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ADVANTAGES OF HOMEOPATHIC LICORICE-BASED NANOMEDICINES AS NOVEL THERAPEUTIC MATERIALS

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Abstract. Licorice (Glycyrrhiza glabra L.) is renowned for its traditional medicinal and homeopathic applications against numerous diseases. As the main triterpenoid compound derived from licorice extract, glycyrrhizin (GL) has been identified to possess wide-ranging pharmacological effects. GL is hydrolyzed into its aglycone glycyrrhetinic acid (GA) and glucuronide. In addition, flavonoids such as isoliquiritigenin are found in licorice roots. It is well documented that these active components exhibit great potential as anticancer, anti-inflammatory, hepatoprotective, antimicrobial, and antioxidant agents, in particular. However, their poor water solubility, low bioavailability in biological fluids, and possible cytotoxicities hinder their clinical uses. Nanomedicine has opened a new avenue in this context and augmenting the bioavailability and safety of these herbal drugs can aid in developing suitable agents for clinical application. The current review summarizes recent advances in the production of novel licorice-based nanoformulations for the treatment of different illnesses. Various therapeutic effects have been observed in licorice-based nanomedicines including antibacterial, immuno-modulatory, anti-inflammatory, hepatoprotective, regenerative, and drug delivery. The current manuscripts summarized the role of nanomedicine in enhancing the pharmacological effects of licorice-based beneficial agents by providing targeted delivery of more bioavailable products. The application of nanotechnology in the fabrication of licorice-based products can potentially alleviate most of the pathologies and also reduce the toxicity of therapeutic strategies.

Keywords: *Licorice, Glycyrrhetinic acid, Nanotechnology, Bioavailability.*

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1. Introduction

Glycyrrhiza glabra L. (Fabaceae), generally known as licorice, has been utilized in in homeopathic and ayurvedic systems for the treatment of different types of human disorders such as respiratory diseases, immunodeficiency, skin, liver, cancer, joint, and microbial ailments in the ancient time (Wahab *et al*., 2021). Moreover, various bioactive constituents of this plant such as glycyrrhizin (GL), glycyrrhetinic acid (GA), and isoliquiritigenin perform versatile pharmacological actions (Sharifi-Rad *et al*., 2021). However, several studies have reported the toxicological effects *of G. glabra* extracts

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(Wahab *et al*., 2021). Moreover, low water solubility and bioavailability limit its clinical application (Zhao *et al*., 2021).

Nanotechnology offers distinct advantages in the realm of pharmaceutical and biomedical sciences such as drug delivery, bioimaging, photodynamic therapy, and biosensing since it can provide a platform for more water soluble, biocompatible, safe, and cost-effective drugs and/or equipment (Chung *et al*., 2020; Tang *et al.*, 2020; Zeng, *et al.*, 2020). Several investigations have integrated nanotechnology within small molecule-based nanostructures to plummet the toxicity, increase efficacy, and provide targeted delivery of raw materials within the surface modification of prepared nanomaterials (Gao *et al*., 2019; Lee *et al.*, 2020; Tang *et al.*, 2020). Nanomedicine provides researchers with different formulations such as nanoparticles (NPs), polymeric NPs, lipid nanosystems, dendrimers, micelles, liposomes, nanocrystals, etc. (Low *et al.*, 2021).

Different studies have intended to develop nanoparticles (NPs) of GL, GA, and other constituents of licorice for targeting different human diseases (Chopdey *et al*., 2015, Sun *et al*., 2019; Li *et al*., 2021). Moreover, interest in licorice and its derivatives as a basis for drug delivery systems is reported since they can form intermolecular nanocomplexes for targeted delivery and sustained drug release (Wang *et al*., 2016). Therefore, the current review aims to discuss the use of nanotechnology in the fabrication of novel licorice-made NPs for medical purposes. Also, the use of GL and other licorice components in constructing drug delivery systems has been addressed herein.

2. Licorice-based nanoformulations

The use of licorice and its constituents in nanomedicine is a promising therapeutic approach with useful therapeutic specifications such as anti-inflammatory, anticancer, antioxidant, and antimicrobial as well as it's potential in the prevention and treatment of different human pathologies.

In the following section, the therapeutic applications of licorice-based nanoformulations are discussed. Generally, nanotechnology has offered advantages for the biomedical application of licorice-based active components. Some researchers have used licorice bioactive compounds in the surface modification of nanomaterials to enhance the delivery of conventional drugs in a targeted manner. While some studies have applied nanotechnology to improve the solubility and bioavailability of licorice-derived bioactive compounds and benefited from their therapeutic effects (Figure 1).

