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# Recent Advances in Herbal-Based Nanomedicine for Anti-Inflammatory Purposes

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## ABSTRACT

Herbal drugs have been used around the world since ancient times. The effectiveness of herbal drugs depends on their active constituents such as phenolic compounds, flavonoids, terpenoids, and tannins. These compounds were proven to show many therapeutic activities such as anti-inflammatory, antimicrobial and anticancer. However, they have many drawbacks restricting their applications and therapeutic outcomes such as low absorption due to their inability to cross the lipid membrane of the cell. Therefore, they have low bioavailability and efficacy. The nanotechnology is a cutting-edge science that might give a new hope to revitalize the use of herbal drugs. Nano-carrier systems are reported to potentiate the action of herbal drugs, due to their ability to improve their bioavailability. Moreover, herbal nano-medicine could be designed with a surface decoration to be targeted to the effective sites, and thus reducing the therapeutic dose, minimizing side effects with an improvement of their therapeutic outcome.

***Keywords:*** *Herbal drugs; Nanotechnology; Drug delivery system.*

## INTRODUCTION

Inflammation is a protection plan in the higher organisms in response to noxious stimuli as microbial infection, tissue injury, and other noxious conditions[1]. The intruder could be a foreign body, such as a pathogen, thorn, and irritant. Pathogens include bacteria, viruses, parasites, and fungi that cause infections. The most common infectious agent that causes inflammation are bacteria[2] and viruses[3]. Bactria releases substances called Endotoxin. Viruses can initiate inflammation by entering and destroying the body cells[4]. Inflammation is caused by cells deprivation from oxygen and/or nutrients as a result of loss of normal blood flow to the affected area. Oxygen promotes wound healing and is essential for neuroprotection and for other vital activities in cells and thus a reduction of oxygen level imparts a hazardous effect on the cellular function and could be fatal at sometimes[5].

Inflammation is a part of the immune system's response to injury and infection. Without the physiological response of inflammation, wounds would be faster and infections would become deadly. Some receptors involved in the inflammatory process as toll-like receptors, mannose-binding lectin, and nucleotide-binding oligomerization domain-like receptors are major pattern recognition receptors implicated in the inflammatory pathway. Upon activation of these

receptors, they transduce signals intracellularly, for example, kappa -light-chain-enhancer of activated B-cells (NF- κB) that can induce a cellular response. This response involves the induction of adhesion molecules that accelerating inflammation[6]. The inflammatory response begins with the production and release of chemical agents called cytokines by cells in the infected area. These cytokines as interleukins, growth factors, and chemokines[7]. These inflammatory cytokines will help in the activation of immune cells. The leukocytes migrate to the inflamed tissues destroying any infective or injurious agent and remove any cellular debris from damaged tissue. Vasodilation is a normal process that occurs with the inflammation to increase the blood supply to the affected area. Vasodilation causes increase blood flow and resulting in the reduction of blood pressure[9].

The inflammatory response is followed by repair processes designed to regenerate the damaged tissue and fill in the gaps with fibrous tissues[10].

## Types of Inflammation

### Acute inflammation

Acute inflammation lasts only a few days and is characterized by an exudation of plasma protein, fluids, and neutrophilic infiltration. Three main processes are involved[9]:

1) Increase diameter of blood vessels and increase blood flow.
2) Increase vascular permeability.
3) Migration of inflammatory exudate occurs when the primary cause of inflammation is a pyogenic bacterium. This exudate forces the tissue apart, leaving necrotic tissue enriched with neutrophils and pathogens.

There are five key elements characterizing acute inflammation[11]:

- **Redness**: This occurs because the blood vessels become wider and this is accompanied with an increase of blood supply to the capillaries in the affected area and thus the inflamed area becomes reddish in color.
- **Loss of function**: inflammation might be associated with a loss of function, for example, difficulty of moving an inflammed joint, difficulty of breathing, and sensing a smell.
- **Swelling**: This is accompanying the vasodilation process where fluids are excreted into tissues causing swelling
- **Heat**: this happens due to increasing blood flow at the inflamed area.
- **Pain**: the accumulation of fluids at the tissues, is accompanied by increasing the pressure at the nerve ending leading to pain sensation.

### Chronic inflammation

It can continue for months or years and is characterized by mononuclear infiltration, scaring, and vascular proliferation. Common symptoms of chronic inflammation: fever, fatigue, rashes, mouse sores, abdominal pain, and chest pain. Chronic inflammation can occur with the following diseases[12]: allergies, psoriasis, diabetes, and arthritis.

