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Review Article

Terpenes and Terpene Based Nanoformulations: A New Prospect for Arthritis Management

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ABSTRACT

Numerous symptoms, such as redness, swelling, and inflammation on synovial joints, as well as arthritic disorders like juvenile, rheumatoid, and osteoarthritis, are associated with arthritis, a disease that affects people all over the world. There are several medications and treatments for this illness, but in addition to their therapeutic effects, they have a number of side effects. The cause of the illness is still untreated. As a result, the demand for creative and effective treatment approaches is always rising. Many naturally occurring compounds known as terpenes and terpenoids, which are present in a wide variety of medicinal plants, herbs, seeds, leaves, fruits, vegetables, and other natural crude drugs, have shown promise in the current situation as a means of lowering the inflammatory processes that lead to arthritic conditions. This review article primarily examines the antiarthritic potential of some terpenes, including eugenol, eucalyptol, cannabidiol, pinene, friedelin, nerolidol, and others, with regard to their mechanism of action, targets and scientific outcomes. The expanding field of terpene-based nanoparticles is the main focus of this review. In-depth discussions of formulation methods, terpene-based nanoformulations, prospective strategies such as targeted drug delivery of terpene as an active therapeutic molecule, and preclinical data suggesting their potential involvement in treating arthritis are also covered in this review.

INTRODUCTION

Systemic inflammation is a hallmark of rheumatoid arthritis (RA), a chronic inflammatory illness that primarily affects joints. Roughly one percent of the world's population has been diagnosed with RA. RA is responsible for severe morbidity, which can lead to deterioration in the standard of living, deformed joints, and physiological disablement. In addition to its usual symptoms, RA is a difficult autoimmune condition that can lead to a number of long-term issues [1]. Moderate to severe symptoms are experienced by about 13 million people with RA. Data indicates that approximately 18 million people globally experienced RA in 2019. Seventy percent of women over the age of fifty-five suffer from this illness [2].

Unfortunately, there isn't a cure for this illness. Surgery, medications (NSAIDs and steroids), and non-pharmacological approaches are some of the modern therapeutic procedures that simply address the symptoms of the illness rather than its underlying cause. These treatments have limits and possibly unfavorable side effects. It has been discovered that phytoconstituents and natural medications derived from plants are useful in treating RA. These natural solutions effectively treat the symptoms and consequences without causing any negative side effects and are safe. Additionally, weight control, exercise, and a balanced diet are helpful for managing arthritis [3]. Since ancient times, natural products have been utilized to treat a variety of illnesses, which has drawn attention from researchers. In order to uncover the hidden potential and effectiveness of these natural products—which may show to be beneficial in the treatment of arthritis—researchers are conducting ongoing and creative studies. Researchers have turned their attention to alternative choices due to the limitations and complications inherent in contemporary therapy. Many researchers have turned to phytoconstituents because of their efficacy in light of the complexity of contemporary treatment. Terpenes and terpenoids, among other phytochemicals, have been shown to be highly useful in the treatment of disease because of their increased skin penetration, anti-inflammatory, and anti-arthritic qualities [2].

The potential of terpene and terpenoid-based nanoparticles to transform the treatment of arthritis is the main topic of this research, which examines the amazing connection between natural products and cutting-edge delivery technology. We seek to offer a thorough understanding of the terpenes and their mechanisms of action by examining the challenges of several terpenes that are well-known for their anti-arthritic qualities, such as eugenol, cannabidiol, alpha and beta pinene, eucalyptol, nerolidol, friedeline, etc.

Botanical findings and chemical nature of Terpenes

Terpenes are the largest and the most prevalent class of secondary metabolites. The oxygenated forms of terpenes are called terpenoids. Terpene is changed into terpenoids if any more functional groups are added or taken out of its structure. Terpenoids are also created by adding a methyl group or altering its location. Terpenoids are found in many plant parts, including leaves, flowers, rhizomes, and more. They are the secondary metabolite products of aromatic and medicinal plants. They are also found in the form of essential oils in bryophytes (lichens, liverworts, fungi, and algae) and embryophytes (trees, ferns, and shrubs). Additionally, terpenoids and terpenes in the form of essential oil have been reported to be present in marine organisms, insects, and some microorganisms. Isoprene units (C_5H_8) make up terpenes and terpenoids. Monoterpenes ($C_{10}H_{16}$), sesquiterpenes ($C_{15}H_{24}$), diterpenes ($C_{20}H_{40}$), and others are categorized according to the number of isoprene units they contain.[4] Among a variety of natural compounds, terpenes have attracted significant interest because they are safe, efficient, and may have therapeutic effects, particularly for autoimmune and inflammatory conditions. This section highlights the potential of well-reported terpenes as antiarthritic medicines by examining their chemical structures, natural sources, and other health-promoting qualities (Table 1).