3. Anti-cancer effects

3.1. Licorice as a surface modifying agent

The application of nanotechnology to enhance the anti-tumor activity of different synthetic and/or natural compounds has extensively been reported. The majority of research in designing licorice-based nanoformulations is devoted to liver cancer, in which the encapsulation of active components of these plants alone or in combination with other cytotoxic agents has led to a targeted delivery, inhibition of P-glycoproteins (P-gp) as well as macrophage clearance system. GL has been used to encapsulate transferrin-modified piperine by the solvent evaporation method with - 28.0 ± 1.6 mV zeta potential and 112 ± 1.27 nm average particle size of NPs (Li *et al*., 2021). The NPs were internalized rapidly into HepG2 cells by endocytosis within one hour, activated the

apoptotic machinery, and declined mitochondrial membrane potential (Li *et al*., 2021). Also, the *in vivo* results exhibited tumor necrosis induction and up-regulation of pro-apoptotic proteins (Li *et al*., 2021). However, this NP was unable to reduce tumor volume due to the presence of the tumor niche (Li *et al*., 2021).

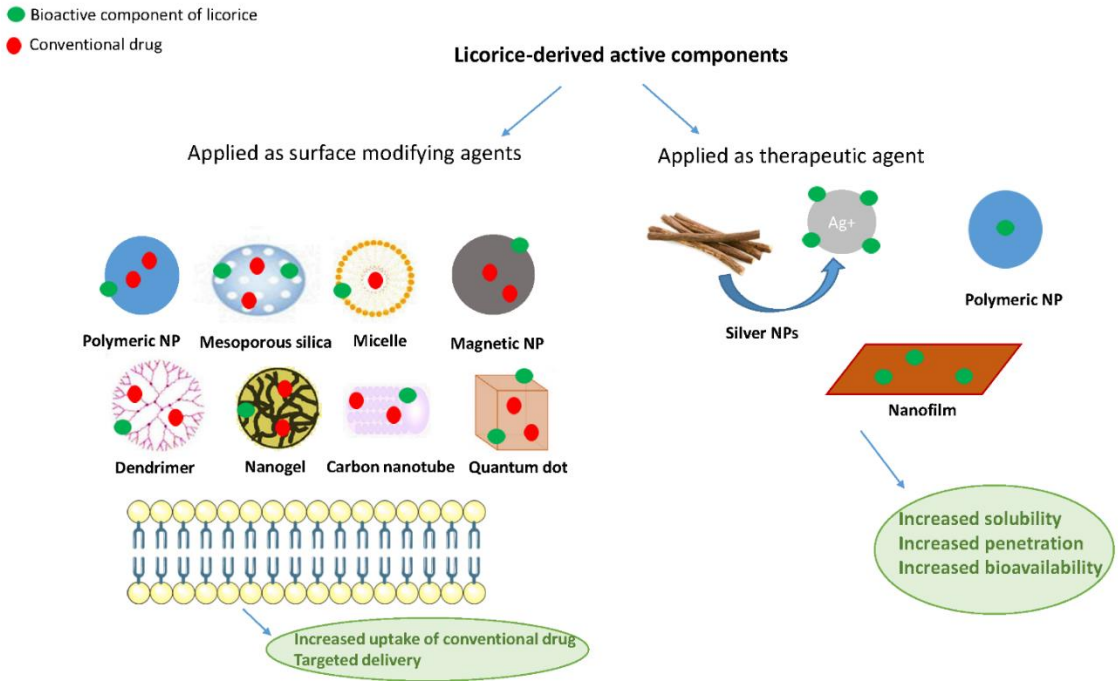

Figure 1. Schematic illustration of licorice-based nanoformulations in biomedical applications. Licorice can be used as an effective bioactive component in designing different nanoformulations as a modyfing agent that increased the pharmacokineticks of the produced nanoparticle. Also, nanotechnoligy can improve poor solubility and bovailibility of licorice when it is used as a therapeutic agent.

In another study, GL-conjugated human serum albumin NPs wrapped with resveratrol NPs were constructed by high-pressure homogenization emulsification for targeting drug delivery in liver cancer (Wu *et al.*, 2017). The mean particle size of NPs using 112.56 µg/mg GL was 108.1 ± 5.3 nm. A continuous slow release of drug from NPs was observed, and GL-conjugated human serum albumin NP wrapping resveratrol NPs showed an increased uptake rate in comparison with pure resveratrol (Wu *et al.*, 2017). Moreover, according to the results of *in vivo* studies in H22 tumor-bearing mice a more effective target orientation toward liver tumors was obtained (Wu *et al.*, 2017). Zu et al. (2013) applied bovine serum albumin (BSA)-coupled GL to encapsulate 10-hydroxycamptotechin (HCPT) for targeted liver tumor delivery and they observed 93.7% drug encapsulation efficiency with a successful wrapping. According to hemolysis analysis, the NPs showed no toxicity and exhibited a slow and continuous release rate. Also, the GL-BSA-HCPT-NPs showed good targeting properties toward hepatocellular carcinoma cells in terms of cellular uptake and proliferation inhibitory effects (Zu *et al*., 2013). GL has been used to enhance the radical scavenging activity of quercetin in the treatment of acute liver injury. For this purpose, GL-incorporated alginate nanogels were prepared. The results showed that these NPs exhibit an 81-fold antioxidant activity (Zhao *et al*., 2021).

