Sanshita et al. Scr Med. 2024 Nov-Dec;55(6):755-72. DOI:10.5937/scriptamed55-52024

REVIEW ARTICLE

Therapeutic Applications of Novel Drug Delivery Systems of Liquorice: An Updated Review on Recent Advancements

Sanshita,[1] Ayushi Taneja,[1] Tanikan Sangnim,[2] Kampanart Huanbutta,[3] Rakesh K Sindhu,[4] Inderbir Singh[1]

Abstract

In recent times, individuals are focusing more on natural substances, primarily due to their safety and non-toxicity. Also, there is an increasing demand by industries for the phytoconstituents that might be incorporated in pharmaceuticals, cosmetics, dietary products and nutraceuticals. Liquorice is one of the widely used Chinese herb since ancient times due to its medicinal properties. It exhibits broad spectrum biological activities such as anti-inflammatory, immunomodulatory, anti-oxidant, anti-cancer, anti-diabetic, anti-microbial properties and is used in the treatment of different diseases such as cancer, inflammation, viral infections, cardiovascular and respiratory disorders. Different novel formulations such as nanoparticles, microparticles, liposomes, nanomicells and self-emulsifying drug delivery system are developed that overcome major limitations of liquorice including its low solubility, stability and less bioavailability. In this review, liquorice's historical background, pharmacokinetics, therapeutic applications, different mechanism of actions is discussed with major emphasis on liquorice encapsulated novel formulations (nanoparticles, nanomicelles, liposomes, niosomes, microparticles, microspheres, self-nanoemulsifying system, self-micro-emulsifying system). Liquorice, a prominent constituent of different dietary products, has aroused the interest of many researchers because of its anti-proliferative capacity, tumour microenvironment manipulation and autophagy activation in numerous cancer types. Nanotechnology-based techniques for enhanced solubilisation, stability and targeted drug delivery have been tested by formulation scientists. Liquorice is enclosed in different novel carriers and encapsulated liquorice displayed enhanced stability, solubility, high encapsulation efficiency, controlled drug release and extended circulation time period.

Key words: *Glycyrrhiza*; Liquorice; Applications; Nanoparticles; Liposomes.

1. Chitkara College of Pharmacy, Chitkara University, Punjab, India.
2. Faculty of Pharmaceutical Sciences, Burapha University, Chonburi, Thailand.
3. Department of Manufacturing Pharmacy, College of Pharmacy, Rangsit University, Pathum Thani, Thailand.
4. School of Pharmacy, Sharda University, Greater Noida, Uttar Pradesh, India.

Citation:
Sanshita, Taneja A, Sangnim T, Huanbutta K, Sindhu RK, Singh I. Therapeutic applications of novel drug delivery systems of liquorice: an updated review on recent advancements. Scr Med. 2024 Nov-Dec;55(6):755-72.

Corresponding author:
INDERBIR SINGH
E: inderbir.singh@chitkara.edu.in

Received: 6 July 2024
Revision received: 29 August 2024
Accepted: 29 August 2024

Introduction

Liquorice (*Glycyrrhiza glabra*) is a sweet and calming herb of a *Fabaceae* family and is widely used from the ancient times in pharmaceutical industries due to its extensive therapeutic applications. Primarily, this herb is from the Mediterranean region, but is also found in China, India, Italy, Spain and Russia. The name *Glycyrrhiza* is originated from the two Greek words "glykos" means sweet and "rhiza" means root.[1] Its chemical formula and molecular weight are $C_{42}H_{62}O_{16}$

and 822.942 g/mol, respectively. Figure 1 represents different constituents of liquorice. Glycyrrhizic acid, liquiritin and isoliquiritin are its major biologically active constituents. It is the most economically valuable herb, having a variety of uses in food supplements, pharmaceuticals, tobacco and cosmetics. *G glabra* is an essential and effective herb that reduces toxicity and increases the therapeutic efficacy when used in combination with other medicinal herbs.[2, 3] It is a rich source of proteins, sugars, polysaccharides, mineral salts, amino acids, starch, gums, sterols, resins and is well-known for its anti-inflammatory, antibacterial, antiviral,[4] antioxidant, expectorant effects[5, 6] also useful for liver detoxification and protection.[7] Liquorice exhibit significant anticancer, anti-depressive, neuroprotective, myocardial cell protecting and detoxification actions. There has been no reported toxicity of liquorice and its constituents so far. But certain adverse effects are documented due to use of high doses over a long time period which leads to serious health illnesses. Nevertheless, this herb can be used for therapeutic purpose in small doses for treating significant ailments and there are no harmful effects.[8]

Various technologies such as acidification-induced precipitation, chromatographic separation (HPLC) and adsorption are used to separate bio-active constituents from liquorice extract. But all these extraction techniques are expensive, having low recovery rate and are time consuming.[9]

Pharmacokinetics

After administration of liquorice and its constituents by oral route, intestinal bacteria having ß-glucuronidase moiety hydrolysed the glycyrrhizic acid (a major constituent of liquorice) to glycyrrhetic acid, which undergoes rapid absorption and is transported readily to the liver by the carrier molecules.[10] It is converted to glucuronide and sulphate conjugates in the liver and then re-hydrolysed to form glycyrrhetic acid. Afterwards, the subsequent reabsorption of glycyrrhetic acid takes place, which results in a substantial delay in plasma terminal clearance.[11] After oral consumption of 100 mg glycyrrhizin in healthier subjects, it was partially absorbed in native form in the intestine and was not observed in plasma, but < 200 ng/mL glycyrrhetic acid was detected in plasma and also minor amount of glycyrrhizin was found in urine.[12]

Therapeutic applications

Liquorice root has been used for the prevention and treatment of different diseases of respiratory, urogenital, cardiovascular and respiratory system, also used for treating skin and eye disorders. It exhibits anti-inflammatory, anti-microbial, anti-tussive, anti-diabetic, antioxidant, anti- rheumatic,[13, 14] immunomodulator, anti-cancer, demulcent and expectorant properties.[15, 16] Liquorice is extensively used to treat chronic cough, asthma and bronchitis. Also effective in depression, Addison's disease, peptic ulcer, rheumatic pain, cancer

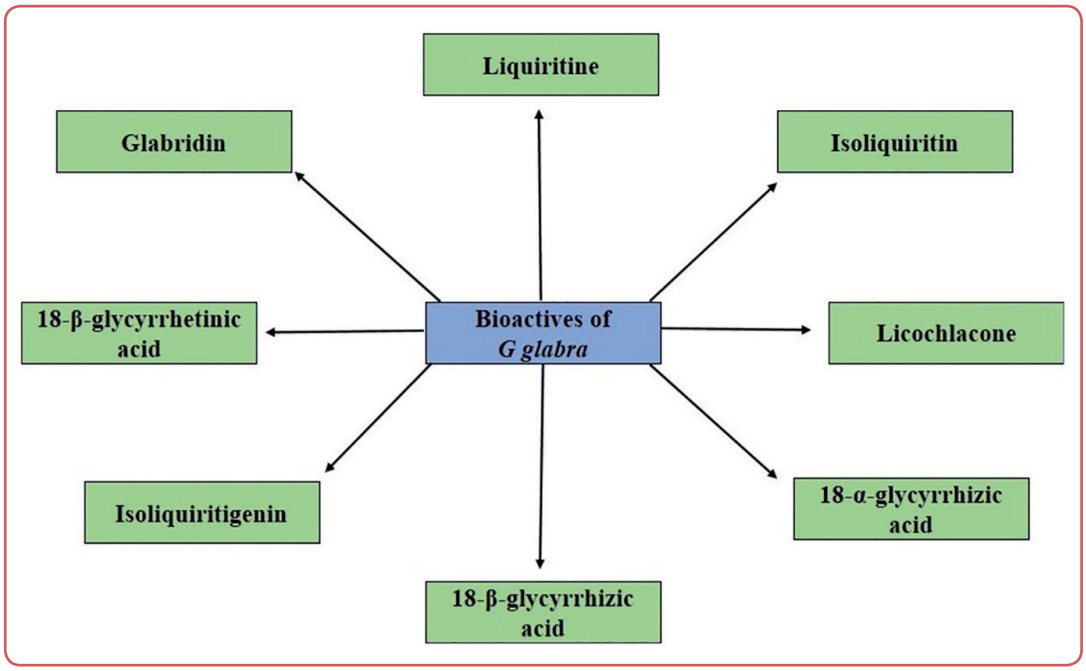

Figure 1: Different constituents of Glycyrrhiza glabra

prevention, in treating inflammatory disorders and mouth ulcers.[17] Its flavonoids are used in treatment of pulmonary inflammation as they reduce the expression of TNF-α, mRNA, elevates water content in lungs and inhibits the inflammatory release mediators. Liquiritin (a major constituent of liquorice) is an anti-tussive agent, provides quick relief from cold, cough and other respiratory infections. It is a cost-effective immunomodulatory agent, boosts macrophages action and stimulates phagocytosis rate, also exhibits anti-influenza activity by blocking viral replication and by acting on neuraminidase enzyme.[14]

G glabra elevates IgA, IgG and IgM antibodies level in blood serum, promotes T-cell expression, up-regulates IL-7, IL-2, IL-6 and anti-tumour cytokines level in serum.[18, 19] The active constituents of *G glabra* show positive results to treat the patients suffering from COVID-19 infection and reduces their hospitalisation rate by preventing the replication, penetration, adsorption of virus and by protecting the lungs from adverse effect of virus infection.[17, 20] The various chemical constituents of different liquorice extracts along with their primary functions are presented in Table 1.

Table 1: Common constituents of liquorice

Constituent	Category	Primary function / property	Ref
Glycyrrhizin	Saponin	Sweetener, anti-inflammatory, anti-viral, hepatoprotective	21
Liquiritin	Flavonoid	Anti-inflammatory, antioxidant	22
Isoliquiritigenin	Chalcone (Flavonoid)	Antioxidant, antitumour, anti-inflammatory	23
Glabridin	Isoflavonoid	Antioxidant, skin-whitening, anti-inflammatory	24
Liquiritigenin	Flavanone	Phytoestrogenic, antioxidant	25
Glycyrrhetinic acid	Triterpenoid	Anti-ulcer, anti-inflammatory, antiviral	26
Formononetin	Isoflavone	Antioxidant, anticancer	27
Coumarins	Phenolic compounds	Antimicrobial, anticoagulant	28
Polysaccharides	Carbohydrates	Immune-modulating, anti-inflammatory	29
Stilbenoids	Phenolic compounds	Antioxidant, anti-inflammatory	30
Tannins	Polyphenolic compounds	Astringent, antioxidant	31

Mechanism of action of liquorice

Mechanism of liquorice in viral infections

Liquorice exhibits potent anti-inflammatory action by reducing the level of free radicals, TNF, prostaglandins (PGE-2), by inhibiting the activation of p38, ERK, JNK genes and by blocking the phosphorylation of IkBα (involved in regulation of NF-kβ, a protein transcription factor that behaves as a central inflammatory mediator). It also limits the release of pro-inflammatory cytokines by blocking the LPS (lipopolysaccharides)-induced IL-8, IL-1β, IL-6 responses and TNF-α associated responses of macrophages.[17] Figure 2 shows the mechanism of action of liquorice in treating microbial/viral infections. External injury such as virus attack leads to production of pro-inflammatory mediators including interleukins, prostaglandins, which result in generation of inflammatory responses by the body that ultimately causes disturbances of homeostasis. Liquorice and its active constituents inhibit the release of inflammatory mediators and block the inflammatory responses, thus providing protection from microbial infections such as viral infections and COVID-19.

