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Review Article

Nanoscale Formulations for Targeted Drug Delivery: Enhancing Stability, Release Control and Therapeutic Efficacy

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ABSTRACT

The present study focuses on the nanoscale formulation technique for pharmacological agent delivery, avoiding the shortcomings of conventional protocols, such as rapid pharmaceutical clearance, limited site-specific accuracy and reduced biological accessibility. The goal of this is that because nanoscale particles can improve stability, control pharmaceutical release and increase penetration, they have emerged as a promising drug delivery technology. Targeted therapies for conditions like septicemia and bronchial asthma can be developed by attaching particular molecular binders to nanoscale particles. This reduces toxicity while maximizing therapeutic efficacy. In summary, this analysis highlights the medicinal delivery potential of nanoscale formulations, including the mechanisms of action of botanical constituents such as flavonoids and triterpenoidal compounds. It also implies that the administration of inflammatory conditions may benefit greatly from the use of nanoscale particles loaded with these compounds.

Keywords: Anticancer, Flavonoid, Nanoparticle, Targeted drug delivery, Toxicity.

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INTRODUCTION

Defending against harmful stimuli like allergens or damaged tissues, inflammatory responses can also result from uncontrollably responding to a range of illnesses, including infections from bacteria, metabolic diseases, cardiac abnormalities and malignant tumours; it is illustrated in (Figure 1). These conditions have a significant financial burden on social systems (Tables 1 and 2). While there are many different therapeutic options to reduce inflammation, such as corticosteroids, non-corticosteroids and immunomodulatory drugs, they are frequently harmful when taken at the higher dosages needed to achieve therapeutic plasma concentrations (Ghasemian *et al*., 2016; Bagad *et al*., 2013; López *et al*., 2021). Therefore, investigating phytogenic treatments is essential to overcome the drawbacks of synthetic pharmaceuticals. Highly valued for their taste, scent, or medicinal properties, botanical substances have been utilized to treat a range of illnesses and metabolic issues in addition to lowering inflammation and neutralizing reactive oxygen species. The purpose of this review is to assess botanical ingredients' ability to reduce inflammation in a variety of disorders, emphasizing their benefits over traditional treatment approaches and investigating their potential as effective substitutes for treating inflammatory diseases.

Drug Delivery Systems

The efficiency of flavonoids as anti-inflammatory agents and their bioavailability have been greatly increased by the application of nanotechnology. Nanoscale particles, such as polylactic acid, Poly (Lactic-Co-Glycolic Acid) (PLGA) and polyoxymethylene glycol, are commonly utilized for phytochemical component transfer and pharmacokinetic parameter modification. For example, it has been shown that polyoxymethylene glycol nanoscale particles increase quercetin's stability, solubilization and circulation persistence in the vascular system (Wang *et al*., 2013). Many morbidities, including high blood sugar levels, elevated blood pressure, infections of the upper respiratory tract, pancreatic and mammary carcinomas and heart abnormalities, have been linked to quercetin's possible therapeutic advantages (Bennet *et al*., 2012; Yu *et al*., 2007; Kumari *et al*., 2012; Cunico *et al*., 2020; Bose and Michniak, 2013; Li *et al*., 2009). However, its poor clinical relevance and efficacy are caused by low intrinsic

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bioactivity (<10%), considerable metabolic degradation (>40%), fast physiological elimination (<1 hr), limited hydro solubility (1 µg/mL) and inactive substances.

To get around these challenges, a variety of delivery modalities have been developed, including inclusion complexes and micelles, phospholipid vesicles, inorganic nanoscale particulates, polymeric nanoscale particulates/microspheres and other nanomaterials. Pentacyclic triterpenoidal substances have not been utilized in medicine despite having advantageous properties, Thus, the efficacy of *in vivo* therapy is not always correlated with its biological consequences (Kaps *et al*., 2021; Ghante and Jamkhande, 2019; Szakiel *et al*., 2012; Xia *et al*., 2017; Yu *et al*., 2020; Shao *et al*., 2020; Patra *et al*., 2018). Figure 2 presents an overview of the general benefits of Drug Delivery Mechanisms (DDMs).

