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REVIEW

Licorice (*Glycyrrhiza glabra* L.)-Derived Phytochemicals Target Multiple Signaling Pathways to Confer Oncopreventive and Oncotherapeutic Effects

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Abstract: Cancer is a highly lethal disease, and its incidence has rapidly increased worldwide over the past few decades. Although chemotherapeutics and surgery are widely used in clinical settings, they are often insufficient to provide the cure for cancer patients. Hence, more effective treatment options are highly needed. Although licorice has been used as a medicinal herb since ancient times, the knowledge about molecular mechanisms behind its diverse bioactivities is still rather new. In this review article, different anticancer properties (antiproliferative, antiangiogenic, antimetastatic, antioxidant, and anti-inflammatory effects) of various bioactive constituents of licorice (*Glycyrrhiza glabra* L.) are thoroughly described. Multiple licorice constituents have been shown to bind to and inhibit the activities of various cellular targets, including B-cell lymphoma 2, cyclin-dependent kinase 2, phosphatidylinositol 3-kinase, c-Jun N-terminal kinases, mammalian target of rapamycin, nuclear factor-κB, signal transducer and activator of transcription 3, vascular endothelial growth factor, and matrix metalloproteinase-3, resulting in reduced carcinogenesis in several in vitro and in vivo models with no evident toxicity. Emerging evidence is bringing forth licorice as an anticancer agent as well as bottlenecks in its potential clinical application. It is expected that overcoming toxicity-related obstacles by using novel nanotechnological methods might importantly facilitate the use of anticancer properties of licorice-derived phytochemicals in the future. Therefore, anticancer studies with licorice components must be continued. Overall, licorice could be a natural alternative to the present medication for eradicating new emergent illnesses while having just minor side effects.

Keywords: licorice, cancer, apoptosis, cell cycle, angiogenesis, treatment, nano-delivery

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Introduction

Since ancient times, humankind has strongly relied on medicinal plants and herbs in the treatment of diverse health conditions, including both benign neoplasms as well as malignant tumors.[1–3] Moreover, according to the World Health Organization (WHO) reports, about 80% of the worldwide population still depend on plant-derived drugs today, whereas several modern medicines have been originally isolated from medicinal plants.[4] It is especially the case for anticancer drugs, of which more than 60% of clinically-approved drugs are directly or indirectly derived from plant kingdom.[5,6] One of the oldest and most frequently described herbs in India, China, Southern Europe is licorice (*Glycyrrhiza. glabra* L.), as its roots have been utilized for alleviating pain and treating gastrointestinal and respiratory symptoms already for centuries.[7–9]

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This plant is believed to have originated in Iraq, being widespread in China, India, Iran, Afghanistan, Spain, Kazakhstan, Tajikistan, Kyrgyzstan, and Russia.[8,9] The extract prepared from licorice roots is very sweet and used worldwide as a flavoring agent in tobacco products, food, cosmetics and herbal remedies, with an estimated annual consumption of about 1.5 kg/person.[10] The earliest written evidence about the use of licorice date back to 2100 BC, when this plant was recommended for its health-promoting and life-enhancing properties.[11] Today, we know that the roots of licorice contain more than 20 triterpenes and about 300 flavonoids, many of which have been described to exert various pharmacological effects, including different chemopreventive and anticancer bioactivities. Considering a continuous increase in the global incidence of new cancer cases,[12–17] identification of novel efficient remedies to manage this dreadful disease is imperative.

Although several comprehensive review articles have been published about chemopreventive and anticancer activities of licorice and its bioactive phytocompounds in the recent years,[7,9,18–22] none of them analyze anticancer properties of its structurally different constituents (eg, triterpenes glycyrrhetinic acid and glycyrrhetic acid; chalcones isoliquiritigenin, licochalcone A and licochalcone E; and isoflavone isoangustone), describing both molecular mechanisms as well as bioavailability of these bioactive components.[23,24] Moreover, the present review article is focused on anticancer action of the major ingredients of licorice not only as separate agents but also in combination with approved chemotherapeutic drugs, administered as free compounds or encapsulated into nanoformulations to target the low bioavailability generally characteristic to natural substances. Therefore, this review represents an integrated contemporary overview, bringing together all the aspects we currently know about anticancer action of licorice, also providing modern solutions to the present bottlenecks associated with cancer prevention.

Literature Search Strategy and Selection Criteria

The electronic databases PubMed, Scopus, and Web of Science were searched for studies published up to 1st June, 2022, assessing the association between licorice and cancer prevention. The major key words used were licorice bioactive components and cancer cell apoptosis or cell cycle arrest or anti-inflammation or antioxidation or antiangiogenesis or antimetastasis. A manual search for additional references was also executed by referring to the reference lists of retrieved articles. The researchers completed blind double-checks, to exclude irrelevant literature by discussing with co-authors. In present review, we searched 656 articles and included 282 publications on anticancer actions of licorice constituents.

Licorice in Food and Medicine

Licorice is a sweetener that can be found in a variety of soft drinks, foods, snacks, and herbal medicines. Its sweet flavor makes it appealing to many manufacturers to mask the bitterness of many products. Licorice based snacks, Egyptian drink "erk soos", Belgian beers, pastis brands, and anisettes are all widely consumed. Tobacco product manufacturers utilize licorice as a flavoring and sweetening agent. Herbal and licorice-flavored cough mixtures, licorice tea, throat pearls, licorice-flavored diet gum, and laxatives are all examples of health items that contain licorice.[25]

Licorice is also utilized in a wide range of medical conditions. Licorice extracts have been utilized as herbal treatments in China and Japan for a long time. The biggest challenge with licorice dosing is that it comes in a variety of forms, including snacks, soft drink and health supplements with varying concentration. It has been observed that production of such health supplements is not strictly controlled. European Union established a temporary upper limit of 100 mg/day for glycyrrhizin consumption (about the amount found in 60–70 g licorice).[26] Based on data from studies involving human volunteers, recognized food committees confirmed a daily maximum of 100 mg in April 2003.[27] Due to limited human toxicity reports food committees are unable to conclude a specific intake dose of GA and ammonium glycyrrhizinate.