## Treatment of inflammation

The best strategies to treat inflammation is removing the cause of inflammation followed by controlling the symptoms of inflammation and this will be explained below.

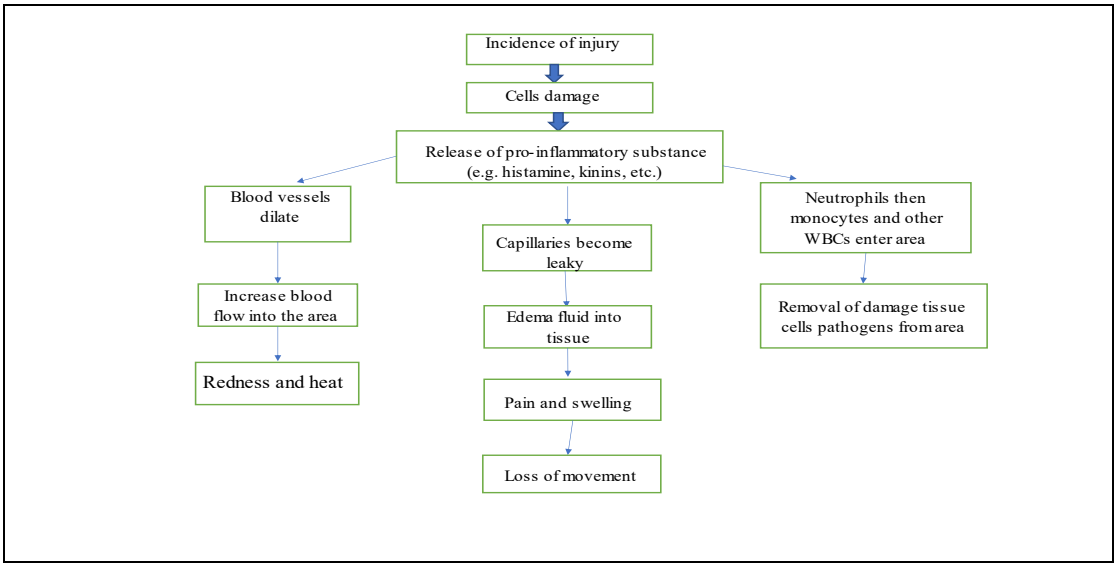



**Figure 1. The body inflammatory response to inflammation.**

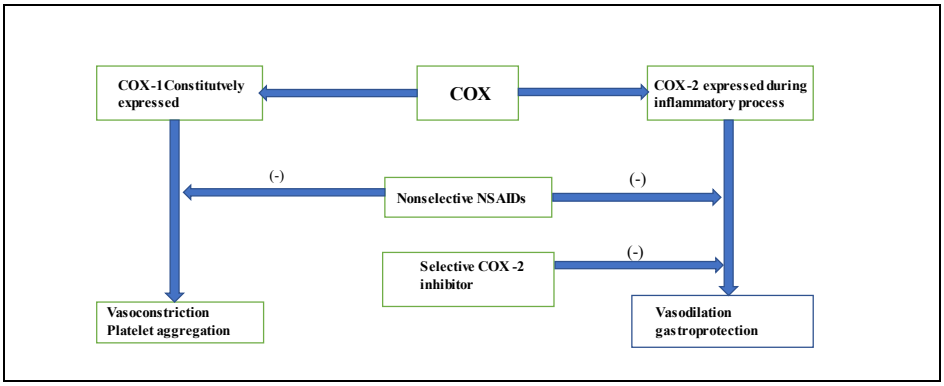



**Figure 2. Mechanism of COX inhibition**

**Nonsteroidal anti-inflammatory drugs (NSAIDs)**

NSAIDs are used for the treatment of pain and inflammation. Worldwide sales have been evaluated by US$5.8 billion[13]. NSAIDs are classified according to their action to[14]:

***Non-selective cyclooxygenase (COX) inhibitors*:** Can inhibit COX-1 and COX-2. It has many limitations like bleeding and ulceration in the gastrointestinal tract, renal, cardiac, and hepatic syndromes. These drawbacks due to inhibition of COX-1 that produce prostaglandin (PEG2) and prostacyclin (PGI2), these prostanoids protect the mucosa by inhibiting the secretion of gastric acid, inducing vasodilation of in the mucosal microcirculation, and stimulating gastric bicarbonates, non-selective COX inhibitors can inhibit platelet aggregation by inhibition of COX-1 and thromboxane $A_2$ ($TXA_2$) [15]. Examples: Diclofenac, Piroxicam, Ibuprofen, and Aspirin.