Eugenol

A phenolic chemical, eugenol is found in several aromatic plant groups, such as clove, ginger, cinnamon, and nutmeg. Among these, cloves (*Eugenia caryophyllus*), which are members of the Myrtaceae family, are said to contain a high percentage of eugenol (40–90%) in their schizolysigenous glands, which are oil glands. Phenylpropanoid or 4-allyl-2-methoxyphenol are its chemical names [12]. By inhibiting the nuclear factor-kappa B (NF-κB) signalling pathway, eugenol demonstrated its anti-inflammatory properties. The transcription-related factor NF-κB regulates many facets of the immune system's innate and adaptive responses and is a crucial modulator of inflammatory responses. In addition to promoting the production of particular pro-inflammatory genes, including cytokines and chemokines, NF-κB is crucial for the regulation of inflammation. Moreover, NF-κB plays a crucial role in regulating the development, activation, and proliferation of innate immune cells and inflammatory T cells [13]. Eugenol also demonstrated strong antioxidant properties. Eugenol's phenolic hydroxyl group, which functions as a hydrogen atom donor, enable it to effectively scavenge and neutralize reactive oxygen species

(ROS) and other free radicals [14]. By halting oxidative damage to biological components including lipids, proteins, and DNA, antioxidants provide a protective impact that lowers oxidative stress and the risk of chronic diseases associated with oxidative stress. Eugenol also decreased the expression of genes linked to inflammation, such as cyclooxygenase-2 (COX-2), IL-1β, and IL-6. This might have happened by stopping NF-κB and TYK2 transcription factors from activating. In another study, eugenol was found to have inhibitory effects on NLRP3 mRNA and protein levels as well as Pannexin-1 (PANX-1) activation. This eventually impacted the NLRP3 inflammatory assembly and triggered the production of IL-1β. Additionally, eugenol reduced high levels of adenosine deaminase that acted on the RNA 1 (ADAR1) transcript, suggesting that it is involved in the post-transcriptional mechanisms that regulate inflammatory responses. By lowering apoptosis, eugenol also effectively decreased the loss of β-cells in response to HG-HL. Additionally, it has the ability to lessen β-cell dedifferentiation brought on by HG-HL by restoring β-cell-specific biomarkers [15]. Numerous studies investigating eugenol's impact on the immune system have revealed that it is a potentially effective chemical for treating a range of inflammatory and autoimmune diseases. Grespan and co-workers have thoroughly assessed the anti-arthritic activity of eugenol *in vivo* utilizing collagen-induced arthritis (CIA) animal models. Eugenol treatment demonstrated notable disease-modifying effects in a CIA animal model. Mice treated with eugenol showed a considerable reduction in the incidence and severity of CIA, which was supported by a significant decrease of mononuclear cell inflammatory mediators in the ankle joints, including tumor growth factor (TGF)-β, interferon (IFN)-γ, and TNF-α. The cell viability was also assessed *in vitro* using the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. The study's findings unequivocally demonstrated eugenol's possible immune-suppressive impact on arthritic joints [16].

Cannabidiol (CBD)

Grijó et al. claimed that plants in the genus Cannabis (*Cannabis sativa* L.) contain a particular kind of bioactive chemical called cannabidiol (CBD) [17]. Roger Adams isolated cannabidiol from cannabis for the first time in 1940 [18]. The chemical formula for cannabidiol is $C_{21}H_{30}O_2$, which was initially reported by Mechoulam et al. in 1963 [19]. IUPAC name of Cannabidiol is 2-[(1R, 6R) cyclohex-2-en-1-yl-3-methyl-6-prop-1-en-2-yl] 1, 3-diol of -5-pentylbenzene. Three structures make up the structure of CBD: a pentyl side chain, a cyclohexene ring, and a phenolic ring. Its pharmacological activity is imparted by the presence of a methyl group at the C1 position in the cyclohexane ring and a hydroxyl group at the C-1′ and C-5′ positions in the phenolic ring [20].