Antioxidant and anti-inflammatory mechanism of liquorice

The phenolic content of *G glabra* is mainly responsible for its antioxidant activity. It shows a strong DPPH radical scavenging effect and inhibits lipid peroxidation. These phenolic groups are highly effective in protecting the body cells or tissues from oxidative stress and also regulates skin homeostasis, thus provide protection from various skin damages. Figure 3 depicts anti-inflammatory and antioxidant mechanisms of liquorice flavonoids. It shows antioxidant effect by inhibiting nitric oxide synthase and COX-2 enzymes, hence results in reduced nitric oxide production, inhibits interleukins, block the generation of reactive oxygen species and protect the body cells from harmful effects of free radicals. It exhibits anti-inflammatory effect by reducing the level of prostaglandins, interleukins and other inflammatory pathways/mediators including MAP3Ks1.

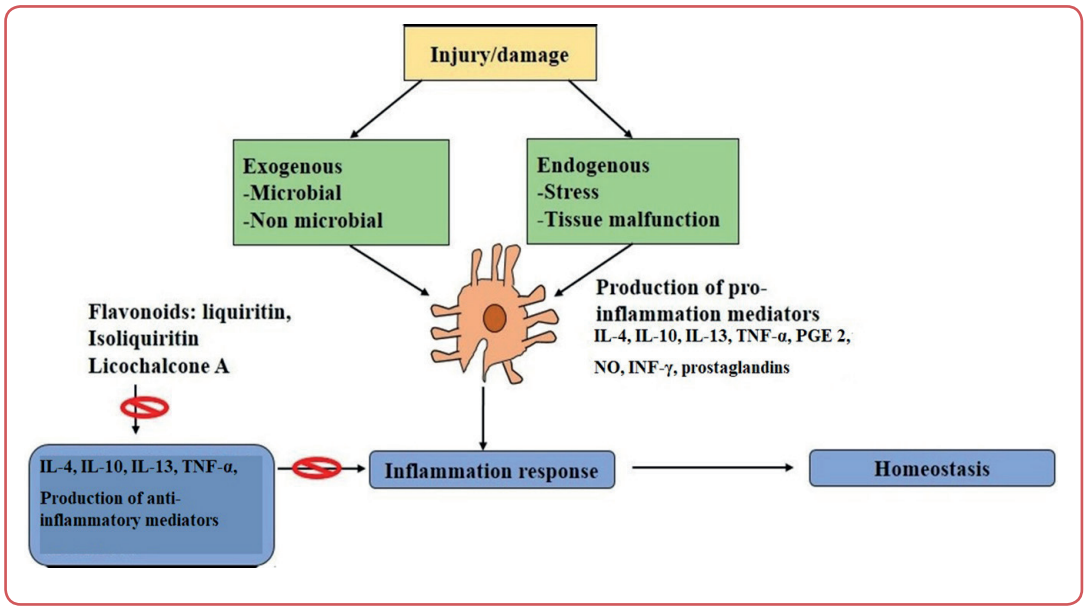

Figure 2: *Mechanism of liquorice in microbial/viral infection*

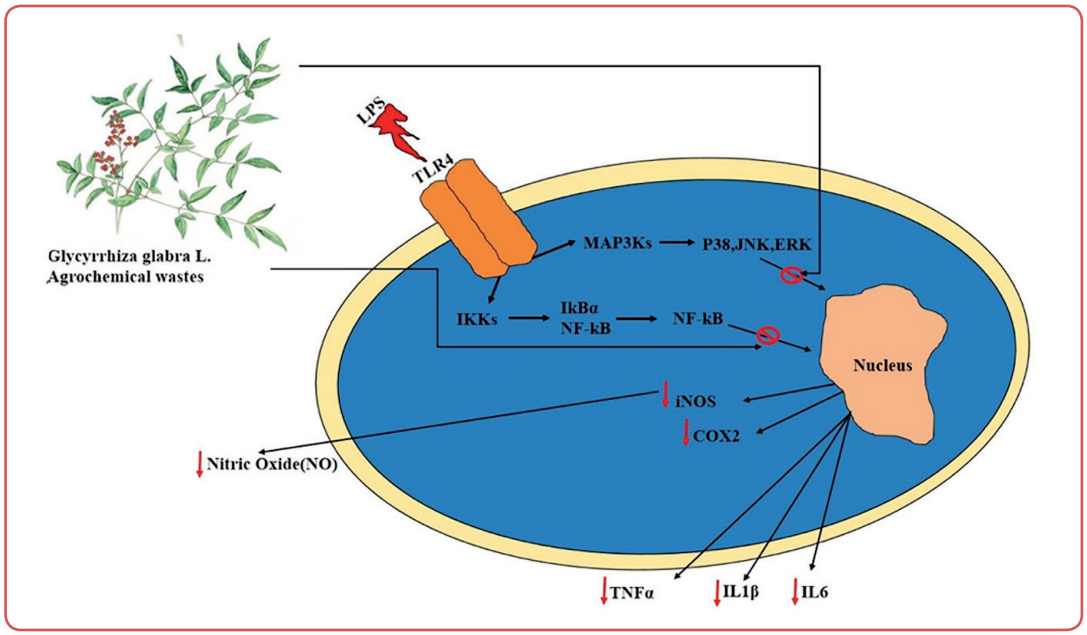

Figure 3: *Antioxidant and anti-inflammatory mechanisms of liquorice flavonoids*

Antidiabetic mechanism of liquorice

Liquorice possesses a significant anti-diabetic action by various mechanisms including regulation of multiple signalling pathways such as PI3K/Akt, AMPK, MAPK, NF-kB and NLRP3, increases the sensitivity of insulin receptor, improves the capability of body to utilise glucose in various tissues and organs by eliminating the free radicals, regulating protein and lipid metabolic disorders and by improving microcirculation in body.[32] Figure 4 depicts anti-diabetic mechanism of *G glabra* extracts.

Anticancer mechanism of liquorice

LicochalconeA (LCA) from liquorice exhibits potent anti-cancer activity. It significantly alters the morphology of cancerous cells, hinders their ability to proliferate and induces apoptosis by arresting the cell cycle at G_2/M Phase.[33] Figure 5 represents the proposed anticancer mechanism of liquorice flavonoids. LCA induces autophagy, inhibits angiogenesis and migration of cancerous cells by regulating MAPK pathway (responsible for tumour proliferation), downregulating P13/