Glycyrrhizin is found in roughly 10–20% of licorice fluid extracts; typical doses of 2–4 mL yield 200–800 mg. According to a study, approximately 2% of frequent users ingest more than 100 mg of glycyrrhizinic acid on a daily basis.[28] Walker and Edwards[29] showed in 1994 that daily oral consumption of 1–10 mg glycyrrhizin, equivalent to 1–5 g licorice, is considered a safe amount for most healthy adults.

Licorice has long been used as an antidote to counteract the toxicity of chemotherapeutic treatment. Licorice is classified as "Rasayana" in Ayurveda (Indian traditional medicine), which indicates it has nourishing, renewing, and strengthening properties. Recent research has shown its significance in a variety of biological functions in the human body, including antioxidant and anti-inflammatory properties, as well as a protective effect on several organs.[30,31] Licorice's Generally Recognized as Safe accreditation allows it to be used in a wide range of foods at usual concentrations. Licorice's sweet flavor makes it appropriate for a variety of uses in foods, such as confectionery and sauces, with the rhizomes and roots being the most commonly utilized plant parts. For example, licorice is used in the flavoring of London drops (candy brand) and Red Vines®. Licorice powder is commonly used to add a unique flavor to sweet chilli sauce and soy sauce in condiments. Glycyrrhiza has been used to cure a variety of diseases in traditional medicine and clinical practice across cultures.[32] However, according to the extraction process,[33] geographical origin,[34,35] drying method,[36] and harvesting period,[37] the observed biological activity of Glycyrrhiza can vary.

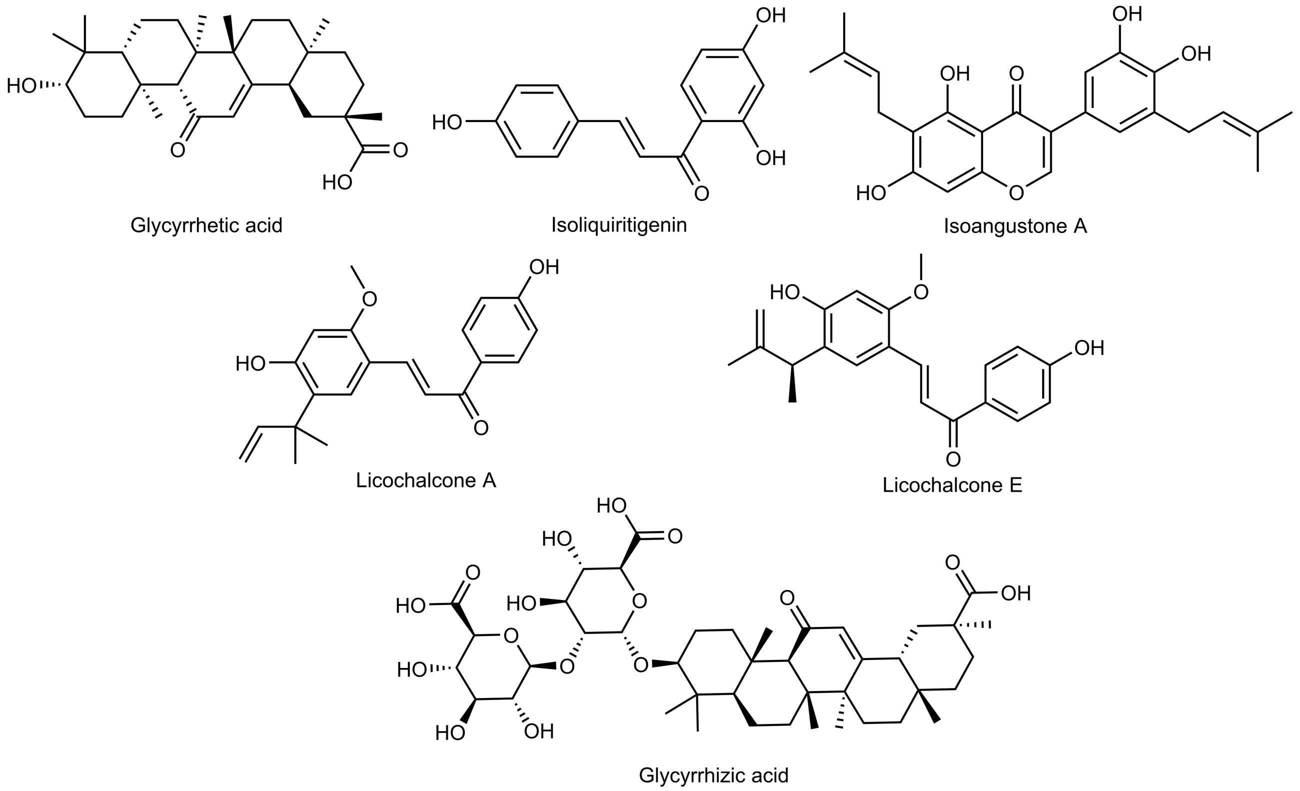
Major Bioactive Constituents of Licorice

Glycyrrhizinic Acid

The main sweet-tasting ingredient of *G. glabra* (licorice) root is glycyrrhizin (or glycyrrhizinic acid or GA). It is a pentacyclic triterpene saponin with a structure that is employed as an emulsifier and gel-forming agent in foods and cosmetics (Figure 1). Enoxolone is its aglycone. It is a glycyrrhetinic acid-containing triterpene glycoside with a wide spectrum of pharmacological and biological properties.[38,39] It comes in the forms of ammonium glycyrrhizin and monoammonium glycyrrhizin when isolated from the plant. GA is an amphiphilic molecule, with the glucuronic acid residues representing the hydrophilic region and the glycyrrhetic acid residue representing the hydrophobic region. The chemical form of GA is $C_{42}H_{62}O_{16}$, with a molecular weight of 822.92 g/mol.[40]

Glycyrrhetic Acid (GLA)

GLA, also known as glycyrrhetinic acid (Figure 1), is a β-amyrin ursane-type pentacyclic triterpenoid derivative obtained by hydrolysis of GA, which comes from the herb licorice.[41] GLA is a glycyrrhizin aglycone.[42] The chemical form of GLA is $C_{30}H_{46}O_4$, with a molecular weight of 470.7 g/mol. Many bioactive pharmaceuticals are synthesized using GLA as a precursor compound.