Nano Drug Delivery Systems

Numerous research investigations have been carried out to determine which botanical compounds and entities from dietary and medicinal flora are effective for treating a variety of clinical disorders. On the other hand, rapid metabolism, limited permeability and instability can all hinder the bio utilization of such herbal bioactive substances, which is essential to their effectiveness (Yadav *et al*., 2011). In order to overcome the drawbacks of conventional therapy, nanoscale pharmaceutical delivery has become a viable method for delivering active ingredients. Pharmacological researchers have taken notice of the special qualities of nano vehicles, such as their increased surface area, quick evacuation from the stomach, controlled delivery to specific sites, increased internalization of cells, better bio utilization and biodistribution, affordability, patient compliance and increased healing efficacy (Yetisgin *et al*., 2020).

Solid Lipid Nanovesicles (SLNs), nanoscale lipid-based entities, have attracted considerable interest worldwide despite the absence of polymeric materials with regulatory approval and their exorbitant price. The stiff core lipid matrix of SLNs provides increased stability of active principles, one of the many benefits they have over liposomal entities (Mishra *et al*., 2018). SLNs also demonstrate improved entrapment efficiency, regulated release for lipophilic drugs and appropriate modification for targeted therapeutics (Satapathy *et al*., 2021). Additionally, SLNs are superior to polymeric nanovesicles in that they can be produced on a large scale, are more stable and do not require organic solvents (Rizvi *et al*., 2019). Many studies have revealed advantageous phytochemical entities from medicinal and dietary flora that can treat a range of pathological disorders. One possible way to improve the distribution of active principles while addressing these issues is through nanoscale pharmaceutical delivery.

Pharmacologists have been drawn to nano vehicles because of their intriguing properties, which include enhanced pharmacokinetics, precise targeting and reduced cytotoxicity. Because of their superior toughness, improved encapsulation efficiency and mass-production feasibility, Lipid-Based Nano Capsules (LNCs) have become the preferred option over polymeric nano capsules. To be more precise, LNCs are very histocompatible since they are made of endogenous and biodegradable lipids; they are more robust because of their stiff lipid core; and they are made with less effort because they don't require complicated polymeric structures during the manufacturing process. In addition, LNCs are more histocompatible than polymeric nano capsules and may be customized for precision therapies, which makes them a desirable choice for effective phytochemical drug administration (Rawat *et al*., 2023; Sharma *et al*., 2019).

Challenges in Formulating Nano Formulations

Nanoscale entities with customized architecture, size and dispersal can often be produced by adjusting fabrication processes, reductive catalysts and stabilizing agents (Roy *et al*., 2019). Due to variations in the phytochemical extracts used, the morphology and dimensions of the nanoscale entities are significantly influenced by them. Consequently, standardizing and producing nanoscale objects with the necessary size, topology and surface characteristics requires optimization of the manufacturing paradigm (Patil and Chandrasekaran, 2020). Although state-of-the-art nanoscale formulations for drug delivery systems are constantly being developed and provide several advantages, there are still some barriers that keep them from being widely deployed. Researchers have challenges while developing and manufacturing nanoscale formulations due to a variety of factors, such as (i) biomaterial characteristics; (ii) fabrication restrictions; (iii) payload capability; (iv) stability; and (v) biological hurdles (Yetisgin *et al*., 2020; Shao *et al*., 2020).

The characteristics of biomaterials, such as their biodegradability or surface moiety charge, can affect their membrane permeability, cytotoxicity and biocompatibility (Santos *et al*., 2019). Producing consistent product batches free of unwanted fabrication byproducts requires an effective and scalable production strategy for nanoscale formulations (Kahraman *et al*., 2017).

Pharmacokinetics of Nano Formulations

Distinct delivery systems allow Nano Formulations to be introduced into the body and precisely target particular body locations. Nanoparticle characteristics including size, concentration, surface electronegativity and hydrogen ion concentration have a significant influence on pharmacokinetic processes, such as absorption and dissolution. A rise in the bloodstream's level of nanoparticles during a single day that is dose-dependent has been demonstrated by empirical evidence, with the liver, kidney and lungs exhibiting the most significant accumulation over a 72-hr period. The results emphasize the significant impact of nanoparticle properties on pharmacokinetic mechanisms and possible toxicity, indicating that urine excretion is the main method of eliminating tiny nanoparticles, while

