overview of the production techniques and difficulties encountered in their industrial development. ACS Materials Au. 2023;*3*(6):600-19.

[13] Amoabediny G, Haghiralsadat F, Naderinezhad S, Helder MN, Akhoundi Kharanaghi E, Mohammadnejad Arough J, et al. Overview of preparation methods of polymeric and lipid-based (niosome, solid lipid, liposome) nanoparticles: A comprehensive review. International Journal of Polymeric Materials and Polymeric Biomaterials. 2018;*67*(6):383-400.

[14] Ganesan P, Narayanasamy D. Lipid nanoparticles: Different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery. Sustainable Chemistry and Pharmacy. 2017;*6*:37-56.

[15] Duong V-A, Nguyen T-T-L, Maeng H-J. Preparation of solid lipid nanoparticles and nanostructured lipid carriers for drug delivery and the effects of preparation parameters of solvent injection method. Molecules. 2020;*25*(20):4781.

[16] Chuang S-Y, Lin C-H, Huang T-H, Fang J-Y. Lipid-based nanoparticles as a potential delivery approach in the treatment of rheumatoid arthritis. Nanomaterials. 2018;*8*(1):42.

[17] Duan Y, Dhar A, Patel C, Khimani M, Neogi S, Sharma P, et al. A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. RSC advances. 2020;*10*(45):26777-91.

[18] Moballegh Nasery M, Abadi B, Poormoghadam D, Zarrabi A, Keyhanvar P, Khanbabaei H, et al. Curcumin delivery mediated by bio-based nanoparticles: a review. Molecules. 2020;*25*(3):689.

[19] Mu H, Holm R. Solid lipid nanocarriers in drug delivery: Characterization and design. Expert opinion on drug delivery. 2018;*15*(8):771-85.

[20] Alam T, Pandit J, Vohora D, Aqil M, Ali A, Sultana Y. Optimization of nanostructured lipid carriers of lamotrigine for brain delivery: in vitro characterization and in vivo efficacy in epilepsy. Expert opinion on drug delivery. 2015;*12*(2):181-94.

[21] Souto EB, Baldim I, Oliveira WP, Rao R, Yadav N, Gama FM, et al. SLN and NLC for topical, dermal, and transdermal drug delivery. Expert opinion on drug delivery. 2020;*17*(3):357-77.

[22] Permana AD, Tekko IA, McCrudden MT, Anjani QK, Ramadon D, McCarthy HO, et al. Solid lipid nanoparticle-based dissolving microneedles: A promising intradermal lymph targeting drug delivery system with potential for enhanced treatment of lymphatic filariasis. Journal of controlled release. 2019;*316*:34-52.

[23] Pramanik S, Mohanto S, Manne R, Rajendran RR, Deepak A, Edapully SJ, et al. Nanoparticle-based drug delivery system: the magic bullet for the treatment of chronic pulmonary diseases. Molecular Pharmaceutics. 2021;*18*(10):3671-718.

[24] Cunha S, Forbes B, Sousa Lobo JM, Silva AC. Improving drug delivery for Alzheimer's disease through nose-to-brain delivery using nanoemulsions, nanostructured lipid carriers (NLC) and in situ hydrogels. International journal of nanomedicine. 2021:4373-90.

[25] Salem LH, El-Feky GS, Fahmy RH, El Gazayerly ON, Abdelbary A. Coated lipidic nanoparticles as a new strategy for enhancing nose-to-brain delivery of a hydrophilic drug molecule. Journal of Pharmaceutical Sciences. 2020;*109*(7):2237-51.

[26] Barani M, Sangiovanni E, Angarano M, Rajizadeh MA, Mehrabani M, Piazza S, et al. Phytosomes as innovative delivery systems for phytochemicals: A comprehensive review of literature. International journal of nanomedicine. 2021:6983-7022.

[27] Rosiaux Y, Jannin V, Hughes S, Marchaud D. Solid lipid excipients as matrix agents for sustained drug delivery. Excipient Applications in Formulation Design and Drug Delivery. 2015:237-71.

[28] Chauhan I, Yasir M, Verma M, Singh AP. Nanostructured lipid carriers: A groundbreaking approach for transdermal drug delivery. Advanced pharmaceutical bulletin. 2020;*10*(2):150.

[29] Lee D, Minko T. Nanotherapeutics for nose-to-brain drug delivery: an approach to bypass the blood brain barrier. Pharmaceutics. 2021;*13*(12):2049.

[30] Subramaniam B, Siddik ZH, Nagoor NH. Optimization of nanostructured lipid carriers: Understanding the types, designs, and parameters in the process of formulations. Journal of nanoparticle research. 2020;*22*:1-29.

[31] Falsafi SR, Rostamabadi H, Assadpour E, Jafari SM. Morphology and microstructural analysis of bioactive-loaded micro/nanocarriers via microscopy techniques; CLSM/SEM/TEM/AFM. Advances in Colloid and Interface Science. 2020;*280*:102166.