Glycyrrhetic acid Isoliquiritigenin Isoangustone A

Licochalcone A Licochalcone E

Glycyrrhizic acid

Figure 1 Chemical structures of major bioactive phytocompounds from licorice.

Isoliquiritigenin (ILG)

Licorice root contains isoliquiritigenin (ILG) (Figure 1), a phenolic chemical component.[43] ILG belongs to the *trans*-chalcone hydroxylated at the C-2', C-4, and C-4' class of chalcones. Chalcones are characterized chemically as α, β-unsaturated biphenyl ketones. In several plants, ILG is a precursor to numerous flavanones. ILG is a biosynthetic precursor and isomer of flavanone liquiritigenin (LG), as well as a number of other flavonoids synthesized through the phenylpropanoid pathway.[44,45] Furthermore, investigations show that ILG and LG are interchangeable by temperature and pH. The chemical form of ILG is $C_{15}H_{12}O_4$, with a molecular weight of 256.25 g/mol.

Isoangustone A (IAA)

IAA (Figure 1) is a flavonoid compound found in the root of licorice. IAA belongs to the isoflavanones family. The chemical form of IAA is $C_{25}H_{26}O_6$, with a molecular weight of 422.5 g/mol.[46]

Licochalcone A (LicoA)

LicoA (Figure 1) is a phenol chalconoid derivative found in and isolated from the roots of the Glycyrrhiza species *G. glabra* (licorice) and *G. inflata*. LicoA is a flavonoid that belongs to the oxygenated retro-chalcones group. Two phenolic hydroxyl groups, a methoxyl group, and an isoprene side chain replace the chalcone nucleus in LicoA.[47] It is one of the main important active components of licorice root.[48,49] The chemical form of Lico A is $C_{21}H_{22}O_4$, with a molecular weight of 338.4 g/mol.

Licochalcone E (LicoE)

LicoE (Figure 1) is a retrochalcone isolated from the root of *G. inflate* and possesses numerous biological and pharmacological properties.[50] The chemical form of LicoE is $C_{21}H_{22}O_4$, with a molecular weight of 338.4 g/mol.

Absorption and Metabolism Studies of Major Licorice Bioactive Compounds

With the high associated toxicity encountered by cancer patients, there is an urgent need to investigate novel ways to protect patients from the side effects of traditional drug delivery systems.[51,52] Licorice is commonly utilized as an ingredient in many traditional medicinal systems, such as traditional Chinese medicine in China, Ayurveda and Siddha in India, and Unani in Southern Europe, and it has been studied for its numerous pharmacological properties, including its anticancer capabilities.[53] Pharmacokinetic studies are required to comprehend the absorption, distribution, metabolism, and excretion (ADME) features of bioactive substances. The ADME properties of licorice bioactive compounds vary because of the natural product class they belong to such as tri-terpenoids and flavonoids as evidenced in Tables 1 and 2, respectively.

Cellular Targets of Licorice Constituents in Cancer

Anti-Inflammatory and Antioxidant Potential

Inflammation that occurs in response to physical, chemical or biological stimuli plays a substantial role in preventing or promoting carcinogenesis through immune surveillance.[54,55] Inflammatory mediators, such as growth factors, cytokines and chemokines, are released by immune cells such as macrophages, neutrophils and lymphocytes.[56] ROS, on the other hand, can play a role in activating the inflammation related transcriptional factors (eg, NF-κB and STAT-3) and contribute to the carcinogenesis processes, including genomic instability, resistance to apoptosis, cellular proliferation, angiogenesis, invasion and metastasis.[57–62] Licorice is known to have significant anti-inflammatory activity and its use in the treatment of inflammatory diseases dates back to ancient times.[63] Many studies have shown that licorice triterpenes, such as glycyrrhizin and glycyrrhetinic acid, and flavonoids, such as dehydroglyasperin C, echinatin, glabridin, glyurallin B, isoangustone A, isoliquiritigenin, licochalcone A-E, licoricidin and licorisoflavan A, have significant anti-inflammatory effects.[63,64] Glycyrrhizin, which has an anti-inflammatory effect similar to the glucocorticoids and mineralocorticoids, can inhibit inflammatory factors and promote the healing of mouth and stomach ulcers.[65] Sun and coworkers[66] have reported that glycyrrhizin suppresses lipopolysaccharide (LPS)-induced inflammatory responses via blocking the high mobility group protein box 1 (HMGB1)-Toll-like receptor 4 (TLR4)-NF-κB pathway. Moreover, glycyrrhizin and 18β-glycyrrhetinic acid have been defined by different

Table 1 ADME Profile of Triterpenoids (GA and Glycyrrhetic Acid) of Licorice

Compound	Pharmacokinetic Parameters	Results	Reference
GA	Absorption	Oral intake: C_{max} = 1.3µg/mL after a dose of 50 mg/kg. AUC = 7.3 ± 1.8 µg.h/mL Intraperitoneal: C_{max} = 238.9 µg/mL after a dose of 50 mg/kg with a mean bioavailability rate of 80% Intravenous: Decreased exponentially after administration	[210]
		Fructose containing molecules hinder the uptake of glycyrrhizin	[211]
	Distribution	Volume of distribution ranges from 37–64 mL/kg to 59–98 mL/kg	[212]
		Does not bind with any plasma proteins	[213]
	Metabolism	Conversion to 18-glycyrrhetic acid 3-O-monoglucuronide and glycyrrhetic acid by intestinal bacteria	[39,214]
		Upregulated CYP3A4 mRNA and protein expression via Pregnane X receptor activation Inhibition of CYP7A1 enzyme due to increased expression of small heterodimer protein	[215]
	Excretion	Excretion profile of 3β-monoglucuronyl-18β-glycyrrhetinic acid was measured as glycyrrhizin is completely metabolized to this by-product Average tmax was found to be 23.9 h Value of C_{max} was found to between 0.49 and 2.69 µg/mL	[216]
Glycyrrhetic acid	Absorption	Inhibitor of P-glycoprotein which affects multidrug resistance	[217]
		Inhibits uptake of sodium and copper ions when co-administered	[218]
	Metabolism	Kaempferol and berberine significantly affect bioavailability at certain time intervals	[219]
		Inhibits metabolism of cortisone and cortisol causing increased half-life and C_{max}	[220]
		Inhibits CYP3A4 enzyme	[221]
		Major route of elimination via glucuronide conjugation in a rapid way	[222]

Abbreviations: AUC, area under curve; Cmax, maximum serum concentration; CYP3A4, cytochrome P450 3A4; GA, glycyrrhizinic acid; tmax, time to peak drug concentration.