The anti-tumor activities of GL have been significantly induced in novel quantum dot (QD) structures (Zhao *et al.,* 2012). Beta-cyclodextrin (β-CD)-conjugated GL-functionalized QDs were synthesized and their anti-tumor effects were evaluated in hepatocarcinoma cells (Zhao *et al*., 2012). These QD-based GL nanostructures entered hepatic cells with better selectivity and induction of irregularities of nuclear shapes, swelling of mitochondria, condensation of peripheral chromatin, plasma membrane blebbing, and generation of apoptotic bodies in TEM images (Zhao *et al*., 2012). Similarly, β-CD/GA-functionalized QDs efficiently prohibited cell growth by an increment of G0/G1 phase arrest and oxidative stress-related mitochondrial malfunction pathway of apoptosis (Zhao *et al*., 2012).

Licorice-based NPs have been reported to deliver both genes and drugs into the tumor region. GA, a hydrolytic product of GL has been used in the construction of nanoformulation against cancer (Tian *et al.,* 2019). For instance, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol-polyetherimide NPs in combination with GA-modified hyaluronic acid have been used for the delivery of Bcl-2 siRNA and doxorubicin into cancerous liver cells (Tian *et al*., 2019). It was shown that the produced NPs were spherical and induced concentration-dependent cytotoxicity in HepG2 cells through concurrent co-delivery of siRNA and doxorubicin into the tumor environment (Tian *et al*., 2019). In Cao et al study, licorice-derived active components were utilized for the delivery of genes into hepatic cells and to enhance their targeting abilities of liver tumors by bypassing entry into lysosomes and through an endocytosis-dependent pathway (Cao *et al.*, 2019).

GL has been utilized to encapsulate ferulic acid as a naturally occurring chemotherapeutic agent (El-Marakby *et al*., 2017). Surface decoration of NPs with GL increased active targeting of ferulic acid *in vitro,* and drug accumulation *in vivo* in the liver (El-Marakby *et al*., 2017). Likewise, GL-modified *O*-carboxymethyl chitosan NPs have increased the targeted delivery of paclitaxel into HCC with biphasic release and 83.7% encapsulation efficiency (Shi *et al.,* 2012). GL-modified *O*-carboxymethyl chitosan NP significantly enhanced the internalization of paclitaxel into SMMC-7721 liver cancer cells and promoted antitumor effects of the drug *in vivo* without any hepatic and/or systemic toxicity (Shi *et al*., 2012). In another study, GL was conjugated with low molecular weight chitosan through an inotropic gelation strategy (Mishra *et al.*, 2014). *In vitro* release tests showed a biphasic pattern of drugs from this carrier and an improved targeted ability was observed *in vivo* (Mishra *et al.,* 2014).

Chopdey et al. (2015) developed GL-conjugated multi-walled carbon nanotubes (GL-MWCNTs) and dendrimers (GL-PPI) for doxorubicin targeted delivery. GL-PPI constructs showed a higher loading of doxorubicin compared to GL-MWCNTs. Decoration of NPs with GL significantly diminished hemolytic toxicity, reduced the IC_{50} of doxorubicin, and resulted in greater apoptosis induction in HepG2 cells (Chopdey *et al.,* 2015).

Another GL-modified chitosan NP was constructed by Lin et al. (2009) by acylation of the amino group of chitosan, and further oxidation of GL. The obtained NPs were spherical with a positive electrical charge and adriamycin association efficiency of 87.5%. According to the biodistribution results, intravenous administration resulted in accumulating concentration in the lung, spleen, and liver of mice, whereas NP concentration showed a downward trend in the kidneys and heart of the animals (Lin *et al.,* 2009). In addition, the liver tissue showed 1.6 times higher levels of adriamycin-

loaded GL-based NPs proposing its preferential distribution in hepatocytes (Lin *et al*., 2009).

3.2. Licorice as an anticancer agent

Our literature search has fetched the use of GA-based nanoformulations against cervical cancer. Aguilar-Rosas and coworkers have developed a mucoadhesive NP system with a prolonged residence time in the vaginal cavity for delivery of GL using poly(methyl vinyl etherco-maleic anhydride) (PVM/MA) *via* solvent displacement method with 198.5 ± 24.3 nm mean particle size and 15.07 ± 0.86 mg/mg polymer loading which could successfully deliver GL into the vaginal cavity (Aguilar-Rosas *et al.*, 2015). Wang et al. developed alginate nanogel particles for simultaneous delivery of GL and doxorubicin, which not only plunges the rapid activated macrophage clearance but also increase the antitumor effects of the aforementioned method in HCC (Wang *et al.*, 2019). Isoliquiritigenin as a flavonoid derivative is also extracted from the root of licorice and has been revealed robust antitumor properties (Qiao *et al*., 2020). However, the poor water solubility of isoliquiritigenin hinders its clinical application (Qiao *et al.*, 2020). It has been shown that isoliquiritigenin nanoformulations can significantly enhance its solubility (Qiao *et al*., 2020). Qiao et al. (2020) have developed isoliquiritigenin nanosuspension using wet media milling with hydroxypropyl cellulose-SSL and polyvinylpyrrolidone-K30 as stabilizers. Both stabilizers showed a higher dissolution rate in comparison with free isoliquiritigenin. Moreover, *in vitro* experiments demonstrated that the constructed nanosuspensions exhibit a higher cellular uptake and lower toxicity in A549 cells (Qiao *et al.*, 2020). Previous studies have shown that bioactive components of natural products are effective on the cancer through mitochondria targeting (Chodari *et al*., 2021) and GA inhibited the mitochondrial enzyme serine hydroxymethyltransferase 2 and limited mitochondrial energy supply of tumor growth (Jin *et al.*, 2022).