***Selective COX-2 inhibitors*:** Selective COX-2 inhibitors were recommended more than non-selective COX inhibitors because it has less gastro-toxicity with no effects on platelets aggregation[16]. The activity of COX-2 is induced by proinflammatory cytokines and produces prostaglandins that mediate the inflammatory response[17]. Examples: Celecoxib, Etoricoxib and Valdecoxib.

**Steroids**

Corticosteroids are mainly known as steroids. They can suppress the immune system and reduce inflammation, which is helpful when it starts attacking healthy tissue. But long-term use of corticosteroids can lead to side effects such as osteoporosis, high blood pressure, and vision problems. When you take corticosteroids, your doctor will weigh the benefits and drawbacks with you[18].

Steroids achieve their anti-inflammatory effect by interaction with transcription factor (NF) -κB, whose inhibition results in the reduction of many cytokines. Steroids could reduce the release of cytokines by inhibiting the expression and generation of cytokines[19].

**Natural products**

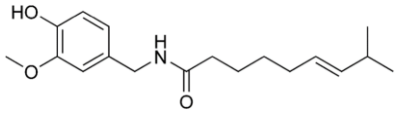
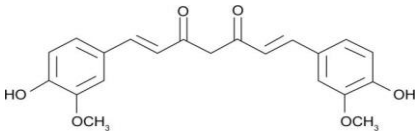
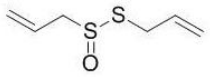
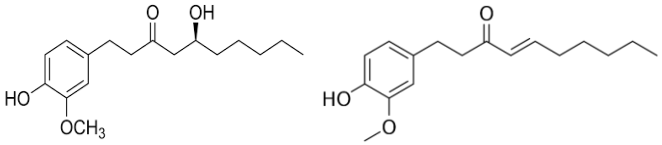
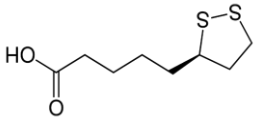
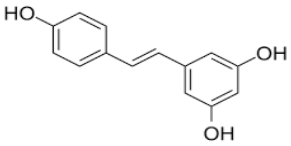
Natural products are medicines derived from plants and micro-organisms as secondary metabolites[20]. They may be used for therapeutic uses as antibacterial, anti-inflammatory, and anti-cancer. Herbal drugs are available in many dosage forms such as tablets, capsules, and powders[21].

Herbal drugs and their constituents are considered beneficial due to their properties, for example, satisfactory potency, ease of availability, cheapness, less or no side effects, more safe, and has a higher efficacy compared to synthetic compounds[22]. However, Herbal drugs have certain limitations such as low water solubility, have low bioavailability due to rapid metabolism and most of them are photosensitive [23]. Nowadays, there are several herbal drugs used for inflammation due to their advantages, Examples of herbal drugs that used as anti-inflammatory:

Resveratrol [24] (RES) is a natural polyphenolic phytoalexin compound. It is produced by more than 70 species of plants in response to stressful situations. The concentration of RES in plants depends on two important factors, the weather, and the presence of fungus. RES can be originated from some fruits, which are part of the human diet, such as blueberries (*Vaccinium spp*.), blackberries (*Morus spp*.), and peanuts (*Arachis hypogaea*)[25].

Resveratrol was reported to be used as an anti-inflammatory [26]. One of the possible mechanisms for its protective activities is by downregulation of the inflammatory responses. This includes the reduction of synthesis and release of pro-inflammatory mediators, modifications of eicosanoid synthesis, inhibition of some activated immune cells, or inhibiting the enzymes,

**Table 1. Chemical structure of medicinal plants**

| Medicinal plants | Chemical structure |
|---|---|
| **Capsaicin**[39] |  |
| **Curcumin**[40] |  |
| **Garlic (Allicin)**[41] |  |
| **Ginger (A-gingerol and B- shogaol)**[42] |  **(A)** **(B)** |
| **Lipoic acid**[43] |  |
| **Resveratrol**[44] |  |

*This review focuses on the importance of encapsulation of herbal medicines to nanoparticles to potentiate drug delivery and overcoming the problems associated with medicinal plants.*

such as cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2), which are responsible for the synthesis of pro-inflammatory mediators through the inhibitory effect of resveratrol on transcription factors like nuclear factor kappaB (NFkappaB) or activator protein-1 (AP-1)[27].