Table 2 ADME Profile of Flavonoids (Isoliquiritigenin, Isoangustone a, Licochalcone A) of Licorice

Compound	Pharmacokinetic Parameters	Results	Reference
Isoliquiritigenin	Absorption	After intraperitoneal injection: t_{max} = 60 min Rapid absorption from GI tract	[223]
	Distribution	After intraperitoneal injection biodistribution was found to be: Liver > kidney > spleen > blood > lung > brain > heart Organ biodistribution achieved at 120 min	[223]
	Metabolism	Hydroxy metabolite is a potent antioxidant but a weaker anti-apoptotic agent	[224]
		Metabolite butein formed by liver microsomes is a potent antioxidant	[225]
		Increases CYP1A1 levels Major route of elimination by glucuronidation	[226]

(*Continued*)

Table 2 (Continued).

Compound	Pharmacokinetic Parameters	Results	Reference
Isoangustone A	Metabolism	Major metabolic routes include hydroxylation, glucuronidation and sulfation	[227]
Licochalcone A	Distribution	Well distributed in liver and mammary tissues	[226]
	Metabolism	Downregulates the activity of CYP2C19, CYP2C8, CYP2C9 and CYP3A4 proteins	[228]
		Time dependent inhibition of CYP3A enzymes	[229]
		Liver microsomal pathway of biotransformation Slow metabolism by phase I pathway as compared to rapid elimination by Phase II pathways Metabolites formed were mainly from oxidation, glucuronidation and glutathione pathways	[230]
		Inhibition of CYP3A4 and P-glycoprotein transporter caused nifedipine overdose	[231]

Abbreviations: ADME, absorption, distribution, metabolism and excretion; GI, gastrointestinal.

investigators as significant inhibitors of inflammatory factors, such as cyclooxygenase-2 (COX-2), HMGP 1, inducible nitric oxide synthase (iNOS), interleukin-6 (IL-6), IL-10, tumor necrosis factor-α (TNF-α), TGF-β, prostaglandin E2 (PGE2), myeloperoxidase (MPO) and nuclear factor-κB (NF-κB).[67–72] Dehydroglyasperin C has been reported to suppress the production of ROS and singlet oxygen radicals, and it exerts anti-inflammatory activities by reducing the DNA binding activity of NF-κB, increasing the expression of MKP-1 and heme oxygenase-1, and inhibiting COX-2 expression via blocking the MKK4 and PI3K pathways.[73–75] Although echinatine, licochalcone A and licochalcone B inhibit IL-6 and PGE2 in LPS-induced macrophage cells, licochalcones B and D reduce the production of TNF-α and monocyte chemotactic protein 1 (MCP-1).[76–78] Moreover, licochalcone C inhibits the NF-κB pathway by reducing the expression of iNOS, ICAM-1 and VCAM-1. Licochalcone E also shows anti-inflammatory activity by suppressing NF-κB and AP-1 and reducing the expression of iNOS and COX-2.[79,80] In addition, glabridin, one of the most studied anti-inflammatory flavonoids isolated from licorice, suppresses inflammatory responses in different cell lines via the NF-κB pathway and inhibition of the expression of various cytokines and chemokines.[81] It has been reported by different researchers that glabridin suppresses the expression of C-X-C motif chemokine ligand 5 (CXCL5), IL-1β, IL-6, IL-8, IL-12, IL-17A, IL-22, IL-23, interferon (IFN)-α/β, iNOS, monocyte chemoattractant protein-1 (MCP-1), nitric oxide (NO), TNF-α, PGE2, COX-2, MPO and lipoxygenase (LOX) and inhibits the activation of the p38 MAPK, ERK, NF-κB and AP-1 signaling pathways (Figure 2).[81] A natural chalcone called isoliquiritigenin, isolated from licorice, also has significant anti-inflammatory activity via inhibition of caspase-1, COX-2, IL-1, IL-6, IL-8, iNOS, TNF-α, NF-κB ligand RANKL and eotaxin-1, and suppression of the NF-κB, MAPK, AP-1 signaling pathways and NLRP3 inflammasome activation.[45,82–87] Furthermore, isoliquiritigenin and isoliquiritin inhibit inhibitory κBα (IκBα) phosphorylation and degradation, and increase the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 in LPS-induced macrophage cells.[88]

The phenolic ingredients, such as chalcones, coumarins, flavonoids, isoflavones and methylated isoflavones, seem to be responsible for the antioxidant activity of licorice (Figure 2). ROS has a high affinity for DNA and other biomolecules. This can result in DNA damage and oncogenic mutations being incorporated into normal cells leading to genomic instability, and finally cancer.[89] Due to the phenolic hydroxyl structure of chalcones, they act as proton donors and combine with a radical to prevent oxidative damage.[90,91] The chalcones isolated from licorice, such as echinatin, isobavachalcone, isoliquiritigenin, and licochalcones A-D, have been reported as powerful antioxidant agents.[76,92,93] Although isobavachalcone and licochalcones A-D suppress NADPH induced lipid peroxidation, echinatin and licochalcone A and B possess strong radical scavenging activity. Licochalcone A and C elevate the expression of antioxidant enzymes, such as catalase, glutathione