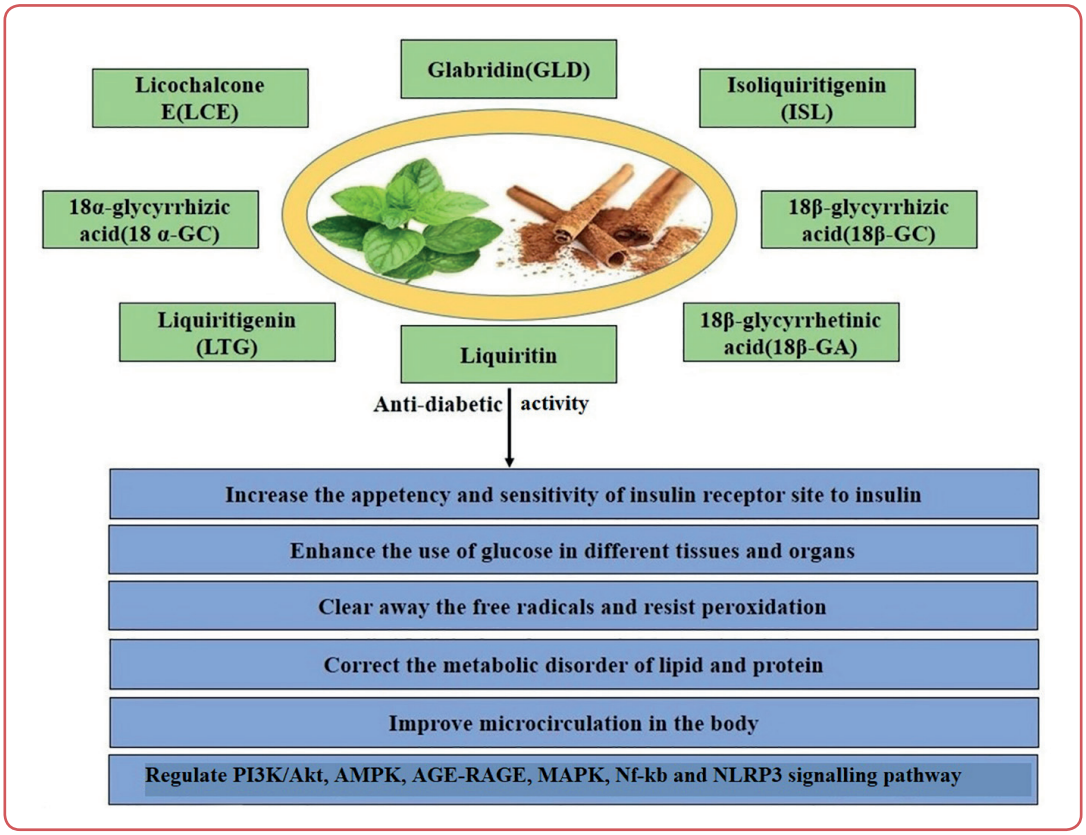

Figure 4: Anti-diabetic mechanism of liquorice

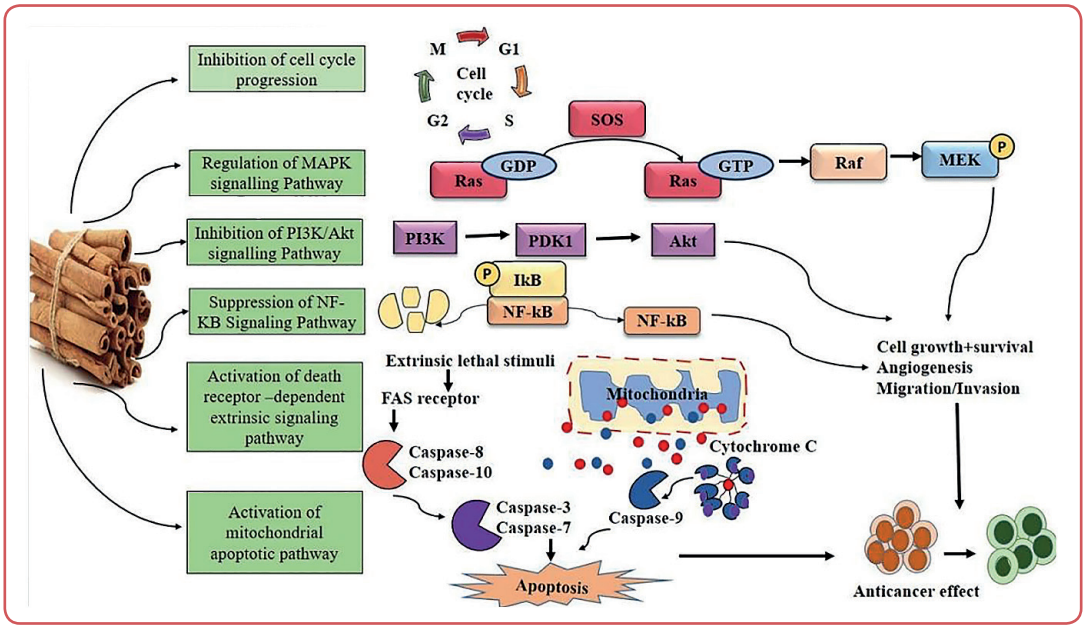

Figure 5: Anti-cancer mechanism of liquorice

Akt and NF-kB pathways (involved in tumour growth and multiplication), promote apoptosis by activation of FAS (death receptor), upregulates mitochondrial apoptosis pathway that result in more release of protease enzymes (caspase-3, caspase-8, caspase-6, caspase-9), which play vital role in programmed destruction of cancerous cells.

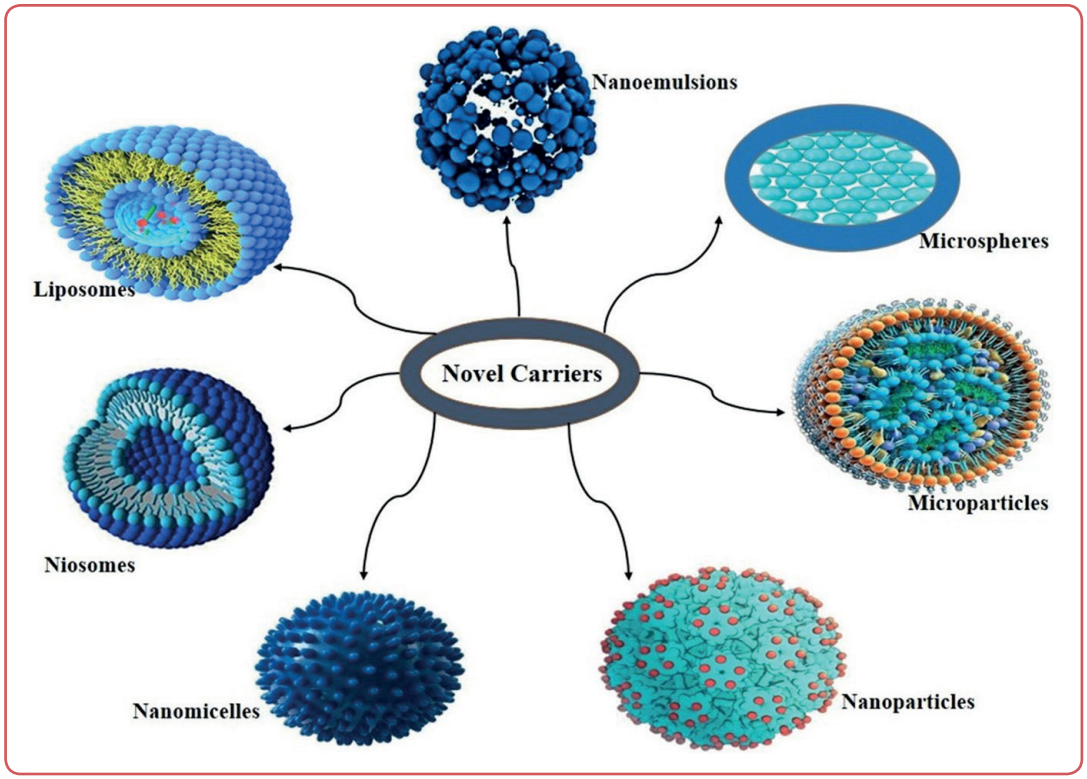

Figure 6: Different liquorice encapsulated novel formulations tions)

Liquorice encapsulated novel formulations

Liquorice is enclosed in different novel carriers such as nanoparticles, nanomicelles, liposomes, niosomes, microparticles, microspheres, self-nanoemulsifying drug delivery system (SNEDDS) and self-microemulsifying drug delivery system (SMEDDS) with the purpose to improve its solubility, stability, biological half-life, therapeutic efficacy and to provide target site specific drug delivery.[34] Figure 6 depicts different liquorice encapsulated novel formulations.

Liquorice nanoparticles

Nanoparticles (NPs) are extremely small molecules, having size in the range of 1-100 nm. They exhibit distinct physicochemical characteristics because of their nano-size and large surface area. The different types of NPs are- metal NPs, polymeric NPs, lipid-based NPs and ceramic NPs. They are synthesised by using top down (eg sputtering, milling, laser ablation) and bottom up (eg spinning, condensation, biological synthesis) approaches. They are extensively used as a carrier for delivery of drug molecules due to their high solubility, better stability, high sensitivity, high reactivity, rapid penetration through biological membrane and target site specific action.[35, 36] As NPs deliver the drug to the targeted site, the total drug dosage and adverse effects are reduced significantly. They are widely used to treat various types of cancers (such as lung cancer, prostate cancer, GIT cancer), rheumatoid arthritis, leukaemia and multiple myeloma.[37]

Bavanilatha et al developed titanium oxide NPs by green synthesis method and the outcome of the study revealed enhanced ant-bacterial and cytotoxic effect of liquorice roots.[38] Sreelakshmy et al prepared silver NPs loaded with liquorice root extracts using green synthesis method and the result indicated that developed nanoformulation exhibited improved bioavailability and therapeutic effect.[39] Liquorice flavonoids loaded nanoparticles were formulated using liquid anti-solvent re-crystallisation method by Wang et al. The study results showed enhanced oral bioavailability and antioxidant effect of liquorice flavonoids.[32] In another study, gold and silver chloride NPs were prepared employing green synthesis and centrifugation methods by Huo et al. The result revealed enhanced therapeutic effectiveness of liquiritin.[40] Cai et al developed *Glycyrrhiza* poly-

saccharide silver NPs by photoreduction synthesis method and the outcome of the study showed enhanced anti-bacterial effect of *Glycyrrhiza* polysaccharides.[41] Silver NPs were formulated using green synthesis method by Khandelwal et al and the study revealed enhanced anti-bacterial and anti-inflammatory effect of liquorice root extracts.[42] In another study, silver NPs were formulated employing Agar well diffusion method by Kalugendo et al. The outcome of the study depicted improved anti-microbial and anti-bacterial activity of *G glabra* stem extracts.[43] Mishra et al developed NPs using green synthesis method and the prepared nanoformulation showed enhanced anti-microbial and anti-bacterial effect of liquorice root.[44]

Nanoparticles are integral to enhancing the bioavailability and efficacy of constituents derived from liquorice, as demonstrated by numerous studies. Liquorice is rich in bioactive compounds such as glycyrrhizin, flavonoids and saponins, which frequently exhibit challenges related to poor water solubility, stability and limited absorption. For example, research indicates that nanoparticles loaded with glycyrrhizin significantly improve solubility and dissolution rates, thereby facilitating greater absorption into the bloodstream. Furthermore, nanoparticles serve to protect these compounds from environmental degradation, ensuring that the active ingredients retain their stability and effectiveness until they reach their intended site of action. A study conducted by Wang et al revealed that liquorice flavonoids encapsulated in lipid nanoparticles exhibited enhanced stability and bioavailability relative to their non-encapsulated counterparts.[45] Moreover, nanoparticles can be specifically engineered for targeted delivery; this was illustrated in a study by Rani et al, where glycyrrhizin-loaded nanoparticles effectively targeted diabetic models, thereby improving therapeutic efficacy in diabetes management.[46] The controlled and sustained release characteristics observed in various polymer-based systems prolong the therapeutic effects of these compounds while minimising the necessity for frequent dosing. Collectively, this amalgamation of improved solubility, stability, targeted delivery and cellular uptake - supported by existing literature - underscores the substantial therapeutic potential of liquorice when administered *via* nanoparticle-based systems.