Ginger[28]the rhizome of zingiber officinale has been widely used as an herbal anti-inflammatory drug, the most pharmaceutically active phenolic ingredients are gingerols and shogaols. Ginger extract can decrease inflammation, swelling, and pain by increasing heat production that is associated with vasoconstriction of adrenergic receptors and suppress the production of pro-inflammatory cytokines[29]. It has been used for health issues as cold, inflammation, GIT disturbance, and migraine[30].

Garlic[22] (*Allium sativum L*), in the last year garlic, was used as an anti-inflammatory. It contains many organosulfur compounds as allicin. Allicin is the major active volatile oil compound, this compound is reported to have biological activities that include anti-inflammatory, antibacterial, antifungal. Although garlic has been used as a biotherapeutic agent its mechanism of action still unclear[31]. But in other studies, it was reported that the anti-inflammatory effect is due to significant inhibition of COX-2 enzyme and thus inhibition of nitric oxide and prostaglandin (PEG2) in macrophage[32].

Chili pepper[33] the most common spices around the world. The most common bioactive component in chili pepper is capsaicin (CAP). CAP has anti-inflammatory effects. It had been formulated as a patch and topical gel for pain relief treatment. The anti-inflammatory effect of CAP is due to inhibition of COX-2 enzyme activity and thus suppresses the production of prostaglandin E2. and induction of nitric oxide synthase (NOS)[34].

lipoic acid [35] is a disulfide derivative of octanoic acid. Alpha-lipoic acid (ALA) is a type of thioctic acid and is naturally produced by plants and animals. It has an anti-inflammatory effect through inhibition of pro-inflammatory cytokines and by inhibition of NF-κB

activation and induction of nitric oxide synthase. It was proved that anti-inflammatory activity correlated with its antioxidant characteristics[36].

curcumin [37] is a hydrophobic ingredient found in a rhizome of the *C. longa*. It is composed of low molecular weight polyphenols. It has been used as a paste to relieve pain. The anti-inflammatory action of curcumin (diferuloylmethane) involves regulating numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status, and enzymes that have been linked to inflammation[38].

**Application of Nanoparticles as a Carrier for Herbal Drugs**

Nanotechnology is considered a relatively new technology that has many applications in different fields. Nanotechnology was applied to develop different pharmaceutical formulations to target the drug into diseased organs while reducing the side effects due to the accumulation of the medicine at the off-target sites. Also, it improves patient compliance compared to conventional therapy[45]. Polymeric nanoparticles are considered a good carrier for hydrophobic compounds as well as being efficient in delivering the medicine over the stratum corneum for topical applications [46], oral administration, and inhalation. These carriers can also be designed to enable controlled (sustained) drug release from the matrix[47]

A nanoparticle is a fine particle that ranges between 1 to 100 nanometers in size. Invisible through the human eye, nanoparticles can show significantly different physical and chemical properties to their larger material counterparts[48].

Nanoparticles are prepared from biocompatible and biodegradable materials such as solid lipids or polymers, either natural (e.g., gelatin, albumin) or synthetic (e.g., polylactides, polyalkylcyanoacrylates). In the body, the drug-loaded nanoparticles are usually released from the matrix by degradation, swelling, erosion, or diffusion[47]. Nanoparticles have a technological advantage as drug carriers include high stability (i.e., long shelf life); high carrier loading (i.e., many drug molecules can be entrapped into the particle-matrix[47].

**The most common delivery system to encapsulate natural products**

***Solid lipid nanoparticles (SLNs)***

They are colloidal carrier systems that contain very purified triglycerides, composed mainly of lipids. These structures are produced from solid lipids and they are stabilized through surfactants. SLNs size ranges from 50 to 1000nm and they can be used for the delivery of drugs by using different routes of administration such as oral and parenteral route, they combine the advantages of liposomes and polymeric nanoparticles as they have low toxicity, high physicochemical stability, and offer good protection against drug degradation[11].

Resveratrol-loaded stearic acid-based SLNs (RLNs) coated with poloxamer 188 as a surfactant were prepared successfully by solvent diffusion–solvent evaporation method. The lipid formulation has a significant 8.035-fold enhancement in the oral bioavailability of resveratrol as compared to a drug suspension. Thus, stearic acid-based RLNs could act as a promising sustained-release system with increased bioavailability for resveratrol after oral administration[49]. It was also found that the oral bioavailability of resveratrol, when encapsulated in these nanoparticles, increased up to 50% (19.2-fold higher than for the control blank solution of the polyphenol)[50].