In 2004, Costa and co-workers examined the anti-inflammatory and anti-hyperalgesic properties of cannabidiol in rats. Carrageenan (0.1 ml intraplantar injection) was used to induce inflammation. In inflamed rats, cannabidiol was administered orally for three days at a dose of 5–40 mg/kg. At the end of treatment, the amount of inflammatory biomarkers in the tissues of inflamed paws, including prostaglandin E2 (PGE2), cyclooxygenase (COX) activity, nitric oxide (NO; nitrite/nitrate concentration), and other oxygen-derived free radicals (malondialdehyde) were measured. It was discovered that rats with carrageenan inflammation had higher levels of these biomarkers. According to the plantar test, the thermal hyperalgesia caused by carrageenan lasted for seven hours. In a dose-and time-dependent way, cannabidiol showed anti-hyperalgesic effects. Tissue COX activity, PGE2 plasma levels, the production of oxygen-derived free radicals, and NO level were all significantly reduced after three doses of cannabidiol [21]. Lowin and co-workers examined the potent anti-inflammatory properties of cannabidiol in individuals with chronic RASF patients. For the study, 40 patients were chosen, 32 of whom were female and 8 of them were male. The impact of cannabidiol on rheumatoid arthritis synovial fibroblasts (RASF) was assessed in terms of intracellular calcium, cell survival, and cytokine production. According to the findings, cannabidiol (≥5 μM) reduces RASF cell survival and proliferation. The opening of the mitochondrial permeability transition pore (MPTP), a protein present in the inner mitochondrial membrane under specific pathological conditions, and the generation of IL-6/IL-8/MMP-3 are two more ways that CBD dramatically increases intracellular calcium mobilization in the inner mitochondrial membrane [22].

Table 1: Source, molecular weight and toxic dose of commonly used terpenes reported for the formulation of nanovesicles.

Terpene	Source	Molecular formula and weight (g/mol)	IUPAC name	Toxic dose /LD50 dose	References
Eugenol	*Eugenia cayrophyllus*	$C_{10}H_{12}O_2$ 164.20	2-Methoxy-4-(prop-2-en-1- yl) phenol	> 2000 mg/kg Oral (rats)	Pathak et al. [5]
Cannabidiol	*Cannabis sativa*	$C_{21}H_{30}O_2$ 314.469	2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol	980 mg/kg oral (rats)	AAT, bioquest [6]
Eucalyptol	Eucalyptus spp.	$C_{10}H_{18}O$ 154.249	1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane	1560 and 2480 mg/kg oral (rats)	Lillian and Becker [7]
Alpha and beta pinene	Pinus spp.	$C_{10}H_{16}$ 136.23	2,6,6 trimethylbicyclo[3.1.1]hept-2-ene	> 2000 mg/kg	Felipe et al. [8]
Friedelin	*Azima tetracantha, Orostachys japonica, Quercus stanophylla, Calophyllum pinetorum, Garcinia prainiana, Garcinia imberti, Garcinia rubroechinata,and Mammea siamensis*	$C_{30}H_{50}O$ 426.7	(4β,5β,8α,9β,10α,13α,14β)-5,9,13-Trimethyl-24,25,26-trinoroleanan-3-one, DA-friedooleanan-3-one, Friedelan-3-one	> 5000 mg/kg	Aswar et al. [9]
Nerolidol	tea trees, neroli, ginger, jasmine, and lavender	$C_{15}H_{26}O$ 222.37	3,7,11-trimethyl-dodeca-1,6,10-trien-3-ol)	>8,000 mg/kg (Mouse) > 2,610 mg/kg (Rats)	DSM, and BSF [10.11]
Limonene	Citrus fruits	$C_{10}H_{16}$ 136.23	1-Methyl-4-(1-methyl ethenyl)-cyclohexene	5 mg/kg (topical) 5g/kg (oral)	Pathak et al. [5]
Cineole	Citrus fruits	$C_{10}H_{18}O$ 154.249	1-methyl-4-propan-2-yl-7-oxabicyclo [2,2,1] heptane	2480 mg/kg Oral (rats) 50 mg/kg Subcutaneous (mice), 100 mg/kg Intramuscular (mice), 2500 mg/kg Oral (mice)	Pathak et al. [5]

Eucalyptol

The word "Eu" which signifies truthful, and calyptus (kalypto), which means to cover, are the sources of the name Eucalyptus. French botanist L'Heritier was the first to describe and name the genus Eucalyptus. The primary active phytoconstituent of eucalyptus oil is eucalyptol (1,8-cineole), a monoterpene oxide that has several medicinal properties, such as antibacterial, antifungal, and anti-inflammatory properties [23]. Numerous studies were conducted to investigate its untapped potential to reduce inflammation, and the findings were positive.