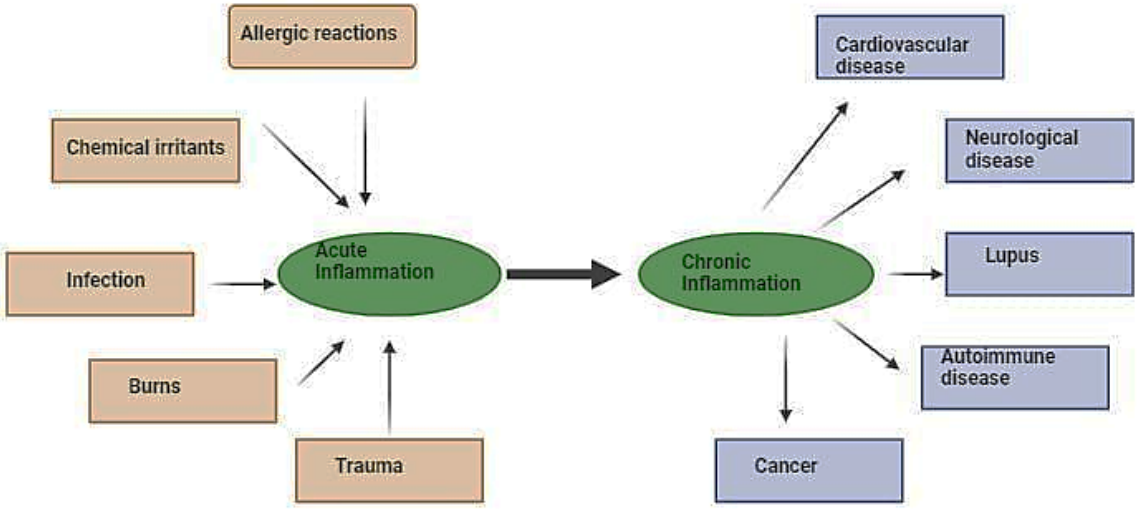

Figure 1: A graphic representation of the various forms of both acute and chronic inflammation.

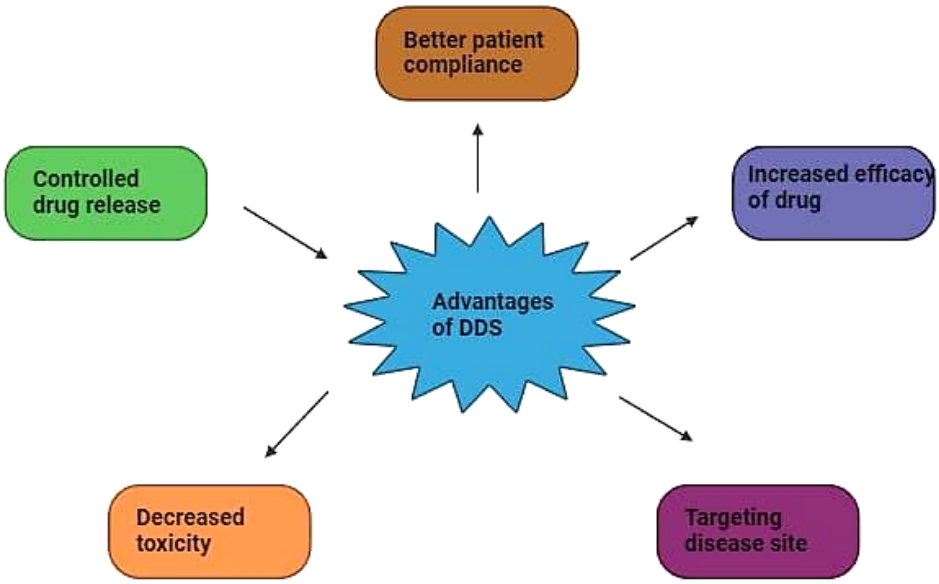

Figure 2: Efficacy of Drug Delivery systems.

feces and the biliary system are the main routes of elimination for bigger ones. The quantity of nanoparticles in circulation rises dose-dependently and is linked to increasing toxicity; the organs most impacted are the liver and splenic ones.