3.3. Licorice nanoformulation against radiotherapy induced damages

GL-based nanoformulations not only have been used in the targeted treatment of cancer but also have been useful in protecting against radiotherapy-induced damages. Chandrasekharan et al. developed silver NPs complexed with GL and assessed their radioprotective effects *in vivo* (Chandrasekharan & Nair, 2012). It was exhibited that this GL-encompassed NP can significantly attenuate the gastrointestinal and hematopoietic damages of radiotherapy in mice exposed to a sublethal dose of radiation (4Gy) (Chandrasekharan & Nair, 2012). Additionally, licorice-related NPs have been proposed to be potential opportunities for the treatment of cancer hyperthermia (Saeedi *et al.*, 2017). In this context, iron oxide magnetic nanoparticles (IONPs) have been fabricated using the oxidative precipitation technique and GL was implemented as the coating agent (Saeedi *et al*., 2017). The outcomes indicated that using GL substantially increased the biocompatibility of IONPs confirmed by the MTT assay on the L929 fibroblast cell line. Moreover, the NPs could effectively induce cell death in an *in vitro* hyperthermia process and might be potential cancer treatment options based on hyperthermia (Saeedi *et al*., 2017).

4. Gastrointestinal disorders

Intestinal mucositis as a common side effect of anti-cancer agents is associated with pain, nausea, bloating, vomiting, and diarrhea (Yu *et al.*, 2022). 5-fluorouracil (5-FU) is one of the frequently used chemotherapeutic agents that have been shown to induce intestinal injury by acting by blocking DNA synthesis. It has been shown that 5-FU acts unselectively against fast proliferating cells of intestine mucosa and induces intestinal mucositis by the following steps (Mohamed *et al*., 2021); formation of reactive oxygen species (ROS) and inflammatory response upon DNA strand breakage followed by the release of the pro-inflammatory cytokines and up-regulation of transcription factor (NF-κB), which in turn proceeds to the epithelial and ulceration phase characterized by necrosis and cell death (Basile *et al.*, 2019). The current treatment options only alleviate harmful unwanted effects of mucositis induced by 5-FU (Atiq *et al.*, 2019). Therefore, the research is focused on identifying novel treatment strategies in particular using herbal products (Endo *et al.*, 2022). GL has been proposed as a potential natural agent against chemotherapy-induced mucositis. However, its low bioavailability hinders the prominent therapeutic properties due to the extensive first-pass effect (Ploeger *et al.*, 2000). In this context, GL-PLGA NPs have been developed by double emulsion technique and tested *in vivo*. Seven days of administration of GL-PLGA NPs could substantially diminish the severity of mucositis which was confirmed with histological and biochemical analysis (Zeeshan *et al*., 2021).

In addition, inflammatory conditions in the intestine and colorectal region demand novel drug delivery routes to pass the acidic environment of the stomach. Budesonide containing amino cellulose-conjugated polycaprolactone was covered onto GL-loaded gelatinous NPs (Ahmad *et al*., 2021). The prepared NPs were spherical and the mean particle size was around 230 nm which could significantly reduce the infiltration of mast cells in the colon, maintained mucin protection, and attenuated the level of pro-inflammatory cytokine (Ahmad *et al*., 2021).

Wu et al. used colon-targeted adhesion core-shell NPs by applying FA-Zein as the core and as the shell to improve the bioavailability of GL, which could be applied in ulcerative colitis (Wu *et al.*, 2021). The structure of these NPs helped in the preservation of GL in the stomach and its release in the colon. DSS-induced ulcerative colitis mouse model showed that GL NPs exhibit higher adhesion in the colon and prohibit the inflammatory cascade (Wu *et al.*, 2021).

In another study, Glycyrrhizae Radix et Rhizoma has been used to prepare carbon dots to treat GI ulceration in mice models of acute alcoholic gastric ulcers (Liu *et al*., 2021). Small spherical NPs (2-10 nm) with no toxicity were prepared which could significantly ameliorate ROS formation and restored the levels of superoxide dismutase (SOD) and nitric oxide (NO) in serum and tissue samples of the animals (Liu *et al*., 2021).

Currently, available oral therapies are not also very useful in treating other GI disorders such as inflammatory bowel disease (IBD) (Kaplan *et al.*, 2021). This is due to inadequate control in the induction and maintenance of the state of remission as well as the relief of symptomatic types of diseases. Zeeshan et al. (2019) developed GL-containing EudragitR S100/poly-(lactic-co-glycolic acid) NPs *via* an improved double-emulsion evaporation technique combined with solvent evaporation coating methods. The fabricated pH-sensitive nanoformulation showed a particle size of 200 nm with a high encapsulation efficacy and sustained drug release capability. The effect of this GL-loaded NP in inflamed colon tissue was investigated and GL-containing EudragitR S100/poly-

(lactic-co-glycolic acid). NPs were shown to decrease free radicals and prevent the release of inflammatory cytokines confirmed by microscopic analysis (Zeeshan *et al*., 2019).