Lavender is an essential oil, it can be loaded to SLNs and formulated as a gel for topical inflammation. SLNs were prepared by using cocoa butter as solid lipid and Tween 80% as surfactant. Lavender has low water solubility and low bioavailability so the encapsulation to SLNs can solve its drawbacks. The anti-inflammatory activity was assessed ex-vivo in the carrageenan-induced edema method. The percentage of inhibition of edema in 1% lavender-based SLNs was found to be 28±0.1% compared to the anti-inflammatory of diclofenac gel 33.6±0.0 5%[51].

Curcumin loaded to SLNs to improve its biopharmaceutical activity, by using lipid (Compritol 888 ATO, soy lecithin, and polysorbate 80. The SLNs were evaluated incomplete Freund's adjuvant (CFA)-induced arthritis in rats. SLNs are a novel approach to deliver curcumin into the inflamed joints[52].

***Liposomes***

Liposomes are spherical small-sized vesicles composed of natural or synthetic lipid bilayers, separated by an aqueous medium in their core. Hydrophilic materials are encapsulated inside the aqueous compartment, while lipophilic materials are adsorbed or incorporated in the lipid bilayers. Liposomes are classified according to their surface charge, size, lipid composition, and method of preparation. The surface charge could be anionic, cationic, or neutral. According to the size and number of lamellae, liposomes can be classified as small, large, or a giant and oligo-, uni- or multi-lamellar, respectively. Liposomes have assisted decrease the side effects of different drugs such as anticancer and antifungal drugs, simultaneously improving their efficacy. Liposomal drug delivery preparations have also been considered in various chronic inflammatory diseases. This is a promising approach since it decreases the side effects of anti-inflammatory drugs on healthy tissues[53].

Curcumin is a polyphenolic compound; it is rapidly metabolized and has poor photostability which limits its use as a therapeutic agent. These drawbacks can

be resolved through encapsulation in liposome by solubilizing curcumin in the phospholipidic bilayer that's enable the delivery of curcumin in an aqueous medium and significantly increase the curcumin effect[54].

Curcumin was loaded to liposome by lipid hydration method. The prepared liposome was characterized it evaluate its anti-inflammatory activity. The pro-inflammatory markers were studied such as IL-6, TNFα, and IL-8. The loaded curcumin formulations showed an increase in encapsulation efficacy and inhibition of pro-inflammatory markers compared to the positive control group which is treated by salbutamol-loaded liposomes[55].

Capsaicin has low solubility in biological fluids and has low bioavailability so it is necessary to be encapsulated in a carrier[56]. Capsaicin can be encapsulated into liposomes to increase its bioavailability and its anti-inflammatory effect. The liposome composed of a phospholipid, cholesterol, sodium cholate, and isopropyl myristate was prepared using the film-dispersion method. The encapsulation of capsaicin in liposomes was increased to 3.34-folds and relatively increase the bioavailability compared to the free drug. The gastric mucosa irritation test was done by oral administration of liposome loaded with capsaicin and free capsaicin. The histopathological study showed that the positive control group has numerous vacuoles and inflammatory cell infiltration could be observed. While the formulation group showed no vacuoles and inflammatory cell infiltration. The high encapsulation of capsaicin relieves its irritation. The liposomal formulation of capsaicin could relieve gastric mucosa irritation[57].

Epicatechin is a natural polyphenolic compound, it has low aqueous solubility and low bioavailability so it can be loaded to liposomes to overcome these limitations. The incorporation of liposomes loaded epicatechin into a chitosan hydrogel improves the anti-inflammatory activity of epicatechin and sustained its effect[58].

***Metallic nanoparticles***

Metallic nanoparticles contain a class of materials that are made from metals such as platinum, gold, and titanium. They show remarkable optical and electronic properties, which make them very helpful in the medical field. They can be fabricated and modulated with several functional groups because their high surface area to volume ratio lets them be conjugated with antibodies, ligands, and vehicles for gene-drug delivery and diagnostic imaging. Moreover, metallic nanoparticles have the potential to carry high doses of drugs and increase their circulatory half-life. Examples of metallic nanoparticles used in research today include iron, silver, zinc oxide, and gold nanoparticles[59].