Liquorice nanomicelles

Micelles are the self-assembly nanocarriers having size in the range of 10-100 nm and are effectively used as a drug delivery vehicle particularly for lipophilic drugs due to their small size, large surface area, high drug encapsulation efficiency, biocompatibility, longevity, better pharmacokinetic profile and targetability. These are prepared using different techniques such as lyophilisation, microphase separation, dialysis, solid dispersion, solvent evaporation and emulsification methods.[47] The functionality of micelles may be determined by their general attributes including size, shape, charge, stability and their composition. Micelles are the novel vehicles for drug delivery as they exhibit better stability, provide targeted delivery, better protection against oxidation, reduce adverse effects of API and provide controlled/sustained drug release. They are widely used for treatment of different type of cancers such as lung cancer, colorectal cancer and gastric cancer.[48, 49]

Song et al developed novel ocular nanomicelles by thin film dispersion method and the study results revealed enhanced encapsulation efficiency, improved anti-bacterial and anti-inflammatory activity of glycyrrhizin.[50] Liquorice chalcone A micelles were prepared by Yang et al employing thin film dispersion method. The results showed developed nanoformulation exhibited enhanced solubility, bioavailability and improved liver protective activity. In another study, glycyrrhizic acid-based self-assembled micelles were formulated using ultrasonic dispersion method by Shen et al and the outcome of study depicted enhanced permeability and therapeutic effect of enclosed drug substance.[51] Wang et al developed glycyrrhiza acid micelles loaded with LCA using thin film dispersion method. The result revealed enhanced permeability and therapeutic efficacy of LCA.[52] Glycyrrhizic acid micelles were prepared by Wang et al employing ultrasonic dispersion method and the result showed improved anti-inflammatory and anti-bacterial activities of glycyrrhizic acid.[8]

Liquorice liposomes

Liposomes are lipid-based self-assembled spherical vesicles (0.01-0.5 µm size) having single or multiple bilayers surrounding aqueous compartment. These are the amphiphilic molecules, hence suitable for delivery of lipophilic and hydrophilic drug substances. They are synthesised using different techniques such as solvent injection, sonication, thin film hydration, double emulsification and freeze-drying methods.[53] They are widely used as a delivery system for the drugs, imaging agents, antibiotics, hormones, proteins, anticancer drugs and nucleic acids because they are stable, biocompatible, non-toxic, provide protection to entrapped substance from degradation, improves biological shelf life of API, provide controlled drug release, exhibits minimal systemic adverse effects, prevents oxidation and enhances the therapeutic effectiveness of encapsulated drug molecule. They are used in cosmetics, cancer treatment, gene therapy, leishmaniasis, brain targeting, also used for drug delivery by different routes including pulmonary, oral, topical and ophthalmic.[54]

Kim et al developed the liposome-in hydrogel complex by swelling method and the prepared nanosystem showed improved stability, enhanced encapsulation efficiency and better skin permeability of liquiritin and liquiritigenin.[55] Wang et al prepared the liposome nanoformulation for liquiritin targeted delivery using film dispersion and freeze-drying methods. The result indicated that formulated liposomal system exhibited enhanced solubility, bioavailability and therapeutic efficacy.[52] Liposomal dry powder containing liquorice was formulated using thin film evaporation method by Viswanathan and the developed liposomes displayed improved encapsulation efficiency and enhanced anti-bacterial effect of *G glabra* extract.[56] In another study, liquorice encapsulated liposomes were prepared by Akhlaghi et al using thin film evaporation method. The result revealed that developed liposomal nanoformulation showed non-toxicity, provided controlled drug release and improved stability of liquorice hydro-alcoholic extracts.[57] Castangia et al formulated the liposomal nanoformulation for liquorice delivery using percolation method and the prepared liquorice encapsulated liposome displayed improved stability, high encapsulation efficiency and better local therapeutic effect of herbal extract.[58] Ultra-deformable liposomes were prepared by Barone using thin layer evaporation technique for glycyrrhizate delivery. The developed nanoformulation was biocompatible, deformable, exhibited enhanced skin permeability and promoted the drug accumulation in different sites.[59]

Liquorice niosomes

Niosomes are self-assembled microscopic vesicles consisting bilayer of non-ionic surfactant and cholesterol that encloses aqueous compartment. The lipophilic substances are encapsulated in bilayer and hydrophilic substances are entrapped in the aqueous central compartment.[60] They are prepared using different techniques such as microfluidisation, thin film hydration, sonication and ether injection method. Niosomes are biocompatible, non-immunogenic, amphiphilic, biodegradable, stable, non-toxic, inexpensive drug delivery vehicles and are used to deliver the drug molecules as they exhibit flexibility, high stability, better penetration across skin, provide sustained/controlled drug release, enhances therapeutic efficacy of encapsulated molecules. They are used to deliver the drugs used in the treatment of various diseases such as cancer (ovarian cancer, breast cancer, lung cancer), HIV, inflammation, melanoma and viral infections.[61, 62]

Akhlaghi et al developed *G glabra* loaded nanoniosomes by thin film hydration method. The formulated niosomes displayed controlled release and non-toxicity of liquorice extracts to normal healthier body cells.[63] Niosomes were also prepared by Marianecci et al using thin film evaporation method. The developed nanosystem showed better skin tolerability, non-toxicity and improved anti-inflammatory action of glycyrrhizinate.[64] Akhlaghi et al developed stimuli-responsive nanoniosomes using thin film hydration method. The prepared nanosystem exhibited better cellular uptake, improved anticancer and anti-microbial potential of *G glabra* root extract.[45] In another study, Marianecci et al formulated niosomes using thin layer evaporation method. The result reported that liquorice encapsulated niosomes were non- toxic and exhibited improved anti-inflammatory responses of ammonium glycyrrhizinate.[65] The different liquorice encapsulated novel formulations have been represented systematically in Table 2.

Table 2: Different novel formulations of liquorice

N	Novel formulation	Method of preparation	Therapeutic applications	Ref
1	Nanoparticles	Green synthesis method	Enhanced antibacterial and cytotoxic effect of liquorice roots	37
2	Nanoparticles	Green synthesis method	Improved bioavailability and therapeutic effect of liquorice extracts	38
3	Nanoparticles	Liquid antisolvent recrystallisation	Enhanced oral bioavailability and antioxidant effect of liquorice flavonoids	31
4	Nanoparticles	Green synthesis, centrifugation	Enhanced therapeutic effectiveness of liquiritin	40
5	Nanoparticles	Photoreduction synthesis	Improved anti-bacterial effect of glycyrrhiza polysaccharides	41
6	Nanoparticles	Green synthesis	Enhanced anti-bacterial and anti-inflammatory effect of liquorice root extracts	42
7	Nanoparticles	Agar well diffusion method	Improved anti-microbial and anti-bacterial activity of *G glabra* stem extracts	43
8	Nanoparticles	Green synthesis	Enhanced anti-microbial and anti-bacterial effect of liquorice roots	44
9	Nanomicelles	Thin-film dispersion	Enhanced encapsulation efficiency anti-bacterial and anti-inflammatory effect of glycyrrhizin	50
10	Nanomicelles	Ultrasonic dispersion	Exhibited high permeability and therapeutic effect of glycyrrhizic acid	51
11	Nanomicelles	Thin-film dispersion	Enhanced permeability and bioavailability of licochalcone A	52
12	Nanomicelles	Ultrasonic dispersion	Improved anti-inflammatory and anti-bacterial action of glycyrrhizic acid	8
13	Liposome-hydrogel complex	Swelling	Enhanced encapsulation efficiency and better skin permeability of liquiritin and liquiritigenin	55
14	Liposomes	Film dispersion, freeze drying	Enhanced solubility, bioavailability and therapeutic efficacy of liquiritin	52
15	Liposomes	Thin film hydration	Improved encapsulation efficiency and anti-bacterial effect of G glabra root extract	56
16	Liposomes	Thin film preparation	Improved stability, provide controlled drug release and showed non-toxicity to normal healthier cells	57
17	Liposomes	Percolation	Improved stability, high encapsulation efficiency and enhanced local therapeutic effect of herbal extract	58
18	Liposomes	Thin layer evaporation	Biocompatible, deformable, exhibited enhanced skin permeability of glycyrrhizate and also promote drug accumulation in different sites	59
19	Nanoniosomes	Thin film hydration	Exhibited controlled drug release and non-toxicity of liquorice extract to normal healthier cells	63
20	Niosomes	Thin layer evaporation	Better skin tolerability, non-toxicity and improved anti-inflammatory action of glycyrrhizinate	64
21	Nanoniosomes	Thin film hydration	Better cellular uptake, improved anticancer and anti-microbial potential of *G glabra* root extracts	57
22	Niosomes	Thin layer evaporation	Non-toxic, exhibited improved anti-inflammatory responses of glycyrrhizinate	65

Liquorice microparticles

These are tiny solid particles having size in the range of 1-1000 µm and are of two types: microsphere and microcapsule. In microspheres drug is equally distributed in matrix and may be present in suspended form or in dissolved state,[66] while in microcapsule, drug is enclosed by membrane or shell core and form a reservoir. These are suitable vehicle to deliver the drug at target site without any adverse effects to normal healthier body cells and also achieve the effective therapeutic concentration at a specific site.[67] They exhibit several advantages such as they can be easily injected into the tissue, provide protection to drug from environmental degradation, can be applied topically, masks bitter unacceptable taste, reduces side effects of drug, minimises oxidation of encapsulated substance and enhances drug targeting.[68, 69]

Sui et al developed the glycyrrhizic acid encapsulated microparticles by supercritical anti-solvent process that showed enhanced entrapment efficiency and improved therapeutic effect.[70] Liquorice and ginger loaded microparticles were prepared using ultrasonication process by Jan et al. The result indicated that formulated mi-

croparticles exhibited improved encapsulation efficiency and therapeutic effect of herbal extracts.[71] Liquorice encapsulated microparticles were prepared by Salvi et al using emulsification technique that showed enhanced drug release, improved encapsulation efficiency and therapeutic effect of *G glabra* root extract.[72] Neelima et al developed the microparticles for liquorice targeted drug delivery by solvent evaporation process. The formulated microparticles attained high concentration and provided prolonged release of herbal extract.[73] In another study, Al-Shdefat et al prepared the microparticles loaded with liquorice by spray drying process. The developed microparticles showed better entrapment efficiency and improved sexual behaviour activity of glycyrrhisin in male rats.[74]

Liquorice microspheres

Microspheres are solid spherical particles ranging in size between 1-1000 µm. These are prepared using natural, semi synthetic, synthetic polymers and gums/waxes by different techniques such as coacervation method, spray drying, spray congealing and ionic gelation method. Drug content, nature of polymer, molecular weight of the polymer and type of excipients are the major factors that affect synthesis of microspheres. These are multiparticulate drug delivery vehicle that exhibit numerous advantages over the conventional dosage forms and provide sustained/controlled drug delivery, reduces dose frequency, delivers the drug at target site, improves stability and bioavailability of drug molecules.[75, 76] They play a key role in different fields including cell sorting, diagnosis and genetic engineering.[77]

Harwansh et al developed the glycyrrhizin loaded mucoadhesive microspheres by emulsification-crosslinking technique. The formulated microspheres were safe, effective for oral route delivery, showed improved drug absorption and better gastro-protective effect.[78] Visht et al developed the glycyrrhetinic acid encapsulated microspheres by emulsification and heat stabilisation process. The result revealed that the prepared microspheres displayed high reproducibility, high encapsulation efficiency and maximal mucoadhesive properties.[79]

Liquorice self-nanoemulsifying drug delivery system (SNEDDS)

SNEDDS are an isotropic mixture of natural or synthetic oils, surfactants and co-surfactants having globule size not more than 100 nm. The different techniques used for preparation of SNEDDS include micro fluidisation, high pressure homogeniser, high energy approach, sonication and phase inversion method. Various factors affecting SNEDDS synthesis are: high dose drugs, capability to maintain the drug in solubilised state and risk of precipitation. These are oil-based approaches suitable for drugs that exhibit low dissolution rate and inadequate absorption.[80, 81] These delivery systems promote frequent oral distribution of lipophilic drugs, which is crucial to increase oral bioavailability. SNEDDS are extensively used to enhance the low aqueous solubility and poor bio-availability of class II and class IV drugs of BCS classification.[82] These delivery systems show numerous advantages compared to conventional dosage forms as they possess high drug payload, high solubility, high bioavailability, targeted drug delivery and minimal dosage frequency by enhancing the pharmacokinetic properties of the encapsulated drug.[83, 84] SNEDDS seems to be a suitable, commercially viable strategy for future development.