5. Antimicrobial effects

Antimicrobial effects of licorice have been reported against different types of microorganisms (Nirmala & Selvaraj, 2011). Moreover, licorice extracts have been applied as different types of nanoformulations in this context. Roque et al. incorporated the ethanolic extract of licorice into mucoadhesive NPS including PLA, PLGA, and alginate, and subsequently used them as oral gel, film, and toothpaste (Roque *et al*., 2018). NPs with the size of 100-900 nm were prepared and exhibited high encapsulation efficacy. Besides, *in vitro* studies indicated that extract-loaded oral film, followed by extract-loaded alginate toothpaste, displayed the highest inhibitory effects against oral candidiasis (Roque *et al.*, 2018). In another study, Ag NPs were synthesized from licorice polysaccharides (GP) derived from the root and stem of licorice (Cai *et al*., 2019). The resultant GP-stabilized Ag NPs were incorporated into a biopolymeric film of curdlan and assessed for a potential antibacterial effect (Cai *et al*., 2019). The results indicated that produced nanocomposites were revealed to possess a significant antibacterial effect confirmed by images of the inhibition rings after plating (Cai *et al*., 2019). This antibacterial effect of licorice-based NPs has also been used in designing novel vaccines against gram-negative bacteria, which secret outer membrane vesicles (OMVs) as spherical nanostructured proteolipids (Cai *et al*., 2019). Although OMVs have immunostimulatory effects, their poor size homogeneity and low structural stability restrict their use in clinical applications (Cai, Dai et al. 2019). Huang et al. developed a stable OMV vaccine by coating self-assembled GL NPs with OMVs (Huang *et al*., 2022). The produced nanovaccine efficiently entered into the macrophages through micropinocytosis-mediated and clathrin-dependent endocytotic pathways and stimulated cell growth, cytokine secretion, and M1 polarization. Moreover, this novel vaccine exerts higher forms of *Bordetella bronchiseptica* (Bb)-specific antibody, and thus higher proliferation of lymphocytes (Huang, Nan et al. 2022). In addition, a higher ratio of CD4+/CD8+ T cells and CD19+ B cells were obtained from animals, whose splenic lymphocytes were immunized with the aforementioned vaccine (Huang *et al*., 2022). As a result, higher levels of Th1/Th2/Th17 cytokines were produced (Huang *et al*., 2022). Licochalcone A, derived from licorice, has been utilized in the preparation of solid lipid NPs for their potential effects against schistosoma infection (Silva *et al.*, 2021). NPs were prepared *via* the encapsulation of licochalcone A in SLNs by a modified shear homogenization technique. The resultant NPs exhibited high encapsulation efficacy, dispersity, and satisfactory particle size. The use of SLNs substantially reduced the cytotoxicity and hemolytic specifications of licochalcone A, while *in vivo* tests showed the effectiveness of these SLNs against *S. mansoni* (Silva *et al*., 2021).

The use of licorice-based NPs in the possible treatment of COVID-19 was also recently introduced. Zhao et al. developed GL NPs *via* the hydrothermal method and coated them with PEG-Cy5. (Zhao *et al*., 2021). The results of *in vitro* studies showed that GL NPs prohibit the growth of the murine coronavirus mouse hepatitis virus A59 (MHV-A59) and thus attenuate the further release of the pro-inflammatory cytokines (Zhao *et al.*, 2021). Mounting evidence demonstrates the association of different pathological events such as hepatitis, thymic degeneration, autoimmune hepatitis-like disorders, transient demyelination, and hyperglobulinemia following MHV-A59

infection (De Albuquerque *et al*., 2006). Moreover, MHV-A59 can also affect the respiratory tract and lung tissues and cause an acute inflammatory response similar to SARS-CoV (Yang *et al.*, 2014). Therefore, different studies have proposed that MHV-A59 might be a suitable alternative model for SARS-CoV-2 (Guo *et al*., 2021). On the other hand, GL NPs have shown anti-inflammatory and antiviral effects and have significantly reduced organ damage *in vivo*. In the study of Zhao et al. (2021) an amino bond attached Cy5-labeled PEG to the surface of GL NPs. The produced NP was injected into the tail vein of MHV-A59-infected animals. Infected mice showed an intense fluorescence in the lung, kidneys, and livers indicating a higher likelihood of the preferential distribution of GL NPS to these tissues (Zhao *et al*., 2021). Also, the treatment of animals with GL NPS significantly prohibited the release of pro-inflammatory cytokines (Figure 3) (Zhao *et al.*, 2021).