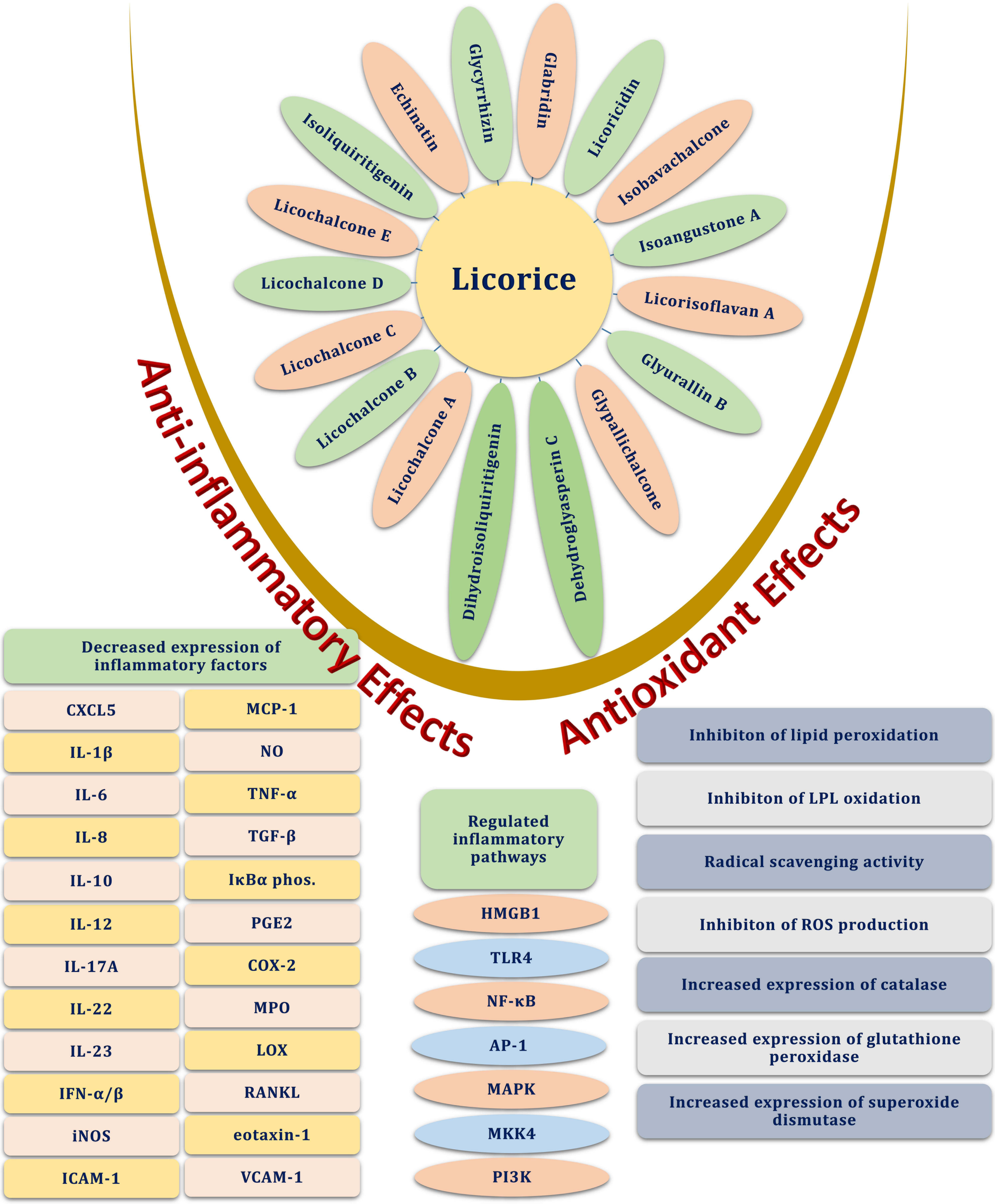


Figure 2 Anti-inflammatory and antioxidant activities of licorice and its constituents.

Abbreviations: AP-1, activator protein 1; COX-2, cyclooxygenase-2; CXCL5, C-X-C motif chemokine ligand 5; HMGB1, high mobility group protein box 1; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase ICAM-1, intercellular adhesion molecule 1; IκBα phos, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha phosphate; LOX, lysyl oxidase; LPL, lipoprotein lipase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MKK4, mitogen-activated protein kinase kinase 4; MPO, myeloperoxidase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B; NO, nitric oxide; PGE2, prostaglandin E2; PI3K, phosphatidylinositol 3-kinase; RANKL, receptor activator of nuclear factor kappa-Β ligand; ROS, Reactive oxygen species; TGF-β, transforming growth factor-β; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule 1.

peroxidase and superoxide dismutase.[94,95] Moreover, dihydroisoliquiritigenin inhibits glutamate-induced oxidative stress in neuronal cells, and glypallichalcone acts as an inhibitor of LPL oxidation.[96,97] Similar to the chalcone derivatives, coumarin compounds in licorice have significant radical scavenging activity.[98,99] Moreover, saponins and polysaccharides isolated from licorice have been reported to exert antioxidant activities.[100–102] Consequently, it seems that the triterpenes, chalcones, coumarins, flavonoids, isoflavones and methylated isoflavones have significant antioxidant activity inhibiting the processes of carcinogenesis, and these contents of licorice have great potential as novel anticancer agents.

Apoptosis and Cell Cycle Arrest

Cancer is one of the leading diseases affecting human life and is caused by various reasons, such as environmental pollution and unhealthy lifestyle.[103–106] Apoptotic cell death is known to regulate cancer cell proliferation, invasion and survival. Intrinsic and extrinsic apoptosis are the two major pathways induced by chemotherapeutics to inhibit tumor proliferation (Figure 3). Inhibition of apoptosis is considered to be an important mechanism toward drug resistance. In recent years, the interest has shifted to exploring apoptotic phytochemicals for cancer treatment and overcoming drug-resistance with lower side-effects.[56,107–111] The anticancer properties of licorice were studied in MCF-7 (breast cancer) and HepG2 (liver cell carcinoma) cell lines where licorice root extract was used to synthesize gold nanoparticles (AuNPs). It was observed that 50 µg/mL and 23 µg/mL of the synthesized AuNPs could successfully inhibit the growth of MCF-7 and HepG2 cell lines, respectively.[112] Similar results were obtained in a study conducted by Vlaisavljević et al[113] where different cancer cell lines, such as SiHa, HeLa (cervical), T47D, MDA-MB-361, MDA-MB-231, and MCF7 (breast), and A2780 (ovarian), were treated with licorice extract and it was found that 30 µg/mL extract induced apoptosis or necrosis in the cells, inhibiting tumor growth.