Wei et al developed self- nanoemulsifying drug delivery system of liquiritin by homogenisation technique and the prepared nanosystem showed better drug release rate, increased bioavailability, long retention time and improved anti-hyperuricemic effect of liquiritin.[85] Upadhyay et al formulated the glycyrrhetinic acid loaded SNEDDS using homogenisation. The developed nanosystem exhibited improved dissolution and better bioavailability rate.[86] In another study, Cao et al prepared the isoliquiritigenin encapsulated self-nanoemulsifying drug delivery system by homogenisation that showed enhanced solubility, bioavailability and therapeutic efficacy of liquorice extracts.[87]

Liquorice self-microemulsifying drug delivery system (SMEDDS)

SMEDDS are the isotropic blend of solid or liquid surfactants and natural or synthetic oils.[88] These are transparent microemulsion with droplet size not more than 100 nm and oil concentration less than 20 % as compared to 40-80 % in self-emulsifying delivery system. Different techniques used for SMEDDS synthesis are: sonication, spray drying, melt granulation and spheronisation. Nature and dose of the drug, polarity of the lipophilic phase, susceptibility to digestion is some of the major factors that affect synthesis of SMEDDS. These are simple to produce formulations that are physically stable and are the promising delivery system that improves the rate and extent of drug absorption, also enhances drug solubility and bioavailability.[89] Numerous advantages of SMEDDS are ease of manufacture, easy to scale up and exhibit reduction in inter and intra-subject variability.[90]

Zhong et al developed the liquorice loaded self-microemulsifying drug delivery system by homogenisation and sonication method. The formulated nanosystem showed improved solubility and bioavailability rate of liquorice. Zhang formulated the isoliquiritigenin encapsulated self-microemulsifying drug delivery system using stirring and homogenisation. The developed nanoformulation exhibited improved drug release rate, better bioavailability and enhanced anti-hyperuricemic effect of liquoriceconstituents. Other liquorice encapsulated novel formulations have been represented systematically in Table 3.

Miscellaneous novel formulations

Apart from above-described novel formulations, liquorice is enclosed in various other carriers to enhance its bioavailability and therapeutic efficacy. Such novel formulations are mentioned as:
- Ethosomes are novel lipoidal carriers having high ethanol percentage. These nanocarriers are mainly developed for the efficient and effective delivery of drug molecules across the skin into deeper layers and are used extensively as drug carrier due to their large surface area, high flexibility, non-toxicity, better stability and high encapsulation efficiency. They are employed in treatment of various diseases such as microbial infection, inflammation and menopausal symptoms in females.[91] Im NR developed the liquiritigenin and liquiritin loaded ethosomes by thin membrane hydration method and the formulated nanosystem showed improved entrapment effi-

Table 3: Various novel formulations of liquorice

N	Novel formulation	Method of preparation	Therapeutic applications	Ref
1	Microparticles	Supercritical anti-solvent process	Enhanced entrapment efficiency and therapeutic effect of glycyrrhizic acid	70
2	Microparticles	Ultrasonication	Improved encapsulation efficiency and therapeutic efficacy of *G glabra* extracts	71
3	Microparticles	Emulsification	Enhanced drug release and encapsulation efficiency of *G glabra* root extracts	72
4	Microparticles	Solvent evaporation	Developed microformulation showed high drug concentration and provided prolonged drug release	73
5	Microparticles	Spray drying	Better entrapment efficiency and improved sexual behaviour activity of glycyrrhizin in male rats	74
6	Microspheres	Emulsification-crosslinking technique	Safe, effective for oral route delivery, improved drug absorption and better gastro-protective effect of glycyrrhizin	78
7	Microspheres	Emulsification and heat stabilisation process	Exhibited reproducibility, high encapsulation efficiency and maximal mucoadhesive properties of glycyrrhetinic acid	79
8	Self-nanoemulsifying drug delivery system	Homogenisation	Better drug release rate, increased bioavailability, longer retention time and improved anti-hyperuricaemic effect of liquiritin	85
9	Self-nanoemulsifying drug delivery system	Homogenisation	Improved dissolution and bioavailability rate of glycyrrhetinic acid	86
10	Self-nanoemulsifying drug delivery system	Homogenisation	Enhanced solubility, bioavailability and therapeutic efficacy of liquorice extracts	87

Table 4: Liquorice encapsulated miscellaneous novel formulations

N	Novel formulation	Method of preparation	Therapeutic applications	Ref
1	β-cyclodextrin inclusion complex	Saturated aqueous solution	Enhanced solubility, bioavailability and antitumour efficacy of liquiritin	93
2	Hydrogel	Chemical cross-linking	Optimal rheological and adhesive characteristics, enhanced skin permeability and anti- microbial efficacy of isoliquiritigenin	95
3	Nanoemulsion	Spontaneous emulsification	Increased enzymatic activity, reduced lipid peroxidation and better wound healing potential of liquorice extracts	85

ciency and enhanced skin permeability. Hydrogel is the three-dimensional polymeric network holding excess amount of water. They possess high flexibility, biocompatibility, long half-life, high mechanical strength, low interfacial tension, versatility and photostability. They are used in different fields such as pharmaceuticals, agriculture, food industry, diagnosis and tissue engineering.[92] Hydrogel containing isoliquiritigenin was formulated by Kwon using chemical cross-linking technique that showed optimal rheological and adhesive characteristics, enhanced skin permeability and anti- microbial efficacy.[93]

Nanoemulsions are the colloidal dispersions having size in range of 50-1000 nm and consists of two immiscible liquids that are mixed using emulsifying agents to produce a single homogeneous phase. They are widely used as drug delivery vehicles due to their better stability, permeation, viscosity, pH, shelf life, surface tension, osmolarity, also shows quick absorption, non-toxicity, protection against hydrolysis and enhanced drug bioavailability.[94] In a study, Kazemi et al developed the nanoemulsion loaded with liquorice extract by spontaneous emulsification method. The prepared nanoemulsion exhibited increased enzymatic activity, reduced lipid peroxidation and better wound healing potential.[95] Cyclodextrins encapsulate drug molecules resulting in the formation of inclusion complexes. This inclusion complex encloses compounds by hydrophobic or Vanderwall's interactions between the complex walls and drug molecules. These are used as a drug delivery vehicle because of their better stability, high drug loading capacity and ability to increase the therapeutic efficacy of enclosed molecule.[96] Wang et al prepared the β-cyclodextrin inclusion complex loaded with liquiritin by saturated aqueous solution process. The developed inclusion complex exhibited enhanced solubility, bioavailability and antitumour efficacy.[85] The liquorice encapsulated miscellaneous novel formulations have been represented systematically in Table 4.

Pre-clinical studies

Rani et al evaluated the anti-diabetic activity of liquorice loaded NPs in type-2 diabetic rats. The nanoformulation was administered for 21 days to rats and study result concluded that liquorice loaded NPs showed significant reduction in blood glucose level.[46] Anti-cancer activity of *G glabra* was evaluated on mice by Zhang et al. During dosing process, the body weight and growth rate of tumour in mice were monitored. The result revealed that *G glabra* encapsulated micelles exhibited strong inhibitory effect on tumour growth. Bernela et al conducted a study on Wistar rats with a dose of 20 mg/kg and 40 mg/kg of liquorice loaded NPs to confirm the improved anti-inflammatory effect of liquorice. The trial result concluded that encapsulation of liquorice in nanoparticle leads to enhancement in its bioavailability and anti-inflammatory action.[97] Anti-microbial effect of *G glabra* in treatment of lung infection was evaluated by Chakotiya et al. The trials were conducted on albino rats with a dose of 20 mg/kg and 80 mg/kg. The different parameters such as body weight, temperature, bacteraemia (presence of bacteria in blood) were monitored for 48 h. The study result revealed that *G glabra* extract at 80 mg/kg dose were highly effective in treating lung infection caused by *Pseudomonas aeruginosa.*[98] Orlando et al conducted a pre-clinical study on rats to evaluate the antioxidant action of herbal extracts of *G glabra*, *Vicia faba* and *U rhyncophylla.* The effect of different herbal extracts on nitrites, prostaglandins and on lactate dehydrogenase were evaluated during study. The result concluded that extract of different herbs (*G glabra, Vicia faba* and *U rhyncophylla*) were highly effective in treatment of stress associated disorders.[99] Mishra et al conducted study on albino rats to determine the biodistribution pattern of glycyrrhizin loaded chitosan NPs for target site specific delivery of lamivudine and the trial result concluded the presence of high drug concentration in liver tissues because of quick

uptake of NPs by phagocytic cells.[100] Pre-clinical study on female mice was also performed by Shi et al to evaluate tissue distribution and anti-carcinoma efficacy of formulated glycyrrhizin-chitosan NPs. The study result revealed that glycyrrhizin promoted the internalisation and rapid cellular uptake of paclitaxel.[101]

Toxicological concerns associated with liquorice novel formulations

Novel carriers have unique properties such as small size and large surface area that enhances the risk of toxicity. Major factors responsible for their toxicity are dose, route of administration and extent of distribution within the body. Numerous harmful effects of different herbal novel formulations are documented in studies. For example, protein and herbal based nanoparticles have been shown to cause hepatotoxicity, nephrotoxicity as well as increases the oxidative stress and have the potential to enter the cell nucleus. It is still unknown how the safety and risk ratio affect the producer and the patient.[102] Furthermore, because of their high biocompatibility, novel carriers can migrate throughout the body, as a result they have capability to pass across the biological cell membranes, skin barriers and blood brain barrier, which leads to non-specific interaction within the body and enhanced toxicity at the cellular and tissue level. The possible toxicological effects of novel formulations are immunotoxicity, oxidative stress, DNA damage, cytotoxicity, mutations and neurotoxicity.[103]

Marketed liquorice encapsulated formulations

The different marketed liquorice encapsulated novel formulations have been represented systematically in Table 5.