To minimize potential negative effects, it is imperative to customize the size and concentration of nanoparticles according to the the area of the target and the degree of inflammation. Moreover, surface modification using Ethylene Diamine Tetra Methylene Phosphonic Acid (EDTMP) has been shown to lessen the cytotoxicity of nanoparticles by lessening the oxidative stress that is caused by high nanoparticle concentrations (Imperiale *et al.*, 2019; Chen *et al.*, 2017).

Inflammation

In response to external stimuli, the immune system produces inflammation as a defense mechanism in response to things like pathogen invasions, cellular destruction, toxic substances, or ionizing radiation (Medzhitov, 2010; Ferrero *et al.*, 2007; Nathan and Ding, 2010; Zhou *et al.*, 2016). Usually, this defensive reaction restores tissue homeostasis and reduces inflammation by reducing the likelihood of infection or trauma through cellular and molecular processes. Leukocyte mobilization, pro-inflammatory mediator release and altered vascular permeability are all significant outcomes of this process (Chertov *et al.*, 2000). Irritation manifests as irritation, edema, heat, discomfort and tissue dysfunction because of localized inflamed, vascular and immune cell reactions to injury or infection (Takeuchi *et al.*, 2010). An array of factors, mostly pertaining to the upper respiratory tract and nasal cavities, can cause inflammation,

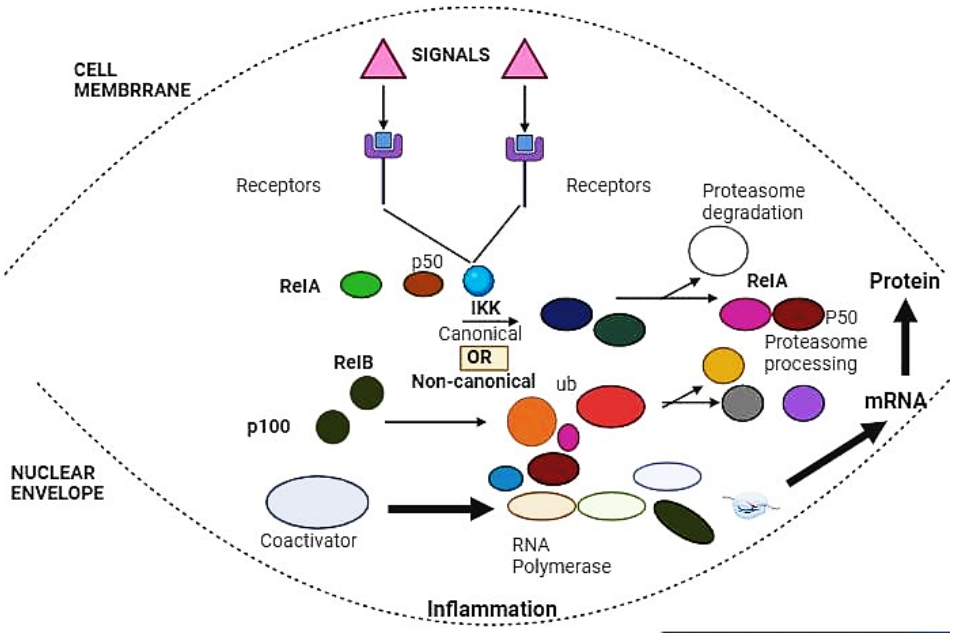

Figure 3: The method by which NFκB operates.