A synergistic evaluation of the preventive anti-inflammatory impact of eucalyptol-rich essential oil and flurbiprofen was conducted. Both *in vitro* and *in vivo* features were examined in this work, with noteworthy outcomes. For the investigation, albino wistar rats of both sexes were employed. The membrane stabilization assay method was used to conduct the *in vitro* anti-inflammatory test. Carrageenan and histamine-induced paw oedema, cotton pellet-induced granuloma, and Complete Freund's adjuvant-induced arthritis models were employed to assess the acute and chronic inflammation (*in vivo*). Groups treated with 500 mg/kg of *E. globulus* oil and 10 mg/kg of flurbiprofen alone showed significantly ($p<0.05$) poorer *in vitro* membrane stabilization effects than the oil-drug combination, according to the study's findings. In all *in vivo* models, 500 + 10 mg/kg of the oil-drug combination showed significantly ($p<0.05$) greater anti-inflammatory, analgesic, and antipyretic effects than 500 mg/kg of *E. globulus* oil alone. Comparing serum samples from animals treated with 500 + 10 mg/kg of oil-drug combination to the diseased control (arthritic) group, qRT-PCR analysis showed a significant ($p < 0.05$) down-regulation in TNF-α and IL-4 expression. Overall, the study demonstrates that the anti-inflammatory, analgesic, and antipyretic effects of flurbiprofen and *E. globulus* essential oil were superior to those of either medication alone [23].

Friedelin

Friedelin, sometimes known as "cork alcohol," is a pentacyclic triterpene that was initially extracted from cork bark and tissues in 1807 using alcohol. A variety of plants from the Rosaceae, Combretaceae, Clusiaceae, Tilaceae, Celastraceae, Asteraceae, Fabaceae, Salicaceae, and Myrtaceae families were later found to contain it. Additionally, it was said to have been isolated from lower plants such as algae, lichens, fungus, and mosses. Friedelin's potential health benefits, such as its anti-inflammatory, antioxidant, anticancer, and antibacterial properties, have been investigated [24]. Examining the specific research findings is crucial as we move beyond the general investigation of friedelin's health advantages, particularly in relation to chronic inflammatory disorders like arthritis. Notably, a comprehensive investigation was conducted to examine friedelin's anti-inflammatory, analgesic, and antipyretic properties in wistar rats and mice. Friedelin was isolated using hexane extract from the leaves of the *Azima tetracantha* Lam. plant. Column chromatography was used to isolate friedelin. Several models were employed to produce inflammation, including acetic acid-induced vascular permeability, cotton pellet-induced granuloma, adjuvant-induced arthritis, carrageenan-induced hind paw oedema, and croton oil-induced ear oedema. The acetic acid-induced abdominal constriction reaction, the formalin-induced paw licking response, and the hot-plate test were used to assess friedelin's analgesic efficacy. The yeast-induced hyperthermia test in rats was used to assess friedelin's antipyretic properties. Friedelin (40 mg/kg) significantly reduced paw edema (52.5%) in rats with acute inflammation caused by carrageenan and 68.7% in an ear oedema model caused by croton oil. Friedelin also decreased the formation of granuloma tissue (36.6%) in inflammation caused by cotton pellets at the same dosage. Additionally, it was discovered that animals with adjuvant-induced arthritis had thinner paws (54.5%). Additionally, Friedelin exhibits considerable ($P<0.05$) analgesic action in the paw-licking response caused by formalin and the abdominal constriction response induced by acetic acid. According to the study's findings, friedelin had strong analgesic, antipyretic, and anti-inflammatory properties and may be a useful drug for the management of inflammatory illnesses [25].