6. Anti-inflammatory effects

Licorice-derived active components have shown anti-inflammatory effects in different tissues (Ma *et al*., 2013). In addition, the application of novel delivery systems can enhance the effectiveness of these compounds. For instance, subcutaneous injection of house dust-containing liposomes could significantly plummet the severity of symptoms in patients with bronchial asthma (Basomba *et al.*, 2002) or T-cell epitope-containing nanoemulsions substantially alters the level of IgE in a downward trend (Kitaoka *et al.*, 2015). GL has been shown to exert anti-inflammatory effects in the nasal mucosa and diminish the generation of pro-inflammatory cytokines and GL micelles have been successfully utilized in the induction of cellular immune response which can be used for allergen-specific immunotherapy (Pashkina *et al.*, 2021).

In another study, GL was loaded into PLGA NPs and its effects were assessed in allergic asthma *in vivo* (Chen *et al.*, 2022). The prepared NPs could release 67% of loaded GL after 10 hours and could significantly inhibit the release of inflammatory cytokines, *i.e.* interleukin (IL)-4, IL-5, IL-13, and IL-25, and reduce cellular hyperplasia, hypersecretion of mucus, and eosinophilic inflammation (Chen *et al.*, 2022). Additionally, GL dendrimer micelles have shown robust anti-inflammatory effects in acute lung injury (Choi *et al.*, 2021). In this study, cholesterol-conjugated histidine- and arginine-grafted polyamidoamine (PamHR) in combination with GL has been developed. GL not only acts as an anti-inflammatory agent but also facilitates intracellular gene delivery (*e.g.* the heme oxygenase-1 (HO-1) gene) (Choi *et al*., 2021). This might be due to the membrane-destabilizing effects of GL and the interaction of GL with its receptors (Choi *et al*., 2021). Moreover, in the lipopolysaccharide-exposed murine macrophage-like cell line, the aforementioned micelle decreased the level of tumor necrosis factor-α which proposes its potential as an anti-inflammatory effect (Wang *et al.*, 2013).

Core-shell nanocarriers for the simultaneous delivery of GL and budesonide against rheumatoid arthritis have been developed (Ansari *et al*., 2021). In this study, GL-loaded gelatin NPs were constructed and coated with budesonide-encapsulated amino cellulose-grafted polycaprolactone (PCL-AC), which resulted in the formation of 200 nm NPs (Ansari *et al*., 2021). The *in vivo* test results indicated that GL-containing NPs noticeably reduce joint swelling and erythema, attenuate bone erosion, inhibit collagen destruction, and restore the articular structure. Furthermore, NPs ameliorated the levels of inflammatory biomarkers including IL-1β, TNF-α, iNOS, and COX-2 (Ansari *et al.*, 2021).

GL has been loaded into polycationic chitosan and polyanionic gum katira prepared by the ionic complexation technique (Bernela *et al*., 2016). Then, *in vivo* bioavailability test showed an enhanced anti-inflammatory effect of the produced encapsulated GL in katira/chitosan gum NPs against paw inflammation of rats exposed to carrageenan. Also, drug release tests showed that GL was released from the NPs *via* zero-order kinetics with the mechanism of release being a combination of diffusion and erosion of the polymer matrix (Bernela *et al.*, 2016).

7. Wound healing effects

Despite extensive research in developing different pharmaceutical compounds in this context, optimal effects are not usually observed due to the complexity of this multifaceted evolutionary process (Boateng *et al*., 2008). Advances in nanotechnology have been applied in promoting the wound healing efficiency of different synthetic and natural agents. Licorice extracts have been used in the construction of phenytoin-loaded copper NPs as monodispersed particles with a cubic and hexagonal morphology (Saddik *et al*., 2020). The results of the assay and the analysis of the maximum loaded monolayer capacity explained the adsorption mechanism of phenytoin on the surface of copper NPs. Stimulated epidermal regeneration and accelerated granulation and tissue formation were observed following the implementation of NPs in an excisional wound model in rats while the level of inflammatory markers was diminished. Moreover, the kinetic assessment showed that the adsorption reaction subsequent to the pseudo-second order whereas the thermodynamic markers showed that the adsorption procedure was endothermic and physical in nature, and happened instinctively (Saddik *et al*., 2020). Hou et al. (2021) investigated the possibility of targeting the signaling pathway of the high mobility group box 1 *via* a licorice-based solution to treat diabetic keratopathy. For this purpose, a genistein-encapsulated dipotassium glycyrrhizinate-based micelle ophthalmic solution was prepared and optimized with a mean particle size of 29.50 ± 2.05 nm, and encapsulation efficiency of 98.96 ± 0.82%. Acceptable ocular tolerance and high corneal permeation, as well as antioxidant effects, were achieved *in vivo* (Hou *et al*., 2021). Also, ocular re-epithelization and nerve regeneration were observed after ocular topical administration in association with down-regulation of the high mobility group box 1 and its receptors advanced glycation end products and toll-like receptor 4 as well as inflammatory factors, i.e. IL-6 and IL-1β (Hou *et al.*, 2021). In another study, a hybrid nnanoscafold was prepared using licorice extract and PVA/collagen by co-axial electrospinning method. The produced nanoscaffolds had a diameter of 119-154 nm with ideal moisture management properties. Also, *in vitro* antibacterial and *in vivo* wound healing assessment revealed acceptable antibacterial and healing performance (Hasan & Shahid, 2022). In a similar study, licorice/collagen/chitosan/PVA nanofibrous mat with enhanced wound healing and antibacterial effects was developed (Shahid *et al*., 2022).