Table 5: Marketed formulations of liquorice

N	Company name	Brand name	Composition	Therapeutic applications
1	*Livestamin*	Liquorice	Liquorice 500 mg, capsule	Aids in hormonal balance and improves digestion
2	*Inlife*	*Liquoriceyashtimadhu, Glycyrrhiza glabra*	Yashtimadhu, *Glycrrhiza glabra*, 20 % Glycyrrhinic acid	Treats heart burn, acid reflux and improves digestion
3	*Urban platter*	Mulethi powder	Vitamins, fats, cholestrol, sodium, potassium, proteins, carbohydrates	Aids throat ache and improves digestion
4	*VLCC Natural Sciences*	Liquorice cold cream	Rose petals, liquorice extracts, vitamin E	Heals and softens the rough dry skin and prevents skin breakouts
5	*Eva Naturals*	Skin brightening serumliquorice extract	Lactic acid, vitamin E, CoQ10, vitamin C, organic aloe	Eliminate spots, brightens and softens the face

Future perspectives

Liquorice (*G glabra*) is a widely used herb that offers a plethora of applications. To ensure its site-specific delivery, novel formulations demonstrate significant therapeutic potential in the management of a variety of diseases, including cancer, inflammation and COVID-19 infection. These innovative formulations offer promising prospects for the treatment of diverse illnesses in the future. They help to enhance the bioavailability, as well as the therapeutic efficacy of liquorice and protect it from early degradation. They possess the capability to effectively address the limitations inherent in traditional therapies, heralding a new era in early disease detection and treatment that could enhance overall patient survival rates. Furthermore, the molecular configuration of liquorice plays a crucial role in creating an amphiphilic compound capable of self-assembly to generate nanoparticle-like formations. The use of *in-silico* tools and molecular modelling pave the way to obtain an in-depth understanding of the molecular interactions and dynamics of

liquorice. Molecular docking studies can also help understand the binding affinity of liquorice with different biological targets.

Numerous research studies have highlighted enhanced pharmacological benefits following the encapsulation or integration of liquorice into nanostructures. The amalgamation of cutting-edge technologies like 3D printing can also help to refine the drug delivery systems and progress towards the avenue of personalised medicine. Due to the complexities and innovations in these delivery systems the addressal of regulatory concerns are also essential. These will help to streamline the pathway from drug development to commercialisation. While further investigations are warranted to explore nanotoxicological and immunological implications in greater depth, leveraging nanomedicines may represent a promising novel approach for advancing the utilisation and enhancement of liquorice-based nanoformulations in the future.

Conclusion

Liquorice (*G glabra*) is a widely used herb from the ancient times in pharmaceutical field, cosmeceutical and food industries. Its roots have been utilised in the treatment of various ailments, particularly cancer, microbial infection and inflammatory disorders. Different bioactive components of liquorice are glycyrrhetinic acid, isoflavones, glycyrrhizin. These are responsible for anti-inflammatory, anti-cancer, antioxidant, antimicrobial and hepatoprotective actions. Liquorice exhibits low solubility, less stability, short biological half-life. In order to overcome all such limitations and to enhance the therapeutic efficacy of liquorice, different novel formulations such as nanoparticles, nanomicelles, microparticles, liposomes, hydrogels, ethosomes etc are developed. All these novel formulations improve its solubility, stability, protect normal healthier body cells, also provide target site specific drug delivery that ultimately leads to enhanced biological effect. These developed liquorice encapsulated novel formulations are the effective and efficient tool for treatment of various diseases and disorders.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

Acknowledgement

The authors gratefully acknowledge Chitkara College of Pharmacy, Chitkara University, Punjab, India, for support and institutional facilities.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Sanshita (S):
0009-0001-6838-7219
Ayushi Taneja (AT):
0000-0002-3534-7704
Tanikan Sangnim (TS):
0000-0002-9332-384X

Kampanart Huanbutta (KH):
0000-0001-8188-153X
Rakesh K Sindhu (RKS):
0000-0003-2619-4643
Inderbir Singh (IS):
0000-0002-1860-4246

Author contributions

Conceptualisation: TS
Methodology: TS
Validation: AT
Formal analysis: S
Resources: RKS
Data curation: S
Writing - original draft: S
Writing - review and editing: AT
Visualisation: KH, IS
Supervision: KH, IS
Project administration: RKS, IS

References

1. Pastorino G, Cornara L, Soares S, Rodrigues F, Oliveira MBP. Liquorice (Glycyrrhiza glabra): A phytochemical and pharmacological review. Phytother Res. 2018;32:2323-39. doi: 10.1002/ptr.6178.
2. Hosseinzadeh H, Nassiri-Asl M. Pharmacological effects of Glycyrrhiza spp. and its bioactive constituents: update and review. Phytother Res. 2015;29:1868-86. doi: 10.1002/ptr.5487.
3. Gumpricht E, Dahl R, Devereaux MW, Sokol RJ. Licorice compounds glycyrrhizin and 18β-glycyrrhetinic acid are potent modulators of bile acid-induced cytotoxicity in rat hepatocytes. Int J Biol Chem. 2005;280:10556-63. doi: 10.1074/jbc.M411673200.
4. Bhardwaj S, Kaur J, Kaur A, Kaur S, Jindal A, Singh, I. Herbal bioactives for the management of influenza viral infection. Int J Infect Dis. 2022;85-99. doi: 10.1002/9781119818779.ch4.
5. Tanaka A, Horiuchi M, Umano K, Shibamoto T. Antioxidant and anti-inflammatory activities of water distillate and its dichloromethane extract from licorice root (Glycyrrhiza uralensis) and chemical composition of dichloromethane extract. J Sci Food Agric. 2008;88:1158-65. doi: 10.1002/jsfa.3191.
6. Takhshid MA, Mehrabani D, Ai J, Zrepoor M. The healing effect of licorice extract in acetic acid-induced ulcerative colitis in rat model.Comp Clin Pathol. 2012;21:1139-44. doi: 10.1007/s00580-011-1249-9.
7. Rahnama M, Mehrabani D, Japoni S, Edjtehadi M, Firoozi MS. The healing effect of licorice (Glycyrrhiza glabra) on Helicobacter pylori infected peptic ulcers. J Res Med Sci. 2013;18:532.
8. Tao W, Dong Y, Su Q, Wang H, Chen Y, Xue W, et al. Liquiritigenin reverses depression-like behavior in unpredictable chronic mild stress-induced mice by regulating PI3K/Akt/mTOR mediated BDNF/TrkB pathway. Behav Brain Res. 2016;308:177-86. doi: 10.1016/j.bbr.2016.04.039.
9. Wahab S, Annadurai S, Abullais SS, Das G, Ahmad W, Ahmad MF, et al. Glycyrrhiza glabra (Licorice): A comprehensive review on its phytochemistry, biological activities, clinical evidence and toxicology. Plant J. 2021;10:2751. doi: 10.3390/plants10122751.
10. Nazari S, Rameshrad M, Hosseinzadeh H. Toxicological effects of Glycyrrhiza glabra (licorice): a review. Int J Phytother. 2017;31:1635-50. doi: 10.1002/ptr.5893.
11. Liu J, Banuvar S, Viana M, Barengolts E, Chen SN, Pauli GF, et al. Pharmacokinetic interactions of a licorice dietary supplement with cytochrome p450 enzymes in female participants. Drug Metab Dispos. 2023;51:199-204. doi: 10.1124/dmd.122.001050.
12. El-Saber Batiha G, Magdy Beshbishy A, El-Mleeh A, Abdel-Daim M, Prasad Devkota H. Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of Glycyrrhiza glabra L. (Fabaceae). Biomolecules. 2022;10:352. doi: 10.3390/biom10030352.
13. Sharma T, Sharma P, Chandel P, Singh S, Sharma N, Naved T, et al. Circumstantial insights into the potential of traditional Chinese medicinal plants as a therapeutic approach in rheumatoid arthritis. Curr Pharm Des. 2022;28:2140-9. doi: 10.2174/1381612828666220324124720.
14. Grienke U, Braun H, Seidel N, KirchmairJ, Richter M, Krumbholz A, et al. Computer-guided approach to access the anti-influenza activity of licorice constituents. J Nat Prod. 2014;77:563-570. doi: 10.1021/np400817j.
15. Dastagir G, Rizvi MA. Glycyrrhiza glabra L. (Liquorice). Pak J Pharm Sci. 2016;29:1727-33.
16. Puri V, Nagpal M, Singh I, Singh M, Dhingra GA, Huanbutta K, et al. A Comprehensive review on nutraceuticals: therapy support and formulation challenges. Nutrients. 2022;14:4637. doi: 10.3390/nu14214637.
17. Bisht D, Rashid M, Arya RKK, Kumar D, Chaudhary SK, Rana VS, et al. Revisiting liquorice (Glycyrrhiza glabra L.) as anti-inflammatory, antivirals and immunomodulators: Potential pharmacological applications with mechanistic insight. Phytomedicine. 2022;2:100206. doi: 10.1016/j.phyplu.2021.100206.
18. Ayeka PA, Bian Y, Githaiga PM, Zhao Y. The immunomodulatory activities of licorice polysaccharides (Glycyrrhiza uralensis Fisch.) in CT 26 tumor-bearing mice. BMC Complement Altern Med. 2017;17:1-9. doi: 10.1186/s12906-017-2030-7.
19. Kaur P, Makanjuola VO, Arora R, Singh B, Arora S. Immunopotentiating significance of conventionally used plant adaptogens as modulators in biochemical and molecular signalling pathways in cell mediated processes. Biomed Pharmacother. 2017;95:1815-29. doi: 10.1016/j.biopha.2017.09.081.
20. Bailly C, Vergoten G. Glycyrrhizin: An alternative drug for the treatment of COVID-19 infection and the associated respiratorysyndrome.PharmacolTher.2020;214:107618. doi: 10.1016/j.pharmthera.2020.107618.