Nerolidol

Numerous plants, such as tea trees, neroli, ginger, jasmine, and lavender, naturally contain nerolidol (3,7,11-trimethyl-1,6,10-dodecatrien-3-ol), a sesquiterpene alcohol. It is reported to have

a delicious, lingering, slightly flowery flavor and scent. Nerolidol can more readily interact with intracellular proteins and/or intra-organelle areas and cross the plasma membrane due to its strong hydrophobic nature. For transdermal drug delivery, it is also being explored as a skin penetration booster [26]. Nerolidol is a promising phytoconstituent in the realms of medicine and agriculture because of its varied pharmacological and biological activities [27]. Research on its effects on inflammation has been conducted in recent years, and the results indicate a significant inhibitory effect on inflammation mediators. Over the past years, research has focused on examining its impact on inflammation, showing a notable inhibitory effect on inflammation mediators. The promising anti-inflammatory properties highlighted by Fonsêca, et al. in cararageenan induced inflammation *in vivo*. The studies demonstrated that nerolidol reduced paw edema in rats due to its anti-inflammatory effect. Further investigation of carrageenan-induced peritonitis model revealed that nerolidol reduced the levels of polymorphonuclear cells, tumour necrosis factor (TNF-α), and peritoneal lavage-derived polymorphonuclear cells, as well as the levels of interleukin 1 beta (IL-1b) in LPS-stimulated peritoneal macrophages [28].

Pinene

Pinene is copious terpene which is found in a form of clear liquid in many plants and shrubs with fresh aroma. Eucalyptus, lavender, turpentine, basil, fern, parsley, rosemerry are reported to have rich source of pinene [29]. Structurally they contain two rings (bicyclic terpenes) and exist in two active functional isomers namely α- and β-pinene. Both the compound showed chiral behavior and do not overlap with each other's mirror images. The interaction of these isomers with polarized light differs only [30,31]. Several pharmacological, biological and toxicological activities were reported to these compounds. α- and β-pinene have been studied for a wide range of pharmacological activities, including anti-coagulant, anti-inflammatory, anti-leishmania, antimalarial, antimicrobial, antioxidant, antitumor, and antibiotic resistance modulation effects [29]. The anti-inflammatory activity of pinene has been comprehensively evaluated *in vivo* using lipopolysaccharide (LPS) stimulated peritoneal macrophages inflammation in animal model. The administration of pinene showed remarkable reduction in the level of inflammatory biomarkers such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and nitric oxide (NO), nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) by the suppression of mitogen-activated protein kinases (MAPKs) and the nuclear factor-kappa B (NF-κB) pathway in mouse peritoneal macrophages. The findings of this study concluded that α-pinene can serve as wonder molecule with potent anti-inflammatory effect [32].

Challenges and bioavailability limitations of terpenes and terpenoids

Terpenes and terpenoids showed their promising anti-inflammatory properties against inflamed tissues. The low bioavailability and poor oral absorption significantly restricts their efficacy *in vivo* and also interfere with the therapeutic potential of these compounds. Additionally, limited lipophilicity, dissolution rate, aqueous solubility, and drug permeability, also pose a major challenge to the researchers. These problems have prompted the investigation of advanced strategies such as nanotechnology to enhance the effective delivery of terpenes and terpenoids in many diseases. Various novel drug delivery systems and formulations have been developed to overcome the bioavailability limitations of these compounds. The incapsulation of these compounds in different nanoparticles may improve their stability, solubility, absorption and may also protect them from premature degradation. The novel drug delivery approaches will increase the bioavailability as well as therapeutic efficacy of terpenes and terpenoids [33].

Nanoparticles as Delivery Vehicles

The effective and targeted delivery of terpenes and terpenoids can be achieved by novel drug delivery applications using nanovesicles. These nanovesicles provide an effective pathway to control and target the delivery of terpenes and terpenoids. Incorporation of terpenes and terpenoids within nanoparticles can lead to enhanced bioavailability, better sustained release kinetics and prolong drug release and blood distribution of these compounds can be achieved. Moreover, nanoparticles can facilitate the transport of these compounds across biological barriers and also protect these compounds from enzymatic degradation (Figure 1) [34].