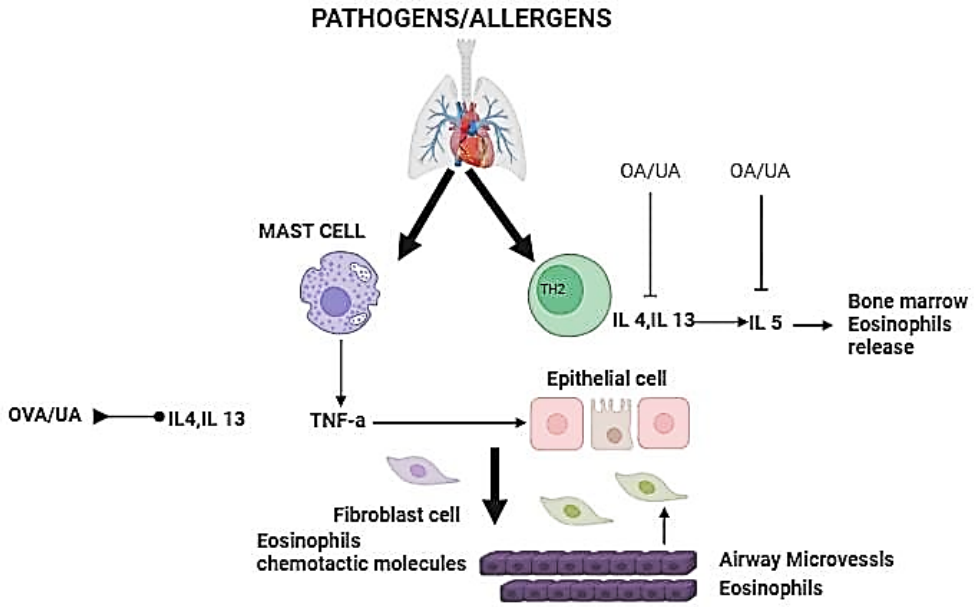

Figure 4: A number of infections and allergens in the environment cause immune cells to release specific cytokines and chemokines, which chemotactically trigger eosinophil infiltration through endothelial cells at the site of inflammation and intensify the inflammatory process.

Table 1: The way that different flavanoids and triterpenoids affect inflammation.

Sl. No.	Phytoconstituents	Plant source	Active compound	Mechanism of action	References
1	Flavanoid	Sambucus canadensis L., Ginkgo biloba L. and Hypericum perforatum L.	Quercetin	Suppression of cyclooxygenase 2 blocking AP-1's attachment the leptin receptor, to extracellular signal-regulated kinase Ob-Ra and Mitogen-Activated Protein Kinase (MAPK) K/p38 kinase.	(Mirza *et al*., 2023; Kwak *et al*., 2016; Shabir *et al*., 2022; Li *et al*., 2016; Serafini *et al*., 2010; Ferraz *et al*.,2020; Cunha *et al*., 2010; Sachs *et al*., 2004; Ntalouka and Tsirivako, 2023; Choy *et al*., 2019; Krishna *et al*., 2024).
2	Flavanoids	Salvadora persica	Luteolin-8 CfucopyraNOSide (LU8C-FP).	Decrease in IL-6.	(Lv *et al*., 2011; Aziz *et al*., 2018).
3	Flavnoids	Ruta graveolens	Rutin	Both Nuclear factor E2-related factor (Nrf) stimulation and Nuclear factor (NF-κB) repression are involved.	(Álvarez *et al*., 2016; Ganeshpurkar *et al*., 2017; Rauf *et al*., 2017;Farzaei *et al*., 2019).
4	Flavanoids	Reseda luteola L	Luteolin	NF-κB, TNF-α and IL-6 reduction inhibition.	(Arampatzis *et al*., 2023; Al-Khayri *et al*.,2022; Choy *et al*., 2019; Muruganathan *et al*., 2022).
5	Flavanoids	Sumach from Venice (Rhus cotinus L.)	Fisetin	Reduced levels of Tumor Necrosis Factor (TNF-α), Interleukin (IL-1β and IL-8).	(Grynkiewicz and Demchuk, 2019; Grynkiewicz and Demchuk, 2019; Choy *et al*., 2019; Garg *et al*., 2019).
6	Triterpenoids	Souroubeasympetala	Betulinic acid	By modulating the NF-kB pathway, betulinic acid reduces the generation of IL-6 and inhibits the formation of nitric oxide.	(Puniani *et al*., 2014; Jeong *et al*., 2009; Lin *et al*., 2015; Yun *et al*., 2003).
7	Triterpenoids	Lisgustrum lucidum	Oleanolic acid	Blocking Liposaccharide (LPS) release, which is a mediator of the synthesis of Cell Adhesion Molecules (CAMs) and High Mobility Group Box 1 (HMGB1).	(VYAS *et al*., 2014; Xia *et al*., 2011; Yang *et al*., 2012; Andersson *et al*., 2011; Lee *et al*., 2013).
8	Triterpenoids	Herbs (such as organum, marjoram, rosemary, lavender and thyme), fruits (such as apple peel) and flowers. *Australian sambucus.*	Ursolic acid	Lower the quantities of IL-1β, IL-6, IL-8 and TNF-α, which are indicators of inflammation.	(Woźniak *et al*., 2015; Jäger *et al*., 2009; Szakiel *et al*., 2012; Zhao *et al*., 2023).
9	Triterpenoids	Americans' ginseng *Sebastianiaadenophora, Crataevanurvala, Bombax ceiba, Leptadeniahastata, Hematanthussucuuba, Shea butter plant species include andriedelianum.*	Lupeol acid	Modifying the mRNA unique to IL-2 and TNF-alpha.	(Saleem, 2009; Beveridge *et al*., 2002; Fernández *et al*., 2001; Vasconcelos *et al*., 2008; Yamashita *et al*., 2002; Lucetti *et al*., 2010).