Garlic can be encapsulated in silver base nanoparticles (G-Ag-NPS) to increase its anti-inflammatory effects. Inflammation may occur due to protein denaturation that allows the production of autoantigens as in rheumatoid disease. G-AgNPs inhibited the protein denaturation even at a lower dose (10μM) and a greater inhibition (85%) of protein denaturation was recorded at (250μM) when compared to a standard drug (diclofenac sodium). Also, G-Ag-NPS can decrease gastric irritation that happens with commercially available anti-inflammatory drugs[60].

Quercetin is a natural flavonoid derived from several fruits as cherries and mango. Recently it has been proved that quercetin can reduce the excessive expression of inflammatory cytokines and inhibition of pro-inflammatory enzymes[61]. Since it has low aqueous solubility and low bioavailability, it was loaded with gold nanoparticles to improve its aqueous solubility and bioavailability. The low dose of quercetin gold nanoparticles (1μg/mL) can decrease inflammation-reducing enzymes (COX-2) compared to a DMSO solution of free quercetin. So encapsulation of quercetin in gold nanoparticles increases its anti-inflammatory activity[62].

***Polymeric nanoparticles***

Polymeric nanoparticles have a matrix structure, it is composed of biodegradable and biocompatible polymers of synthetic or natural origin[63]. The most extensively used synthetic polymers are polyacrylate, polylactide–polyglycolide copolymers, polycaprolactones, and polylactide. Lactide–glycolide copolymer is a widely explored copolymer. Among the several natural polymers, chitosan, albumin, or alginate have been widely explored [64]. Some formulations and process parameters that affect the size, release profile, and stability of the polymeric nanoparticles are the mixing times, drug-to-polymer ratio, molecular weight, the composition of the polymer, solvent, pH, homogenization speed, and solubility of the drug[65].

Polymeric nanoparticles are used for different formulations of drugs by using one of these methods, including, encapsulation, dissolution, entrapment, adsorption, or chemical binding of drug molecules on the surface of polymeric nanoparticles[66]. The drug release kinetics and its characteristics only depend on the drug trapping method and polymer structure [66]. Increasing the bioavailability of drugs into the brain by coating polymers with polysorbates has been reported widely[49].

The ginger active compound (Shogaol) was loaded to PLGA/PLA-PEG-FA nanoparticles by using a versatile single-step surface-functionalizing technique. The therapeutic activity in the treatment of colitis in induced dextran sulfate sodium (DDS) mouse model. After oral administration of PLGA/PLA-PEG-FA

**Table 2. Previous studies on herbal drugs encapsulated into different nanoparticles**

| Anti-inflammatory drug | Carrier system | Result | Reference |
|---|---|---|---|
| Capsaicin | PLGA/ Polymeric nanoparticles | Sustained effect and target the site of action | 68 |
| Capsaicin | O/W nanoemulsion | Decrease side effect and increases anti-inflammatory activity | 69 |
| colchicine | Calcium carbonate/ metallic nanoparticles | Decrease pro-inflammatory mediators and increase anti-inflammatory activity | 70 |
| Curcumin | Exosomes | Increase stability and target specify | 71 |
| Resveratrol | Eudragit 100/PVA polymeric nanoparticles | Decrease inflammatory cytokines, increase anti-inflammatory activity | 72 |
| Quercetin | Zein nanoparticles | Increase bioavailability and sustained effect | 73 |
| Quercetin | Gold metallic nanoparticles | Increase bioavailability | 62 |

nanoparticles shogaol loaded in a hydrogel system significantly relieves the colitis symptoms and accelerates colitis wound heal in DDS mouse model through regulation of the expression level of pro-inflammatory mediators[28].

Glycyrrhizic acid (GA) is the main active component of licorice it has anti-inflammatory activity through inhibition of NF-κB signaling which is responsible for cytokine expression. GA has extensive first-pass metabolism in the intestine and liver which decreases its bioavailability. So, GA was loaded to PLGA nanoparticles for oral administration and preventing the metabolism of drug[67].

Capsaicin has low bioavailability, this limits its use as anti-inflammatory so encapsulation inside PLGA nanoparticles could be sustained and increased its effect[68].

This review article focuses on the encapsulation of herbal products to overcome their drawbacks and improve their anti-inflammatory activity to be applied clinically.

## CONCLUSION

Nowadays world population moves toward medicinal plants for treating inflammation. A huge number of plants were screened for their anti-inflammatory activity but only a few of them reached clinical trials. The reason mainly due to the solubility and bioavailability problems. Herbal drugs have been encapsulated in nanoparticle form to increase not only the bioavailability of poorly soluble herbals but also to improve tissue distribution to have a sustained delivery protecting them from physicochemical degradation.

### Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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