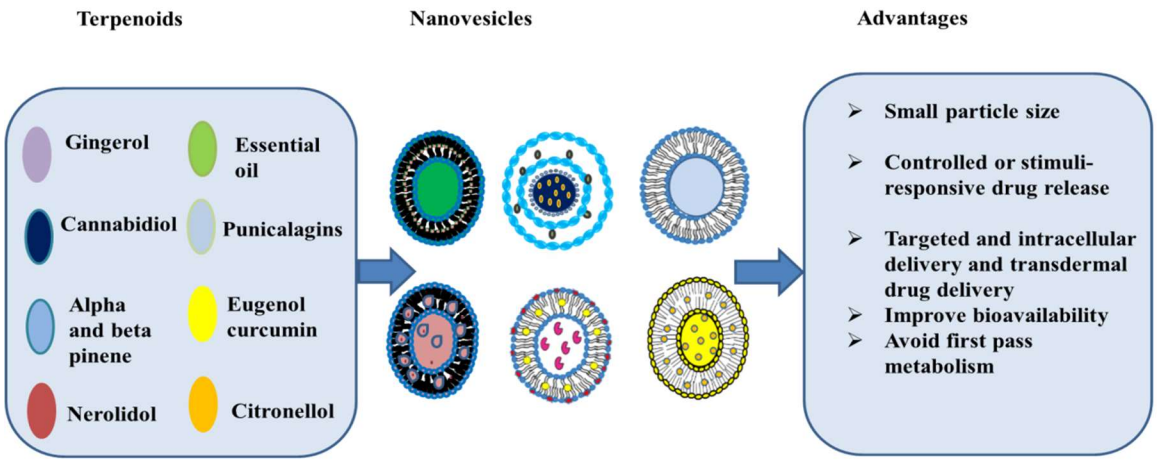

Fig. 1. Elevation of the therapeutic potential of terpenoids and terpenes by developing nanoparticle based delivery systems, which improve stability, bioavailability, and targeted delivery of terpenes to inflamed tissue [33].

Terpenes Based Nanoparticles for Arthritis Management

Innovative research methods have generated a novel bridge between the drug molecule and its delivery to the desired site. Numerous novel nanocarrier-based formulations, known as nanoformulations, have been created to enhance the delivery of effective drug molecules for multipurpose medical needs. Nanoformulations, also known as formulations based on nanotechnology, are flexible systems with a variety of applications and better therapeutic outcomes. The encapsulated small molecules protected drugs from biological environment and enhance targeted, intracellular, transdermal, bio distribution, and stimuli-responsive drug release. In recent years, number of researchers investigated the role of terpenes as penetration enhancers in nano drug delivery systems. The use of terpenes or mixture of terpenes in the preparation of nanovesicles at very low amount reduced the skin barrier resistance. Terpenes when utilized together with nanovesicles provide a promising approach for the treatment of joint disorders [2,35]. Discovery of nanoparticles provide multipurpose areas for controlled and sustained delivery of terpenes and terpenoids (Table 2).

Encapsulation prevents enzymatic degradation of terpenes. Encapsulated terpenes also help to deliver the drug molecule across the skin barrier and prolong the drug release into the bloodstream. Poor bioavailability problem can also be reduced by use of terpenes (Figure 2). For this prospect Jain et al. designed, formulated and evaluated the antiarthritic activity of berberine-loaded invasomes by the thin film hydration method. Invasomes were prepared by ethanol, cholesterol, phospholipid, berberine and eugenol (0.2-0.5%). Eugenol was used as penetration enhancer as well as anti-inflammatory agent. The prepared invasomes were characterized for particle size and shape, zeta potential, entrapment efficiency, and skin permeation studies. Prepared invasomes were incorporated into the gel containing carbomer 940 as gelling agent for transdermal drug delivery. The invasomal gel was evaluated for its organoleptic properties, homogeneity, viscosity, pH, spreadability, extrudability, drug content, skin irritant and stability studies. The *in vivo* analgesic activity of prepared berberine-loaded invasomal gel using the tail-flick hot water immersion method, revealed potential analgesic activity for a prolonged period of time. Furthermore, the antiarthritic activity of berberine-loaded invasomal gel was evaluated in CFA-induced arthritis rat model by measuring paw diameter, which showed a considerable reduction after treatment, as compared to standard gel (Omnigel, 0.1%). Topical application of berberine-loaded invasomal gel improves haematological

factors and normalizes proinflammatory biomarkers. The radiographical analysis of hind paw of rats in CFA model showed bone resorption, definite joint gap reduction, and considerable connective tissue expansion after treatment with prepared berberine-loaded invasomal gel. Histopathological examination of ankle joints also confirms the deeper penetration ability of invasomes through berberine-loaded invasomal gel and produces profound effects. The results revealed that the berberine-loaded invasomal gel has significant antiarthritic activity in the CFA rat model [36].