21. Fiore C, Eisenhut M, Krausse R, Ragazzi E, Pellati D, Armanini D, et al. Antiviral effects of Glycyrrhiza species. Phytother Res. 2008;22:141-8. doi: 10.1002/ptr.2295.
22. Asl MN, Hosseinzadeh H. Review of pharmacological effects of Glycyrrhiza sp. and its bioactive compounds. Phytother Res 2008;22:709-24. doi: 10.1002/ptr.2362.
23. Wang KL, Yu YC, Hsia SM. Perspectives on the Role of Isoliquiritigenin in Cancer. Cancers. 2021;13:115. doi: 10.3390/cancers13010115.
24. Zhang Q, Ye M. Chemical analysis of the Chinese herbal medicine Gan-Cao (licorice). J Chromatogr A. 2009;1216:1954-69. doi: 10.1016/j.chroma.2008.07.072.
25. Alrushaid S, Davies NM, Martinez SE, Sayre CL. Pharmacological characterization of liquiritigenin, a chiral flavonoid in licorice. Res Pharm Sci. 2016;11:355-65. doi: 10.4103/1735-5362.192484.
26. Armanini D, Nacamulli D, Francini-Pesenti F, Battagin G, Ragazzi E, Fiore C. Glycyrrhetinic acid, the active principle of licorice, can reduce the thickness of subcutaneous thigh fat through topical application. Steroids. 2005;70:538-42. doi: 10.1016/j.steroids.2005.01.007.
27. Tay KC, Tan LT, Chan CK, Hong SL, Chan KG, Yap WH, et al. Formononetin: a review of its anticancer potentials and mechanisms. Front Pharmacol. 2019;10:820. doi: 10.3389/fphar.2019.00820.
28. Zang Y. Pharmacological Activities of coumarin compounds in licorice: a review. Nat Prod Commun. 2020;15. doi: 10.1177/1934578X20953954.
29. Aipire A, Mahabati M, Cai S, Wei X, Yuan P, Aimaier A, et al. The immunostimulatory activity of polysaccharides from Glycyrrhiza uralensis. Peer J. 2020;8:e8294. doi: 10.7717/peerj.8294.
30. Kim HJ, Seo JY, Suh HJ, Lim SS, Kim JS. Antioxidant activities of licorice-derived prenylflavonoids. Nutr Res Pract. 2012;6:491-8. doi: 10.4162/nrp.2012.6.6.491.
31. Mamedov NA, Egamberdieva D. Phytochemical constituents and pharmacological effects of licorice: a review. Plant Human Health. 2019;3:1–21. doi: 10.1007/978-3-030-04408-4_1.
32. Wang J, Zhang YS, Thakur K, Hussain SS, Zhang JG, Xiao GR, et al. Licochalcone A from licorice root, an inhibitor of human hepatoma cell growth via induction of cell apoptosis and cell cycle arrest. Food Chem Toxicol. 2018;120:407-17. doi: 10.1016/j.fct.2018.07.044.
33. Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. Arab J Chem. 2019;12:908-31. doi: 10.1016/j.arabjc.2017.05.011.
34. Kumari S, Goyal A, Garg M. Phytoconstituents based novel nano-formulations: an approach. ECS Transactions. 2022;107:7365. doi: 10.1149/10701.7365ecst.
35. Singh V, Kumar A. Antioxidant Potential of Glycyrrhiza glabra L. roots: In-Vitro Evidences. J Pharm Technol Res. 2022;8:9-13. doi: 10.15415/jptrm.2020.81002.
36. Ealia SAM, Saravanakumar MP. A review on the classification, characterisation, synthesis of nanoparticles and their application. Mater Sci Eng. 2017;263:032019. doi: 10.1088/1757-899X/263/3/032019.
37. Harish V, Tewari D, Gaur M, Yadav AB, Swaroop S, Bechelany M, et al. Review on nanoparticles and nanostructured materials: Bioimaging, biosensing, drug delivery, tissue engineering, antimicrobial, and agro-food applications. J Nanomater. 2022;12:457. doi: 10.3390/nano12030457.
38. Bavanilatha M, Yoshitha L, Nivedhitha S, Sahithya S. Bioactive studies of TiO2 nanoparticles synthesized using Glycyrrhiza glabra. Biocatal Agric Biotechnol. 2019;19:101131. doi: 10.1016/J.BCAB.2019.101131.
39. Sreelakshmy V, Deepa MK, Mridula P. Green synthesis of silver nanoparticles from Glycyrrhiza glabra root extract for the treatment of gastric ulcer. J Dev Drugs. 2016;5:152. doi: 10.4172/2329-6631.1000152.
40. Huo Y, Singh P, Kim YJ, Soshnikova V, Kang J, Markus J, et al. Biological synthesis of gold and silver chloride nanoparticles by Glycyrrhiza uralensis and in vitro applications. Artif Cells Nanomed Biotechnol. 2018;46:303-12. doi: 10.1080/21691401.2017.1307213.
41. Cai Z, Dai Q, Guo Y, Wei Y, Wu M, Zhang H. Glycyrrhiza polysaccharide-mediated synthesis of silver nanoparticles and their use for the preparation of nanocomposite curdlan antibacterial film. Int J Biol Macromol. 2019;141:422-30. doi: 10.1016/j.ijbiomac.2019.09.018.
42. Khandelwal R, Kachhawa C, Arora SK, Ratan JK, Garg R. A Sustainable method for synthesis of silver nanoparticles by using Glycyrrhiza glabra extract. Nanotechnol Environ Eng. 2021;6:58. doi: 10.1007/s41204-021-00154-9.
43. Kalugendo E, Kousalya P. Synthesis of silver nanoparticles using Moringa oleifera seeds, Glycyrrhiza glabra stems, and its anti-methicillin-resistant Staphylococcus aureus activity.Sci Synth. 2019;12:368-70. doi: 10.22159/ajpcr.2019.v12i2.28863.
44. Mohammed HA, AminMA, Zayed G, Hassan Y, El-Mokhtar M, Saddik MS. In vitro and in vivo synergistic wound healing and anti-methicillin-resistant Staphylococcus aureus (MRSA) evaluation of liquorice-decorated silver nanoparticles. J Antibiot. 2023;76:291-300. doi: 10.1038/s41429-023-00603-4.
45. Wang Z, Zhao X, Zu Y, Wu W, Li Y, Guo Z, et al. Licorice flavonoids nanoparticles prepared by liquid antisolvent re-crystallization exhibit higher oral bioavailability and antioxidant activity in rat. J Func Food. 2019;57:190–201. doi: 10.1016/j.jff.2019.04.010.
46. Rani R, Dahiya S, Dhingra D, Dilbaghi N, Kim KH, Kumar S. Evaluation of anti-diabetic activity of glycyrrhizin-loaded nanoparticles in nicotinamide-streptozotocin-induced diabetic rats. Eur J Pharm Sci. 2017;106:220-30. doi: 10.1016/j.ejps.2017.05.068.
47. Ghezzi M, Pescina S, Padula C, Santi P, Del Favero E, Cantù L, et al. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions.J Control Release. 2021;332:312-36. doi: 10.1016/j.jconrel.2021.02.031.
48. Perumal S, Atchudan R, Lee W. A review of polymeric micelles and their applications. Polymers. 2022;14:2510. doi: 10.3390/polym14122510.
49. Jhaveri AM, Torchilin VP. Multifunctional polymeric micelles for delivery of drugs and siRNA. Front Pharmacol. 2014;5:77. doi: 10.3389/fphar.2014.00077.
50. Song K, Yan M, Li M, Geng Y, Wu X. Preparation and in vitro–in vivo evaluation of novel ocular nanomicelle formulation of thymol based on glycyrrhizin. Colloids Surf B. 2020;194:111157. doi: 10.1016/j.colsurfb.2020.111157.
51. Shen C, Shen B, Zhu J, Wang J, Yuan H, Li X. Glycyrrhizic acid-based self-assembled micelles for improving oral bioavailability of paeoniflorin. Drug Dev Ind Pharm. 2021;47:207-14. doi: 10.1080/03639045.2020.1862178.