Licorice contains various flavonoids, such as glabridin, glycyrrhetinic acid, Lico, GA, ILG, and liquiritin.[114] The glabridin exhibits anticancer activities as it activates the caspase cascade and mitochondrial apoptotic pathway leading to apoptosis in cancer cells.[115] It regulates various signaling pathways, such as signal transducer and activator of transcription 3 (STAT-3), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAPK) and extracellular-signal-regulated kinase (ERK) to inhibit proliferation of various cancer cells, and induces apoptosis of these cells. Glabridin induced apoptosis in Huh7 liver cancer cells by cleaving caspase-9 levels

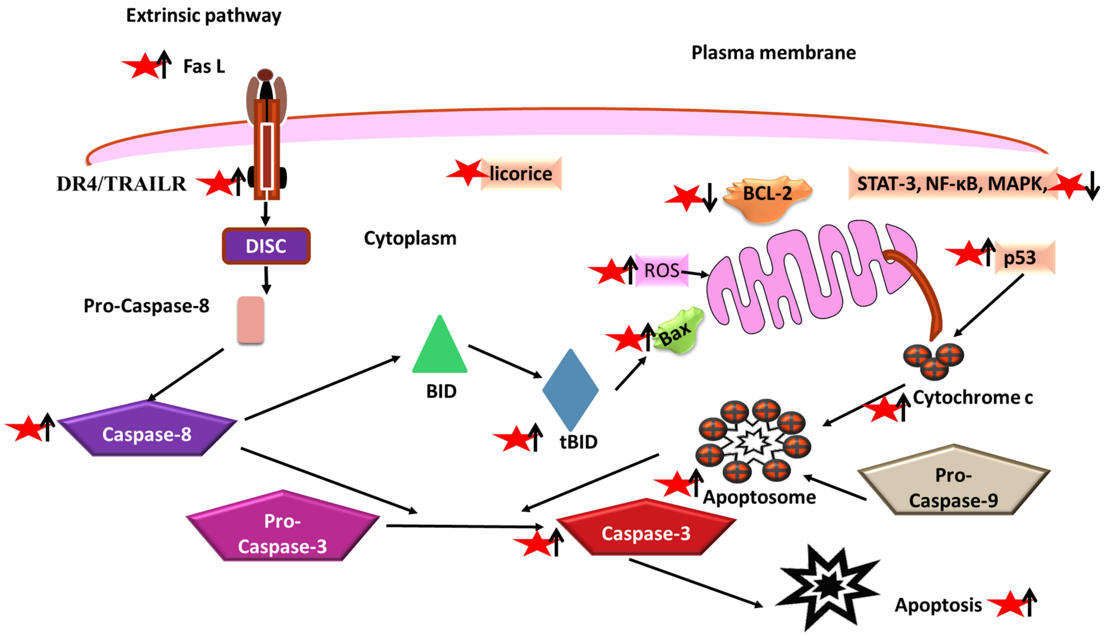


Figure 3 Suggested apoptotic mechanisms of bioactive metabolites of licorice. They are known to initiate apoptotic cell death in cancer via intrinsic and extrinsic mechanisms.

Abbreviations: Bax, Bcl-2-associated X protein; BCL-2, B-cell lymphoma 2; DISC, death-inducing signaling complex; DR4, Death receptor; Fas (L), Fas ligand; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B; ROS, reactive oxygen species; STAT-3, signal transducer and activator of transcription 3; tBID, truncated BID; TRAILR, TNF-related apoptosis-inducing ligand.

and increasing the release of cytochrome c (cyt. c),[116] and in SK-BR-3 breast cancer cells by cleaving caspase-9, caspase-8, and caspase-3, and increasing the concentration of PARP.[117] Further, in addition to the caspase cascade, glabridin induced apoptosis in HL-60 acute myeloid leukemia cells by activating the JNK1/2 and p38 MAPK signaling pathways.[118] The glycyrrhetinic acid and its derivatives induce mitochondrial-mediated apoptosis in cancer cells, as it was found in a study conducted by Lin et al[119] where apoptosis was induced by the generation of reactive oxygen species (ROS) when NTUB1 (human bladder cancer cells) were exposed to glycyrrhetinic acid 25. Another derivative of glycyrrhetinic acid, 18β- glycyrrhetinic acid (GRA) caused apoptosis in MCF-7 by activating the mitochondrial death cascade, caspase-9 and release of cyt. c. GRA had no inhibitory effect on the MCF-10 A (normal mammary epithelial cells).[120] In another study, it was found that GRA was capable of inducing cell cycle death in HepG2 cells by arresting cell growth in the G1-phase and inducing apoptosis at a higher concentration.[121] Another triterpene compound exhibiting antitumor properties is glycyrrhizin which is isolated from the roots of licorice. The antitumor activity of glycyrrhizin has been demonstrated in DU-145 and LNCaP human prostate cancer cells. Glycyrrhizin induces apoptosis in both cell lines in a concentration-dependent and time-dependent manner.[122] Further, the GA, another flavonoid extracted from the roots of licorice also induces apoptosis and suppresses the proliferation of MDA-MB-231 breast cancer cells by increased generation of ROS.[123] GA induces cell cycle arrest at G1/S phase in gastric cancer cells by downregulating the cyclin E1, cyclin E2, and cyclin D1-3 levels causing cell death in these cancer cells.[124]