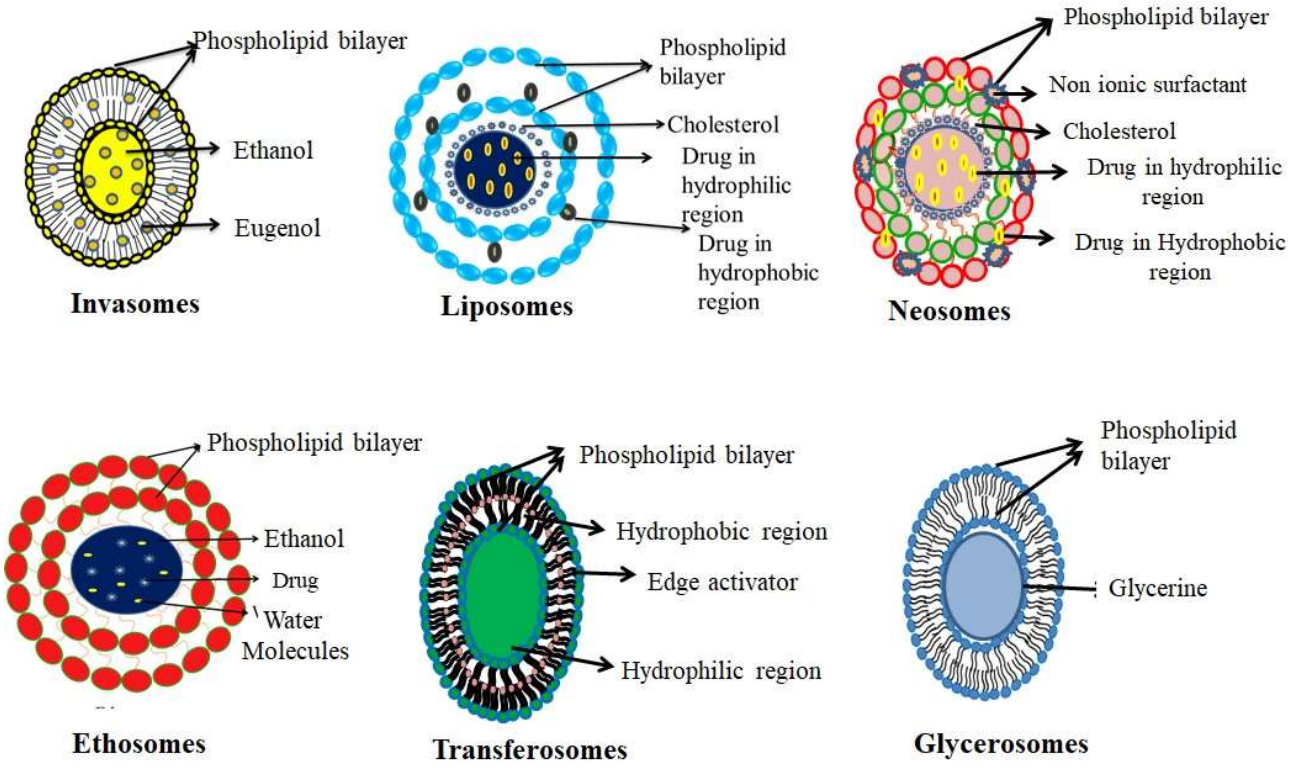

Fig. 2: Reported nanovesicles with incorporated terpenes [34].

In another study, Shakeel et al. investigated the antiarthritic potential of nanostructured clove oil (CO) (*Syzygium aromaticum) in* FCA-induced arthritic rats along with its delivery applications. The ultra-small nanostructured lipid carriers co-loaded with CO (CONCs) were developed through an aqueous titration method followed by microfluidization. The prepared nanostructures were spherical in shape (particle size 120 nm). Other characterization parameters like zeta potential (−27 mV) and entrapment efficacy (84.5%) were also determined. High performance thin layer chromatography (HPTLC) analysis revealed presence of eugenol as the primary components with Rf value of 0.58. The antiarthritic effects of the produced nanoformulations were investigated using the protein denaturation method *in vitro*. CONCs were compared with standard (Voltaren; diclofenac gel) product. The results revealed that the standard products showed a percentage inhibition of 86.91, however, CONC showed 82.73 percent inhibition. The above finding demonstrated the antiarthritic effect of developed nanoformulations. *In vivo* antiarthritic activity was performed against FCA model. Inflammation was induced by subplantar FCA injection. The paw volume of all group animals was measured. Both the standard and the CONC formulation resulted in a significant reduction in paw volume. Cartilage regenerative activity and the level of AST, ALT, and ALP enzymes increased in all groups treated with FCA. The increased level of serum enzymes in arthritic rats was dramatically lowered after treatment with CONC and Voltaren gel. TNF-α and IL-6 levels were found to be considerably