52. Wang Q, Wei C, Weng W, Bao R, Adu-Frimpong M, Toreniyazov E, et al. Enhancement of oral bioavailability and hypoglycemic activity of liquiritin-loaded precursor liposome. Int J Pharm. 2021;592:120036. doi: 10.1016/j.ijpharm.2020.120036.
53. Liu P, Chen G, Zhang J. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. Molecules. 2022;27: 1372. doi: 10.3390/molecules27041372.
54. Farooque F, Wasi M, Mughees MM. Liposomes as drug delivery system: an updated review. J Drug Deliv Ther. 2021;11:149-58. doi: 10.22270/jddt.v11i5-S.5063.
55. Kim SJ, Kwon SS, Jeon SH, Yu ER, Park SN. Enhanced skin delivery of liquiritigenin and liquiritin loaded liposome in hydrogel complex system. Int J Cosmet Sci. 2014;36:553-60. doi: 10.1111/ics.12156.
56. Viswanathan V, Pharande R, Bannalikar A, Gupta P, Gupta U, et al. Inhalable liposomes of Glycyrrhiza glabra extract for use in tuberculosis: formulation, in vitro characterization, in vivo lung deposition, and in vivo pharmacodynamic studies. Drug Dev Ind Pharm. 2019;45:11-20. doi: 10.1080/03639045.2018.1513025.
57. Akhlaghi M, Eftekharivash L, Taebpour M, Afereydoon S, Ebrahimpour M, Mehrizi MZ, et al. Improving the therapeutic performance of glycyrrhiza glabra hydroalcoholic extract using liposomal nano-carriers and their characterization. Dis Diagn. 2022;11:39-48. doi: 10.34172/ddj.2022.09.
58. Castangia I, Caddeo C, Manca ML, Casu L, Latorre AC, Díez-Sales O, et al. Delivery of liquorice extract by liposomes and hyalurosomes to protect the skin against oxidative stress injuries. Carbohyd Polym. 2015;134:657-63. doi: 10.1016/j.carbpol.2015.08.037.
59. Barone A, Cristiano MC, Cilurzog F, Locatelli M, Iannotta D, Di Marzio L, et al. Ammonium glycyrrhizate skin delivery from ultradeformable liposomes: A novel use as an anti-inflammatory agent in topical drug delivery. Colloids Surf B. 2020;193:111152. doi: 10.1016/j.colsurfb.2020.111152.
60. Bhardwaj P, Tripathi P, Gupta R, Pandey S. Niosomes: A review on niosomal research in the last decade. J Drug Deliv Sci Tech. 2020;56:101581. doi: 10.1016/j.jddst.2020.101581.
61. Ag Seleci D, Seleci M, Walter JG, Stahl F, Scheper T. Niosomes as nanoparticular drug carriers: fundamentals and recent applications. J Nanomater. 2016;3:2016. doi: 10.1155/2016/7372306.
62. Gharbavi M, Amani J, Kheiri-Manjili H, Danafar H, Sharafi A. Niosome: a promising nanocarrier for natural drug delivery through blood-brain barrier.Adv Pharmacol Sci 2018;2018:6847971. doi:10.1155/2018/6847971.
63. Akhlaghi M, Taebpour M, Lotfabadi NN, Naghib SM, Jalili N, Farahmand L, et al. Synthesis and characterization of smart stimuli-responsive herbal drug-encapsulated nanoniosome particles for efficient treatment of breast cancer. Nanotechnol Rev. 2022;11:1364-85. doi: 10.1515/ntrev-2022-0080.
64. Marianecci C, Rinaldi F, Mastriota M, Pieretti S, Trapasso E, Paolino D, et al. Anti-inflammatory activity of novel ammonium glycyrrhizinate/niosomes delivery system: human and murine models. J Control Release. 2012;164:17-25. doi: 10.1016/j.jconrel.2012.09.018.
65. Marianecci C, Rinaldi F, Di Marzio L, Mastriota M, Pieretti S, Celia C, et al. Ammonium glycyrrhizinate-loaded niosomes as a potential nanotherapeutic system for anti-inflammatory activity in murine models. Int J Nanomedicine. 2014;9:635-51. doi: 10.2147/IJN.S55066.
66. Jyothi N, Harekrishna Roy N, Lakshmi Prasanhti V, Sri Vajrapriya A. Brief review of microparticle drug delivery system. World J Pharm Sci. 2016;5:701-12.
67. Padalkar AN, Shahi SR, Thube MW. Microparticles: an approach for betterment of drug delivery system. Int J Pharm Res Dev. 2011;3:99-115.
68. Kohane DS. Microparticles and nanoparticles for drug delivery. Biotechnol Bioeng. 2007;96:203-9. doi: 10.1002/bit.21301.
69. Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. Microparticles, microspheres, and microcapsules for advanced drug delivery. Sci Pharm. 2019;87:20. doi: 10.3390/scipharm87030020.
70. Sui X, Wei W, Yang L, Zu Y, Zhao C, Zhang L, et al. Preparation, characterization and in vivo assessment of the bioavailability of glycyrrhizic acid microparticles by supercritical anti-solvent process. Int J Pharm. 2012;423:471-9. doi: 10.1016/j.ijpharm.2011.12.007.
71. Jan R, Gani A, Dar MM, Bhat NA. Bioactive characterization of ultrasonicated ginger (Zingiber officinale) and licorice (Glycyrrhiza Glabra) freeze dried extracts. Ultrason Sonochem. 2022;88:106048. doi: 10.1016/j.ultsonch.2022.106048.
72. Salvi N, Choudhary GP. Formulation and development of microparticles containing herbal plant extract. J Drug Deliv Ther. 2019;9:89-92.
73. Neelima S, Pratap CG. Development and characterization of polymeric microparticles containing Murrayakoenigii leaves extract for management of diabetes mellitus. J Pharmacogn Phytochem. 2019;8:2438-42.
74. Al-Shdefat R, Ali BE, Anwer MK, Fayed MH, Alalaiwe A, Soliman GA. Sildenafil citrate-Glycyrrhizin/Eudragit binary spray dried microparticles: A sexual behavior studies on male rat. J Drug Deliv Sci Technol. 2016;36:141-9. doi: 10.1016/j.jddst.2016.10.004.
75. Chaudhari A, Jadhav KR, Kadam VJ. An overview: Microspheres as a nasal drug delivery system.Int J Pharm Sci. 2010;5:8-17.
76. Murtaza G, Ahamd M, Akhtar N, Rasool F. A comparative study of various microencapsulation techniques: Effect of polymer viscosity on microcapsule characteristics. Pak J Pharma 2009;22:291-300.
77. Vani M. Formulation and evaluation of sustained release microspheres of acetazolamide by solvent evaporation technique. IJPRE. 2009;6:1-8.
78. Harwansh RK, Deshmukh R. Formulation and evaluation of sodium alginate and guar gum based glycyrrhizin loaded mucoadhesive microspheres for management of peptic ulcer. Indian J Pharm Educ Res. 2021;55:728-37. doi:10.5530/ijper.55.3.145.
79. Visht S, Kulkarni GT. Studies on the preparation and in vitro-in vivo evaluation of mucoadhesive microspheres of glycyrrhetinic acid isolated from liquorice. Bangladesh Pharm J. 2015;18:30-7. doi: 10.3329/bpj.v18i1.23511.
80. Soni GC, Prajapati SK, Chaudhri N. Self nanoemulsion: advance form of drug delivery system.World J Pharm Sci. 2014;3:410-36.

81. Gupta P, Kumar P, Sharma NK, Pawar Y, Gupta J. Self nano emulsifying drug delivery system: a strategy to improve oral bioavailability. World J Pharm Sci. 2014;3:506-12.
82. Singh B, Bandopadhyay S, Kapil R, Singh R, Katare OP. Self-emulsifying drug delivery systems (SEDDS): formulation development, characterization, and applications. Crit Rev Ther Drug Carr Syst. 2009;26:427-521. doi: 10.1615/critrevtherdrugcarriersyst.v26.i5.10.
83. Shafiq-un-Nabi S, Shakeel F, Talegaonkar S, Ali J, Baboota S, Ahuja A, et al. Formulation development and optimization using nanoemulsion technique: a technical note. AAPS Pharm Sci Tech. 2007;8:E12-E17. doi: 10.1208/pt0802028.
84. Anton N, Benoit JP, Saulnier P. Design and production of nanoparticles formulated from nano-emulsion templates—a review. J Control Release. 2008;128:185-99. doi: 10.1016/j.jconrel.2008.02.007.
85. Wang Q, Zhang K, Weng W, Chen L, Wei C, Bao R, et al. Liquiritin-hydroxypropyl-beta cyclodextrin inclusion complex: preparation, characterization, bioavailability and antitumor activity evaluation. J Pharm Sci. 2022;111:2083-92. doi: 10.1016/j.xphs.2022.03.021.
86. Upadhyay P, Farooqui H. Optimization and characterization of self nano emulsifying drug delivery system loaded with 18-β glycerrhetinic acid. J Pharm Res Int. 2021;33:304-24. doi: 10.9734/jpri/2021/v33i59A34275.
87. Cao M, Wang Y, Jing H, Wang Z, Meng Y, Geng Y, et al. Development of an oral isoliquiritigenin self-nano-emulsifying drug delivery system (ILQ-SNEDDS) for Effective treatment of eosinophilic esophagitis induced by food allergy. J Pharm. 2022;15:1587. doi: 10.3390/ph15121587.
88. Dokania S, Joshi AK. Self-microemulsifying drug delivery system (SMEDDS)–challenges and road ahead. Drug Deliv. 2015;22:675-90. doi: 10.3109/10717544.2014.896058.
89. Kim DS, Cho JH, Park JH, Kim JS, Song ES, Kwon J, et al. Self-microemulsifying drug delivery system (SMEDDS) for improved oral delivery and photostability of methotrexate. Int J Nanomedicine. 2019;14:4949-60. doi: 10.2147/IJN.S211014.
90. Akula S, Gurram AK, Devireddy SR. Self-microemulsifying drug delivery systems: an attractive strategy for enhanced therapeutic profile. Int Sch Res Notices. 2014;2014:964051. doi: 10.1155/2014/964051.
91. Chauhan N, Vasava P, Khan SL, Siddiqui FA, Islam F, Chopra H, et al. Ethosomes: A novel drug carrier. Ann Med. 2022;82:104595. doi: 10.1016/j.amsu.2022.104595.
92. Kasai RD, Radhika D, Archana S, Shanavaz H, Koutavarapu R, Lee DY, et al. A review on hydrogels classification and recent developments in biomedical applications. Int J Polym Mate. 2022;72:1-11. doi: 10.1080/00914037.2022.2075872.
93. Kwon SS, Kong BJ, Park SN. Physicochemical properties of pH-sensitive hydrogels based on hydroxyethyl cellulose–hyaluronic acid and for applications as transdermal delivery systems for skin lesions. Eur J Pharm Biopharm. 2015;92:146-54. doi: 10.1016/j.ejpb.2015.02.025.
94. Gurpreet K, Singh SK. Review of nanoemulsion formulation and characterization techniques. Indian J Pharm Sci 2018;80:781-9. doi: 10.4172/pharmaceutical-sciences.1000422.
95. Kazemi M, Mohammadifar M, Aghadavoud E, Vakili Z, Aarabi MH, Talaei SA. Deep skin wound healing potential of lavender essential oil and licorice extract in a nanoemulsion form: Biochemical, histopathological and gene expression evidences. J Tissue Viability. 2020;29:116-24. doi: 10.1016/j.jtv.2020.03.004.
96. Cid-Samamed A, Rakmai J, Mejuto JC, Simal-Gandara J,Astray G. Cyclodextrins inclusion complex: Preparation methods, analytical techniques and food industry applications. Food Chem. 2022;384:132467. doi: 10.1016/j.foodchem.2022.132467.
97. Bernela M, Ahuja M, Thakur R. Enhancement of anti-inflammatory activity of glycyrrhizic acid by encapsulation in chitosan-katira gum nanoparticles. Eur J Pharm Biopharm 2016;105:141-7. doi: 10.1016/j.ejpb.2016.06.003.
98. Chakotiya AS, Tanwar A, Srivastava P, Narula A, Sharma RK. Effect of aquo-alchoholic extract of Glycyrrhiza glabra against Pseudomonas aeruginosa in mice lung infection model. Biomed Pharmacother. 2017;90:171-8. doi: 10.1016/j.biopha.2017.03.055.
99. Orlando G, Chiavaroli A, Leone S, Brunetti L, Politi M, Menghini L, et al. Inhibitory effects induced by Vicia faba, Uncariarhyncophylla, and Glycyrrhiza glabra water extracts on oxidative stress biomarkers and dopamine turnover in HypoE22 cells and isolated rat striatum challenged with 6-hydroxydopamine. Antioxidants. 2019;8:602. doi: 10.3390/antiox8120602.
100. Mishra D, Jain N, Rajoriya V, Jain AK. Glycyrrhizin conjugated chitosan nanoparticles for hepatocyte-targeted delivery of lamivudine. J Pharm Pharmacol. 2014;66:1082-93. doi: 10.1111/jphp.12235.
101. Shi L, Tang C, Yin C. Glycyrrhizin-modified O-carboxymethyl chitosan nanoparticles as drug vehicles targeting hepatocellular carcinoma. Biomater Res. 2012;33:7594-7604. doi: 10.1016/j.biomaterials.2012.06.072.
102. Bahadar H, Maqbool F, Niaz K, Abdollahi M. Toxicity of nanoparticles and an overview of current experimental models. Iran Biomed J. 2016;20:1-11. doi: 10.1016/j.biomaterials.2012.06.072.
103. Ajdary M, Moosavi MA, Rahmati M, Falahati M, Mahboubi M, Mandegary A, et al. Health concerns of various nanoparticles: A review of their in vitro and in vivo toxicity. J Nanomater. 2018;8:634. doi: 10.3390/nano8090634.