10	Triterpenoids	Centella asiatica	Asiatic acid	Control of NOS, IL-1β, COX-2 and IL-6.	(Nagoor *et al.*, 2018; Kamble *et al.*, 2017; Patil *et al.*, 2015; Yang *et al.*, 2018).
11	Triterpenoids	Olea europaea	Maslinic acid	Preventing the synthesis of Tumour Necrosis Factor alpha (TNF-α) and nitric oxide.	(Lozano *et al.*, 2014; Ooi *et al.*, 2023; Lu *et al.*, 2009; Banno *et al.*, 2005; Kim *et al.*, 2005; Huang *et al.*, 2011).
12	Triterpenoids	Planta odorum, Nerium oleander	Oleandrin	Reduced Phosphatidylinositol 3-Kinase (PI3K), phosphorylated Ak strain transforming (Akt) and inhibition of NF-κB.	(Zhai *et al.*, 2022; Khan *et al.*, 2010; Atay *et al.*, 2018).

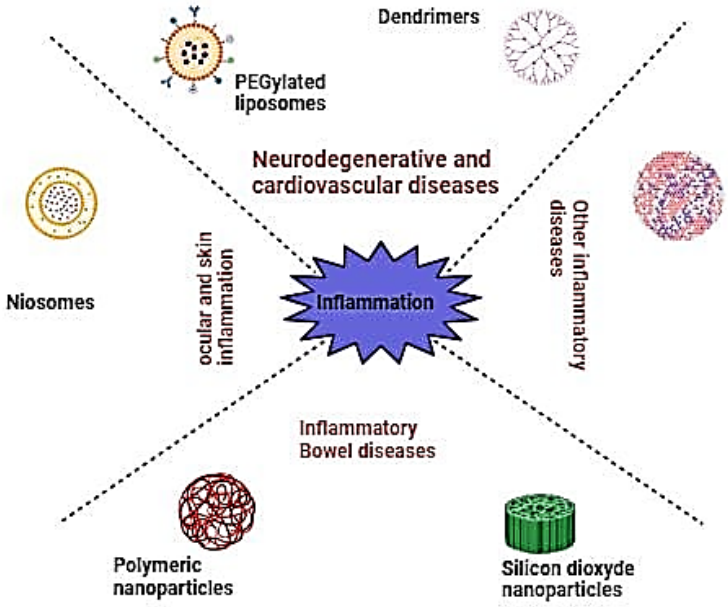

Figure 5: Recent nanomedicines for the treatment of inflammation.

such as pathogenic invasions, severe temperature swings, toxic chemicals, physical trauma and abnormalities in health.

A defective multi systemic response to airway stimulation, including effector cells and pro-inflammatory mediators, is the hallmark of asthma, a chronic inflammatory airway illness. Sepsis, on the other hand, is a potentially fatal reaction to pathogenic invasion that releases pro-inflammatory mediators and damages numerous organs. Individuals may have symptoms like hypotension, pyrexia, decreased urine production, impaired hemostasis, increased vascular permeability and loss of smooth muscle tone. These illnesses have been treated with synthetic medications such as corticosteroids, leukotriene receptor antagonists and antimicrobials (Yatoo *et al.*, 2018; Jamtsho *et al.*, 2024; Bjorkman, 1998; Ricciotti and FitzGerald, 2011; Rainsford, *et al.*, 2007; Bermas, *et al.*, 2014; Shaikh *et al.*, 2012; Juthani *et al.*, 2017; Moskovtchenko and Cognet, 1976; Ayroldi *et al.*, 2012; Celotti and Laufer, 2001).