higher in FCA-induced arthritic rats ($p < 0.01$), whereas treatment with the CONC formulation effectively reduced these elevated levels. This study provides a proof of concept to treat RA with a new strategy utilizing essential oils via nanodelivery [37].

Table 2: Some reported terpene/terpenoid based nanovesicles and their pharmacological action

Vesicular system	Method of preparation	Incorporated terpenes/drug	Composition	Research outcomes	Reference
Liposomes	Film hydration method	*Salvia triloba* and *Rosmarinus officinalis* essential oils.	Phospholipid, cholesterol and essential oils.	Prolonged and sustained release of the essential oil, preserving or even enhancing the functional and biological properties. Possess antioxidant, antiinflammatory and antibacterial activities	Risaliti et al. [38]
Glycerosomes	Dispersion method	*Thymus capitatus* (TC) and *Citrus limon* var. pompia (CLP)	lecithin and TC essential oil or CLP, water and glycerol	Inhanced Antimicrobial activity	Pinna et al. [39]
Glycerosomes	Reverse-phase evaporation method.	*Speranskia tuberculata* essential oil and paeoniflorin	Phospholipid, Cholesterol and glycerol	Essential oil mediated glycerosomes increased the transdermal delivery of paeoniflorin and show 1.8-fold higher intensity than that of the common glycerosomes for Rheumatoid arthritis	Zhang et al. [40]
Terpenosomes	Thin film hydration method	Eugenol, fenchone or limonene	Phosphatidylcho-line	Terpenosomes loaded with fenticonazole nitrate and eugenol showed higher entrapment efficacy, biocompatibility and increased ocular drug delivery	Albash et al. [41]
Herbosomes	Spray drying method	Punicalagins	Phosphatidylch-oline and herbal extract/ constituent	Enhanced the serum concentration of punicalagins 2.5 times higher than the conventional extract and improved antioxidant activity	Vora et al. [42]
Phytosomes	Anti-solvent precipitation technique	Gingerol	Phospholipid, chitosan and phytoconstituents	Better sustained-release profile and prolonging the oral absorption rate of gingerol through effective antibacterial activity towards respiratory infection	Singh et al. [43]
Invasomes	Film hydration method	Eugenol	Phospholipid, cholesterol, berberine and ethanol	Permeation of berberine was enhanced and found to be 31-fold ex vivo through skin. Anti-inflammatory, anti-arthritic activity showed significant increase compared to control.	Jain et al. [36]
Transferosomes	Thin film and sonication method	6-Gingerol	phospholipid sodium cholate	Improved skin absorption, sustained drug release, and increased antioxidant activity. Formulation was found to be more effective in pain management.	Ghazwani et al. [44]

Conclusion and Future Prospects

To sum up, this comprehensive review has revealed the possibility of using terpenes and terpene-based nanoparticles as effective treatments for RA. Conscientious analysis of particular terpenes such as eugenol, eucalyptol, cannabidiol, pinene, friedelin, and nerolidol has elucidated their potential therapeutic applications and anti-arthritic properties against inflammation. The discovery of nanovesicles is a positive aspect of overcoming the bioavailability-related problems of terpenes. The developing field of terpene based nanovesicles demonstrated by formulations like invasomes, terpenosomes, transferosomes, neosomes, herbosomes etc. offers new opportunities for the delivery of active drug molecules at desired sites with improved bioavailability. Looking ahead, the focus of forthcoming studies should be on eliminating the lost knowledge gaps. These can include conducting additional clinical trials, improving delivery methods, and investigating synergistic pairings. Indeed, for terpenes and terpenoids to be successfully used in clinical settings, issues including assuring ideal nanoparticle design, scalability, and cost-effectiveness must be resolved.

Conflict of Interest

None

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