[32] Formica ML, Real DA, Picchio ML, Catlin E, Donnelly RF, Paredes AJ. On a highway to the brain: A review on nose-to-brain drug delivery using nanoparticles. Applied Materials Today. 2022;*29*:101631.

[33] Keservani RK, Sharma AK, Kesharwani RK. Nanocarriers for brain targeting: principles and applications: CRC Press; 2019.

[34] Shah NV, Seth AK, Balaraman R, Aundhia CJ, Maheshwari RA, Parmar GR. Nanostructured lipid carriers for oral bioavailability enhancement of raloxifene: Design and in vivo study. Journal of advanced research. 2016;*7*(3):423-34.

[35] Gupta R, Chen Y, Xie H. In vitro dissolution considerations associated with nano drug delivery systems. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2021;*13*(6):e1732.

[36] Kim Y, Park EJ, Kim TW, Na DH. Recent progress in drug release testing methods of biopolymeric particulate system. Pharmaceutics. 2021;*13*(8):1313.

[37] Mircioiu C, Voicu V, Anuta V, Tudose A, Celia C, Paolino D, et al. Mathematical modeling of release kinetics from supramolecular drug delivery systems. Pharmaceutics. 2019;*11*(3):140.

[38] Qu F, Geng R, Liu Y, Zhu J. Advanced nanocarrier-and microneedle-based transdermal drug delivery strategies for skin diseases treatment. Theranostics. 2022;*12*(7):3372.

[39] Chavda VP, Patel AB, Mistry KJ, Suthar SF, Wu Z-X, Chen Z-S, et al. Nano-drug delivery systems entrapping natural bioactive compounds for cancer: recent progress and future challenges. Frontiers in oncology. 2022;*12*:867655.

[40] Siafaka PI, Üstündağ Okur N, Karavas E, Bikiaris DN. Surface modified multifunctional and stimuli responsive nanoparticles for drug targeting: current status and uses. International journal of molecular sciences. 2016;*17*(9):1440.

[41] Bakshi H, Nagpal M, Singh M, Dhingra GA, Aggarwal G. Treatment of psoriasis: a comprehensive review of entire therapies. Current drug safety. 2020;*15*(2):82-104.

[42] Xu Y, Zhao M, Cao J, Fang T, Zhang J, Zhen Y, et al. Applications and recent advances in transdermal drug delivery systems for the treatment of rheumatoid arthritis. Acta Pharmaceutica Sinica B. 2023;*13*(11):4417-41.

[43] Ahamad N, Kar A, Mehta S, Dewani M, Ravichandran V, Bhardwaj P, et al. Immunomodulatory nanosystems for treating inflammatory diseases. Biomaterials. 2021;*274*:120875.

[44] Cao F, Gui S-Y, Gao X, Zhang W, Fu Z-Y, Tao L-M, et al. Research progress of natural product-based nanomaterials for the treatment of inflammation-related diseases. Materials & Design. 2022;*218*:110686.

[45] Hegde M, Girisa S, BharathwajChetty B, Vishwa R, Kunnumakkara AB. Curcumin formulations for better bioavailability: what we learned from clinical trials thus far? ACS omega. 2023;*8*(12):10713-46.

[46] Waghule T, Gorantla S, Rapalli VK, Shah P, Dubey SK, Saha RN, et al. Emerging trends in topical delivery of curcumin through lipid nanocarriers: effectiveness in skin disorders. Aaps Pharmscitech. 2020;*21*:1-12.

[47] Kesharwani D, Paliwal R, Satapathy T, Paul SD. Rheumatiod arthritis: an updated overview of latest therapy and drug delivery. Journal of pharmacopuncture. 2019;*22*(4):210.

[48] Xu X-Y, Meng X, Li S, Gan R-Y, Li Y, Li H-B. Bioactivity, health benefits, and related molecular mechanisms of curcumin: Current progress, challenges, and perspectives. Nutrients. 2018;*10*(10):1553.

[49] Zhu Z, Li J, Ruan G, Wang G, Huang C, Ding C. Investigational drugs for the treatment of osteoarthritis, an update on recent developments. Expert opinion on investigational drugs. 2018;*27*(11):881-900.

[50] Nguyen T-T-L, Duong V-A, Maeng H-J. Pharmaceutical formulations with P-glycoprotein inhibitory effect as promising approaches for enhancing oral drug absorption and bioavailability. Pharmaceutics. 2021;*13*(7):1103.

[51] Singh S, Pathak N, Fatima E, Negi AS. Plant isoquinoline alkaloids: Advances in the chemistry and biology of berberine. European journal of medicinal chemistry. 2021;*226*:113839.

[52] Sahoo DK, Heilmann RM, Paital B, Patel A, Yadav VK, Wong D, et al. Oxidative stress, hormones, and effects of natural antioxidants on intestinal inflammation in inflammatory bowel disease. Frontiers in endocrinology. 2023;*14*:1217165.