These pharmacological categories, although therapeutically beneficial, are also associated with a wide range of adverse reactions, such as fever, gastrointestinal distress, nasal blockage, aural infections, cutaneous manifestations, pruritic eruptions, bronchial irritation, tussive episodes, sinusoidal infections, upper respiratory tract disorders, atopic eczema, cranial discomfort, nausea, laryngeal inflammation, pharyngeal inflammation, viral afflictions, dyspneic episodes, odontalgic pain, vertiginous sensations, gastric dyspepsia and increased levels of hepatocellular enzymes. In contrast, a number of plant components (including flavonoids and triterpenoids) found in phytotherapeutic treatments have been demonstrated to improve immunological response and offer numerous other advantages, which helps to mitigate the drawbacks of traditional treatment

approaches (Altavilla *et al.*, 2009; Lin *et al.*, 2008; Aggarwal *et al.*, 2011). Figure 3 illustrates the mechanistic effects of different coactivational substances and receptors.

In the cytosol, where the Rel and p50 proteins are found, NF-κβ forms a complex with the inhibitory protein Iκβα when it is in its active state. Membrane receptors pick up extracellular signals, which then activate Iκb Kinase (IKK). The IKK then phosphorylates the Iκβα protein, which causes it to get ubiquitinated and eventually be degraded by the proteasome (by the canonical pathway). RelB prefers the non-canonical NF-κβ activation route through RelB. Response Elements (RE) are DNA bindings that induce NF-κβ to translocate into the nucleus and bind. Coactivators and RNA polymerase are drawn to the DNA/NF-κβ complex, which causes the latter to produce mRNA from the DNA and change the cell.

Function of Triterpenoids and Flavonoids in Inflammation

Due to differences in their chemical structures, flavonoids may be divided into six groups: flavones, phenols, flavanonols, isoflavonoids, flavan-3-ols and anthocyanins, are found in a wide range of plant materials, such as fruits, flowers and leaves (Choy *et al.*, 2019; Pollastri and Tattini, 2011; Barreca *et al.*, 2017). Studies have indicated that in the presence of chronic inflammation, triterpenoids and flavonoids impact several redox pathways, including Nuclear Factor kappa B (NFκB). The transcriptional regulation NFκB is activated by inflammatory stimuli, leading to the suppression of the Inhibiting kappa B (IκB) kinase. This finally results in cellular death and a rise in pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α). It has been observed that flavonoids and triterpenoids reduce oxidative stress in a variety of medical conditions, as well as the concentrations Elevated blood serum levels of TNF-α or Interleukin-1 beta (IL-1β), as well as blood mononuclear cells' NFκB transcriptional activity (Chekalina *et al.*, 2018; Indra *et al.*, 2013; Tang *et al.*, 2014; Oyagbemi *et al.*, 2018; Lv *et al.*, 2011; Garg *et al.*, 2019; Ren *et al.*, 2018; Xiong *et al.*, 2018; Lee *et al.*, 2012; Rani *et al.*, 2016; Han *et al.*, 2015; Suchal *et al.*, 2016; Kashyap *et al.*, 2016).

Referring to Figures 4 and 5 depicts the inflammatory mechanism. Diverse treatment methods, such as corticosteroidal

Table 2: Reports of different phytoconstituents in Nanoformulations.

Sl. No.	Plant-based composites	Nanoformulation	Active ingredient	Inflammation-related illness	References
1	Flavanoids	PLGA Nanoparticles	Quercetin	Antimicrobialactivity	(Kaps *et al.*, 2021).
2	Triterpenoids	Gold Nanoparticles	Betulinic acid	Anticancer disease	(Mioc *et al.*, 2018).
3	Triterpenoids	Pentacyclic triterpenoid - Lupeol Nanoemulsion.	Lupeol	Antimalarial illness	(Dwivedi *et al.*, 2023).
4	Triterpenoids	Liposomes	Ursolic acid	Anti malignant tumor action	(Sysak *et al.*, 2023).
5	Triterpenoids	Chitoson Nanodrug Carrier.	Ursolic acid	Antitumor activity	(Shao *et al.*, 2020).
6	Flavanoids	Silver Nanoparticles with Quercetin.	Quercetin	The anti-inflammatory property.	(Wang *et al.*, 2021).
7	Triterpenoids	Acid ursolic nanosuspension.	Ursolic acid	Diabetes type 2	(Nie *et al.*, 2020).
8	Flavanoids	Particles of nanoscale Acetate phthalate of cellulose, silica nanoparticles and nanoparticles The polycaprol act one particles of nanoscale Silica nanoparticles, polycaprolactone nanoparticles and cellulose acetate phthalate.	Quercetin	Anti-rheumaticeffect	(Guan *et al.*, 2021).
9	Flavanoids	Both solid lipid and polymer nanoparticles, solid lipid nanoemulsions, elastic liposomes and nanostructured lipid transporters.	Quercetin, Rutin and Lutein	Topical infectious disorders	(Dwivedi *et al.*, 2023; Derman *et al.*, 2020; Viscusi *et al.*, 2023).
10	Flavanoids	Metallic oxide, silver and gold nanoparticles.	Quercetin	Viral disease	(Jannat *et al.*, 2021).