Another important group of metabolites of licorice is chalcones.[82,125] The chalcones inhibit cancer cell growth by interacting with the protein nucleophiles and inducing autophagy, apoptosis, and cell cycle arrest in cancer cells.[126] Licochalcones A, B, C, and D, ILG, echinate, paratocarpin A, kanzonol C, and isoliquiritin apioside (ISLA) are different kinds of chalcones studied for their anticancer properties. Lico A inhibits cancer cell growth through the mitochondrial pathway by activating the caspase cascade and mediating apoptotic and antiproliferative effects via a Sp1-mediated signaling pathway.[127] There are several studies depicting the anticancer properties of lico A in gastric cancer cells,[128] PC-3 prostate cancer cells,[129] and glioma cells.[130] Lico B exhibits its anticancer activity via caspase-3 activation, Bax expression enhancement,[131] suppressing the expression of CDK1, CDK2 mRNA, cyclin A, antiapoptotic proteins (Mcl-1, Bcl-xL, and Bid), and leading to S-phase arrest.[132] Licochalcones C and D, and kanzonol C have anticancer mechanism similar to licochalcone B.[133–135] Different studies demonstrate the anticancer mechanism of ILG in breast cancer cells arresting the cancer cell growth at G0/G1 phase,[136] A549 non-small-cell lung cancer cells by activation of the protein kinase B survival pathway and caspase cascades,[137] renal cancer cells by ROS generation and STAT-3 pathway inhibition,[138] and oral squamous cells by G2/M cell cycle arrest.[139] Endoplasmic reticulum (ER)-stress) and ROS signaling pathways induce extrinsic and intrinsic apoptosis, leading to the cancer cell death in esophageal squamous cells when treated with echinatin.[140] Tables 3 and 4 represent an overview of various in vitro and in vivo anticancer studies mediated by bioactive compounds of licorice.

Antiangiogenesis Effect

Angiogenesis or neovascularization is considered to play a vital role in tumor proliferation and metastasis.[141–144] In tumors, angiogenesis is intervened by targeting numerous markers that regulate angiogenesis and are considered proangiogenic factors, such as vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs) and basic fibroblast growth factor (bFGF).[145–148] These angiogenesis markers have a broader spectrum of target cells which play an essential role in angiogenesis.[149,150] In a hypoxic condition, tumor cells cause the release of proangiogenic factors, such as VEGFs, epidermal growth factor (EGF), FGF, insulin-like growth factor-1 (IGF1) and transforming growth factor-β1 (TGFβ1)), within the tumor.[151] In tumor cells, VEGF is the main angiogenic activator that stimulates angiogenesis via binding to VEGFR2[152] (Figure 4). Therefore, according to literature, targeting these pathways' inhibitors in angiogenesis by herbal plant extract and isolated phytoconstituents was considered an anticancer treatment approach with clinical importance.

The extract of *G. glabra* used to treat mice with Ehrlich ascites tumor cells showed a reduction in the level of cytokines and decreased VEGF revealing its angioinhibitory potential.[153] Licochalcone A (LicA) is a potent constituent of licorice having various biological properties, such as anti-inflammatory, antiangiogenic and antitumor effects. LicA was reported for its apoptosis inducing potential in prostate cancer via modulating the protein expression of Bcl-2. LicA inhibits the process of angiogenesis and tumorigenesis both in vitro and in vivo by regulating the signaling of VEGFR-2.[154] In addition, LicA also reduced the vessel

Table 3 In vitro Anticancer Effects and Mechanistic Insight of Licorice Bioactive Phytocompounds

Type of Cancer	Cell Lines	Anticancer Effects	Mechanisms	Concentration	Reference
Melanoma	SK-MEL-28 and SK-MEL -5	Induced apoptosis	↓G1 phase, ↓cyclin D1, ↓cyclin E, ↓p-Akt, ↓p-GSK3β, ↓p-JNK1/2, ↓PI3K, ↓MKK4, ↓MKK7	10–20 μM	[46]
Glioma	C6	Suppressed cell proliferation	↓Cell viability, ↑cytotoxicity towards cancer cells, ↑antitumor activity, ↓cell number, ↑differentiated morphology, ↑reversion of tumor cells to the normal differentiated cells, ↓topoisomerase IIγ	1, 10, 25, 50, 75, and 100 μM	[232]
Nasopharyngeal	C666-1 cells	lncRNA-regulated mechanism	↓lncRNA, ↓AK027294, ↑production of EZH1, ↑caspase-3, ↑caspase-8, ↑caspase-9	0.25, 0.5, and 1 mg/mL	[233]
Nasopharyngeal	C666-1	Induced apoptosis	↑Antiproliferative properties, ↑apoptosis rate, ↑percentage of down-regulated amino acids and lipids leading to decreased metabolic disorders, ↓cell proliferation, ↓cell viability, ↑caspase-9 protease activities, ↑caspase-3	0.2, 0.5, and 1 mg/mL	[234]
Pharyngeal squamous	FaDu	Induced apoptosis	↑Cytotoxicity towards cancer cells, ↑number of dead cancer cells, ↑chromatin condensation, ↑Fas, ↑cleaved caspase-8, ↑Bax, ↑apoptotic protease-activating factor 1, ↑caspase-9, ↑p53, ↓Bcl-2, ↑cleaved caspases-3, ↑cleaved PARP	0,12.5,25 and 50 μg/mL	[202]
Adenoid cystic	ACC-2 and ACC-M	Induced autophagic and apoptotic cell death	↓mTOR, ↑appearance of membranous vacuoles, ↑formation of acidic vesicular organelles, ↑punctate pattern of LC3 immunostaining, ↓autophagic flux, ↓apoptosis, ↓LC3- II/LC3-I ratio, ↓ cleavage of LC3, ↓autophagic flux, ↑caspase-3, ↑Bax/Bcl-2 ratio, ↑PARP-cleavage, ↓phosphorylated-S6 (downstream target of mTOR)	5–20 μM	[235]
Colon	HT-29	Induced apoptosis	↓Proliferation, ↓viability of cells, ↑cell death of cancer cells, ↓HSP90	50,100,150, and 200 μg/mL	[236]
Non-small cell lung cancer	H1975 A549	Inhibited metastasis	G0/G1 growth phase cycle arrest, ↓number of cells at both S growth phase and G2/M growth phase, ↓cyclin B1 and cyclin A2, ↓p21 (CDK inhibitor), ↑CDK2, ↑ESR1, ↑PPARG, ↑ESRRA, ↑PRKACA, ↑CXCL8, ↑PLAA, ↑RXRB, ↑MAPK14 levels of CDK4, ↓cyclin D1, ↓CDK4-Cyclin D1 complex	200,400,600 and 800 μg/mL	[237]
Gastric	MKN28	Inhibited metastasis	↓Proliferation and metastasis, ↓migration and invasion, ↑LC3II/LC3I ratio, ↑Beclin 1, ↓p62, ↓p-Akt, ↓p- mTOR	0,5,10,15 and 20 μM	[238]
Hepatocellular	MHCC97-H, LO2, and SMMC7721	Induced apoptosis and autophagy	↓Cell viability and proliferation, ↑apoptosis frequency, ↑Bax, ↑cleaved-caspase-3, ↑cleaved PARP, ↑endogenous LC3-II, ↓ Bcl- 2, ↓P62, punctate LC3, ↓p-Akt, ↓p-PI3K, ↓p- mTOR	12.5, 25, and 50 μM	[239]
Hepatocellular	HuH7 and HepG2	Induced autophagy	↑Autophagosome number, ↑ROS generation, ↑TSC1/2 complex, ↑PRAS40, ↑ CTMP, ↑PP2A, ↑ PDK1 and ↑Rubicon ↑LC3 II, ↑cleaved-PARP, ↑cleaved-caspase-3	10,20,50,100 μM	[240]
Renal	Caki	Induced apoptosis	↑Cleavage of caspase-9, caspase-7 and caspase-3, and PARP, ↑Bax, ↓Bcl-2, ↓ Bcl-xL, ↑cyt. c release, ↑p53, ↓MDM2, ↑ROS levels, ↓STAT3, ↓cyclin D1 and D2, ↓p-JAK2,	0,5,10,20 and 50 μM	[138]
Breast	MDA-MB -231 triple negative	Induced apoptotic and autophagic-mediated apoptosis	↓Cell cycle progression, ↓cyclin D1, ↑sub-G1 phase population, ↓Bcl-2, ↑ Bax, ↑caspase-3, ↑PARP, ↓mTOR, ↓p-mTOR ↓ULK1, ↓cathepsin B, ↑p62, ↑Beclin1, ↑ LC3, ↑caspase-8	10, 25 and 50 μM	[241]