[53] Jantan I, Ahmad W, Bukhari SNA. Plant-derived immunomodulators: an insight on their preclinical evaluation

and clinical trials. Frontiers in plant science. 2015;6:655.

[54] Sainz-Urruela C, Vera-López S, San Andrés MP, Díez-Pascual AM. Graphene-based sensors for the detection of bioactive compounds: A review. International Journal of Molecular Sciences. 2021;*22*(7):3316.

[55] Tagde P, Tagde P, Islam F, Tagde S, Shah M, Hussain ZD, et al. The multifaceted role of curcumin in advanced nanocurcumin form in the treatment and management of chronic disorders. Molecules. 2021;*26*(23):7109.

[56] Patel SS, Acharya A, Ray R, Agrawal R, Raghuwanshi R, Jain P. Cellular and molecular mechanisms of curcumin in prevention and treatment of disease. Critical reviews in food science and nutrition. 2020;*60*(6):887-939.

[57] Huang T, Liu Y, Zhang C. Pharmacokinetics and bioavailability enhancement of baicalin: a review. European Journal of Drug Metabolism and Pharmacokinetics. 2019;*44*:159-68.

[58] Fuloria S, Mehta J, Chandel A, Sekar M, Rani NNIM, Begum MY, et al. A comprehensive review on the therapeutic potential of Curcuma longa Linn. in relation to its major active constituent curcumin. Frontiers in Pharmacology. 2022;*13*:820806.

[59] Upadhyay S, Dixit M. Role of polyphenols and other phytochemicals on molecular signaling. Oxidative medicine and cellular longevity. 2015;2015(1):504253.

[60] Beloqui A, Solinís MÁ, Rodríguez-Gascón A, Almeida AJ, Préat V. Nanostructured lipid carriers: Promising drug delivery systems for future clinics. Nanomedicine: Nanotechnology, biology and medicine. 2016;*12*(1):143-61.

[61] Rodan K, Fields K, Majewski G, Falla T. Skincare bootcamp: the evolving role of skincare. Plastic and Reconstructive Surgery–Global Open. 2016;*4*(12S):e1152.

[62] Halla N, Fernandes IP, Heleno SA, Costa P, Boucherit-Otmani Z, Boucherit K, et al. Cosmetics preservation: a review on present strategies. Molecules. 2018;*23*(7):1571.

[63] Mannekote JK, Kailas SV, Venkatesh K, Kathyayini N. Environmentally friendly functional fluids from renewable and sustainable sources-A review. Renewable and sustainable energy reviews. 2018;*81*:1787-801.

[64] De Corato U. Improving the shelf-life and quality of fresh and minimally-processed fruits and vegetables for a modern food industry: A comprehensive critical review from the traditional technologies into the most promising advancements. Critical Reviews in Food Science and Nutrition. 2020;*60*(6):940-75.

[65] Pereira L. Seaweeds as source of bioactive substances and skin care therapy—cosmeceuticals, algotheraphy, and thalassotherapy. Cosmetics. 2018;*5*(4):68.

[66] Rajmohan K, Chandrasekaran R, Varjani S. A review on occurrence of pesticides in environment and current technologies for their remediation and management. Indian journal of microbiology. 2020;*60*(2):125-38.

[67] Kanwar R, Rathee J, Salunke DB, Mehta SK. Green nanotechnology-driven drug delivery assemblies. ACS omega. 2019;*4*(5):8804-15.

[68] Ashfaq R, Rasul A, Asghar S, Kovács A, Berkó S, Budai-Szűcs M. Lipid nanoparticles: an effective tool to improve the bioavailability of nutraceuticals. International Journal of Molecular Sciences. 2023;*24*(21):15764.

[69] Chavda VP, Nalla LV, Balar P, Bezbaruah R, Apostolopoulos V, Singla RK, et al. Advanced phytochemical-based nanocarrier systems for the treatment of breast cancer. Cancers. 2023;*15*(4):1023.

[70] Bruni N, Della Pepa C, Oliaro-Bosso S, Pessione E, Gastaldi D, Dosio F. Cannabinoid delivery systems for pain and inflammation treatment. Molecules. 2018;*23*(10):2478.

[71] Khan AR, Yang X, Fu M, Zhai G. Recent progress of drug nanoformulations targeting to brain. Journal of Controlled Release. 2018;*291*:37-64.

[72] Kumar G, Virmani T, Sharma A, Pathak K. Codelivery of phytochemicals with conventional anticancer drugs in form of nanocarriers. Pharmaceutics. 2023;*15*(3):889.

[73] Abdel-Mageed HM, AbuelEzz NZ, Radwan RA, Mohamed SA. Nanoparticles in nanomedicine: a comprehensive updated review on current status, challenges and emerging opportunities. Journal of microencapsulation. 2021;*38*(6):414-36.

[74] Gupta V, Mohapatra S, Mishra H, Farooq U, Kumar K, Ansari MJ, et al. Nanotechnology in cosmetics and cosmeceuticals—a review of latest advancements. Gels. 2022;*8*(3):173.