and non-corticosteroidal ones, are being continually investigated to manage acute inflammatory responses. Unfortunately, these techniques frequently fall short of the intended therapeutic result because of drawbacks including non-specific pharmacokinetic distribution, limited bioavailability, or short half-lives, which force doctors to prescribe higher dosages and cause unintended side effects. Nanoscale particles are becoming more and more popular as a solution to these problems because of their ability to target specific molecular entities, minimize toxicity and negative effects and facilitate controlled release in affected cellular and tissue structures. They also have controlled dimensions, morphology and surface charge.

Nanoscale formulations demonstrate a significant advantage in regulating maintaining the proper ratio of pro-to-anti-inflammatory effectors and using endocytic absorption to target cell phagocytic or inflammatory sentinels in particular. In addition, precision targeting of particular cell populations with nanovehicular systems might greatly improve immune response or intracellular internalization to suppress inflammation. Anti-inflammatory nanopharmaceuticals are the product of significant efforts to develop anti-inflammatory tactics that overcome the constraints of conventional pharmaceutical forms (Maio *et al*., 2021; Cai *et al*., 2021; Jubilee *et al*., 2024; Costanzo *et al*., 2016).

CONCLUSION

The treatment of inflammation could be completely transformed by the combination of nanotechnology and herbal products. Improved patient outcomes can be achieved by using Nano Formulations to optimize drug administration, improve biocompatibility and minimize side effects. This strategy offers a viable treatment for chronic inflammatory illnesses while addressing the drawbacks of traditional therapies. Researchers can develop effective and tailored medicines by using Nano Formulations, which will ultimately change the way disease management is handled. Approaches to personalized treatment are made possible by the adaptability of Nano Formulations, which enable targeted moieties and customized designs. To fully achieve the potential of Nano Formulations and make them a reality for patients, more research is required. Nano Formulations have the potential to significantly improve the lives of millions of people globally by serving as a cornerstone of inflammatory control with further innovation. It appears that the therapy of inflammation has a bright future and Nano Formulations will likely be crucial in determining that future. To realize their full potential, ongoing research is essential.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AP-1: Activator Protein 1; **CAMs:** Cell Adhesion Molecules; **COX-2:** Cyclooxygenase-2; **DDMs:** Drug Delivery Mechanisms; **EDTMP:** Ethylene diamine tetra methylene Phosphonic Acid; **HMGB1:** High Mobility Group Box 1; **IL:** Interleukin; **IKK:** IκB Kinase; **MAPK:** Mitogen-Activated Protein Kinase; **NF-κB:** Nuclear Factor kappa-light-chain-enhancer of Activated B Cells; **NOS:** Nitric Oxide Synthase; **Ob-Ra:** Leptin Receptor Isoform a; **PI3K:** Phosphatidylinositol 3-Kinase; **PLGA:** Poly (Lactic-Co-Glycolic Acid); **RE:** Response Elements; **ROS:** Reactive Oxygen Species; **SLNs:** Solid Lipid Nanovesicles; **TNF-α:** Tumor Necrosis Factor-alpha.

AUTHORS CONTRIBUTIONS

Lokeshvar R: Writing-original draft, Resources, Writing-review and editing. Velmurugan R: Supervision, Conceptualization, Validation. Mahalakshmi Devaraji: Method Validation. Yokesh S, Karthika R, Saran R, Shyam Sundar S: Writing-review and editing.

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