8. Other human diseases

Bone tissue regeneration has been reported using nanoformulation synthesized from licorice-based active components (Sun *et al.*, 2019). It has been shown that isoliquiritigenin-encapsulated mesoporous silica NPs inhibited osteoclast-related bone loss through their effective bone-bioresponsive systems (Sun *et al.*, 2019). Through inhibition of receptor activator of nuclear factor-κB ligand (RANKL)-induced osteoclast

formation attenuates osteolytic capacity, which in turn decreases RANKL-stimulated expression of phosphorylation of mitogen-activated protein kinases, activator protein (AP)-1 component c-Fos, and tumor necrosis factor receptor-associated factor 6 *(Sun et al*., 2019). Also, *in vivo* tests showed that isoliquiritigenin-encapsulated mesoporous silica NPs relieve inflammation-mediated calvarial bone damage (Sun *et al.*, 2019). Similarly, GL and calcium-containing NPs have been shown to reduce osteoporosis in steroid-resistant nephrotic syndrome patients who receive long-term glucocorticoids (Sun *et al.*, 2019). Mesoporous silica NPs have been used to deliver lysine to hepatocytes, while the use of GL significantly increases this targeting (Hou *et al*., 2020). Also, GL has been applied to reduce the side effects of treatment options currently used in alopecia. One of these therapeutic agents is baicalin, a plant-derived bioactive compound. However, its poor water solubility and unstable log P value limit its topical administration as a hair growth-promoting agent. GL-baicalin has successfully increased cellular uptake, topical penetration, and accumulation of baicalin in the skin in vivo (Zeng *et al.*, 2022).

One study has also investigated the effects of GL NPs for their possible anti-hyperglycemic potency in diabetes type II *in vivo* (Rani *et al*., 2017). For this purpose, chitosan and gum arabic were used to produce GL NPs by the ionotropic gelation method. The 3^2 factorial method was used to achieve minimum particle size as well as the highest encapsulation efficiency (Rani *et al.*, 2017).

9. The role of nanotechnology in improving the pharmacokinetics of licorice-based compounds

Although GL is an important saponin-derivative component, it has a low impermeability across the gastrointestinal mucosa and thus exhibits a relatively low bioavailability (Leite *et al*., 2022). Nanotechnology-assisted strategies have been applied to overcome these limitations. GL has been used to encapsulate thymol in ophthalmic solution nanomicelle *via* a film dispersion technique (Song *et al*., 2020). The produced nanoformulations showed high physical stability after 12 weeks and a significantly improved steady-state flux and permeability coefficient as pharmacokinetic parameters. Moreover, the nanomicelle system noticeably enhanced ocular tissue absorption of ophthalmic solution and thus its therapeutic efficacy. In other work, the liposomes of licochalcone A as an important component of licorice were produced using the thin-film dispersion method (Liu *et al.*, 2022). It was reported that the dissolution performance and blood/tissues bioavailability of licochalcone A loaded liposome was significantly higher than that of licochalcone A according to *in vitro* and *in vivo* analysis respectively *(Liu et al*., 2022). In addition, licorice nanoformulation has been utilized to increase the cumulative release and tissue distribution of licorice chalcone A in different organs and plummet the liver toxicity of the drug by improvement in superoxide dismutase and L-Glutathione levels (Yang *et al.*, 2022). In a study conducted by Quan et al. (2021) 18β-glycyrrhetinic acid as an active component of licorice was used to prepare 18β-glycyrrhetinic acid nanocrystals under high-pressure homogenization. Glycyrrhetinic acid nanocrystals showed high drug solubility with a reduction of particle size and increased *in vivo* dermal permeability in mouse skin and Franz diffusion vertical cells. Therefore, the implementation of nanotechnology will improve the pharmacokinetic parameters of licorice and its constituents. Table 1 summarizes the use of nanotechnology in the preparation of licorice-derived nanoformulations.

Table 1. Licorice-based nanoformulations in biomedical applications

Nanomaterial	**Approach**	**Result**	**Animal model/cell line**	**Reference**
Nanoparticle (NP)	GL was used to encapsulate transferrin-modified piperine	In vitro and in vivo anti-tumor effects/ induction of apoptosis and mitochondrial collapse in liver cancer	HepG2 cell line/ 4T1 tumor-bearing mouse model	(Li *et al.*, 2021)
Nanogel	GL-mediated liver-targeted alginate nanogels for quercetin delivery	Enhancing the antioxidant and anti-inflammatory effects of quercetin in acute liver injury	HepG2 cell line	(Zhao *et al*., 2021)
Nanosuspension	Encapsulation of isoliquiritigenin	Increased solubility of isoliquiritigenin, higher cellular uptake, and lower toxicity in	A549 lung cancer cells	(Qiao *et al.*, 2020)
Carbon nanotubes	GL-conjugated multi-walled carbon nanotubes and dendrimers for targeted delivery of doxorubicin	Higher loading of doxorubicin, lower hemolytic toxicity, reduced the IC_{50} of the drug	HepG2 cell line	(Chopdey *et al*., 2015)
Nanoparticle	Vaginal delivery of GL using poly(methyl vinyl etherco-maleic anhydride)	Successful delivery of GL into the vaginal cavity	in vitro pig mucin	(Aguilar-Rosas *et al.*, 2015).
Nanoparticle	GL-containing sliver NPs	Exerted radioprotective effects	Swiss albino mice	(Chandrasekharan & Nair 2012)
Nanoparticle	GL- poly(lactic-co-glycolic acid) PLGA NPs	Increased bioavailability of GL, in vivo attenuation of mucositis	Rat	(Zeeshan *et al*., 2021)
Nanoparticle	Budesonide encapsulation in amino cellulose-conjugated polycaprolactone covered onto GL-loaded gelatinous NPs	Reduced infiltration of mast cells in the colon, mucin protection, and diminished level of proinflammatory cytokine	Rat	(Ahmad *et al.*, 2021)
Nanoparticle	GL-containing core-shell NPs by applying FA-Zein as the core	Increased colon-targeted adhesion, improved bioavailability of GL	Raw 264.7 and NCM 460 cells	(Wu *et al.*, 2021)
Carbon dots	Carbon dot prepared from Glycyrrhizae Radix et Rhizoma	Decreased ROS formation and restored levels of superoxide dismutase (SOD) and nitric oxide (NO) in acute alcoholic gastric ulcer in vivo	RAW264.7 cells/ Mice model of gastric cancer	(Liu *et al.*, 2021)
Nanoparticle	Licochalcone A-containing solid lipid NPs	Antimicrobial effects against Schistosoma infection, and *S. mansoni*	Schistosoma mansoni/Mice	(Silva *et al*., 2021)

Nanoparticle	PEG-Cy5-coated GL NPs	Blockade of the growth of the murine coronavirus mouse hepatitis virus A59 (MHV-A59) and attenuated release of the pro-inflammatory cytokines	Murine coronavirus mouse hepatitis virus A59	(Zhao *et al.*, 2021)
Nanoparticle	GL loaded PLGA NPs	Inhibited release of inflammatory cytokines, reduced cellular hyperplasia, hypersecretion of mucus, and eosinophilic inflammation	Female BALB/c mice	(Chen *et al.*, 2022)
Nanoparticle	GL-containing cholesterol-conjugated histidine- and arginine-grafted polyamidoamine	Increased anti-inflammatory effects, delivery of heme oxygenase-1 gene	Lipopolysaccharide-activated Raw264.7 cells	(Choi *et al.*, 2021)
Nanoparticle	GL-loaded gelatin NPs coated with budesonide-encapsulated amino cellulose-grafted polycaprolactone	Reduce joint swelling and erythema, attenuated bone erosion, inhibited collagen destruction, and restored articular structure in vivo	Rat	(Ansari *et al.*, 2021)
Nanoparticle	GL loaded into polycationic chitosan and polyanionic gum katira	Anti-inflammatory effects against carrageenan-induced hind paw inflammation in vivo	Rat	(Bernela et al., 2016)
Nanoparticle	Licorice extracts-containing phenytoin-loaded copper NPs	Wound healing effects by increasing the expression of dermal procollagen type-I and decreasing the level of inflammatory markers	Rat	(Saddik et al., 2020)
Nanomicelle	Genistein-encapsulated dipotassium glycyrrhizinate-based micelle	Ocular re-epithelization and nerve regeneration in association with down-regulation of HMGB1 and its receptors RAGE and TLR4 as well as inflammatory factors in diabetic keratopathy	Mice	(Hou et al., 2021)
Nanoparticle	Isoliquiritigenin-encapsulated mesoporous silica NPs	Prevention of osteoclast-mediated bone loss through inhibition of receptor activator of nuclear factor-κB ligand (RANKL)-induced osteoclast formation, and attenuated osteolytic capacity of osteoclasts *in vitro*	Mouse primary bone marrow-derived macrophages/rat	(Sun et al., 2019)

Nanoparticle	GL-conjugated mesoporous silica and chitosan NPs	Increased hepatocyte targeting	Hepatocyte cultures	(Hou et al., 2020)
Nanomicelle	Baicalin-encapsulated GL NPs	Increased cellular uptake, improved penetration, and accumulation of baicalin- in the porcine skin predominantly through the hair follicles pathways	Porcine skin	(Zeng et al., 2022)

10. Conclusion

The current manuscripts summarized the role of nanotechnology in enhancing the pharmacological effects of licorice-based therapeutic agents by providing targeted delivery of more bioavailable products. Also, this review provides some ideas for novel effective, and low-toxicity therapeutic strategies that can be readily manufactured using nanotechnology. However, it should be mentioned that further studies are required to validate the possible clinical application of licorice nanoformulations.

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