(*Continued*)

Table 3 (Continued).

Type of Cancer	Cell Lines	Anticancer Effects	Mechanisms	Concentration	Reference
Breast	MDA-MB -231	Induced apoptosis	↓Cell migration, ↓cell proliferation, ↑ mitochondrial membrane potential, ↑DNA damage, ↓ oxidative stress, ↑cleaved-caspase 3 and 9, ↓Bcl-2 expression, ↑E-cadherin ↓Vimentin, ↓N-cadherin, ↑release of cytochrome c from the mitochondria into the cytoplasm, ↑ROS	30–40 μM	[242]
Breast	MDA-MB -231	Exerted anti-inflammatory and antitumorigenic effects	↓NO production, ↓iNOS, ↓LPS/IFN-γ, ↑NF κB, ↑ERK, ↑miR-155, ↓bound p50 and p65	10,50,100 and 200 μM	[243]
Breast	MCF-7	Induced apoptosis	Cell cycle arrest in the G1 phase, ↓Bcl-2, ↑Bax, ↓cyclin D1, ↑PARP cleavage, ↑CIDEA	15, 10, and 5 μg/mL	[244]
Breast	MCF-7	Induced apoptosis	↓Cell viability and proliferation, ↑apoptosis frequency, ↑TFF1 (pS2), ↑CTSD, ↑CDKN1A (an effector of p53), ↑RPS6KA (RSK; MAPK-related) ↑NRIP1 (RIP140, AP-1-related), ↓TP53I11 (p53- related), ↓PRKCD ↓ARHGDIA (a Ras super-family gene)	0.1–100 μM	[245]
Murine mammary	4T1 and MCF-10A	Inhibited metastasis	↓Tumor growth, cell proliferation, ↓VEGF-A, ↓CD31 ↓HIF-1α, ↓iNOS, ↓COX-2	0,1,2.5 and 5.0 μg/mL	[246]
Bladder	T24	Induced apoptosis	↑Nuclear condensation, ↑ nuclear fragmentation, ↑ apoptotic ratio, ↑decrease in the $\Delta\Psi$ m, ↑Bax, ↑ Bim, ↑Apaf-1, ↑caspase-9, ↑caspase-3, ↓Bcl-2, ↑CDK2	10,20,30,40,5, 60.70 and 80 μg/mL	[247]
Bladder	T24	Induced apoptosis	↓Proliferation, ↑ROS,↑apoptosis frequency, ↑mitochondrial dysfunction, ↑caspase-3, ↑PARP cleavage, ↑ER stress; GRP 78, ↑growth arrest, ↑DNA damage-inducible gene 153/C/EBP homology protein (GADD153/CHOP) expression, ↑caspase-12	20, 40, 60, 80, or 100 μM	[248]
Endometrial	HEC-1A, Ishikawa, and RL95-2	Inhibited metastasis	↓Survival rate of cancer cells, ↓N-cadherin, ↑E-cadherin	1, 5, 10, and 20 μM	[182]
Endometrial	Ishikawa, HEC-1A, and RL95-2 cells	Induced apoptosis and autophagy	↓Viability of cancer cells, ↑sub-G1 or G2/M phase arrest, ↑DNA damage, ↑cell cycle arrest, ↑apoptotic cell death, ↑cleaved caspase-3, ↑cleaved PARP, ↑caspase-7/LC3BII, ↑p-ERK, ↑LC3-II, ↑SQSTM1/p62 levels	5, 10, 25, 50, 75, and 100 μM	[249]
Prostate	PC-3	Induced apoptosis and autophagy	↓Proliferation, G0/G1 cell cycle arrest, ↑apoptotic effect, ↑necrosis percentage, LC3B-II protein, ↑LC3B-II/LC3B-I ratio, ↑LC3A, ↑mRNA level ULK1 and AMBRA1, ↑NBR1 and p62	3–200 μg/mL glycyrrhiza extract + 3–100 nM Adriamycin	[250]
Ovarian	OVCAR5 and ES-2	Induced apoptosis	↓Viability of cancer cells, ↑G2/M phase arrest, ↑cleaved PARP, ↑cleaved caspase-3, ↑Bax/Bcl-2 ratio, ↑LC3B-II, ↑Beclin-1	1, 5, 10, 20, 25, 50, 75, and 100 μM	[251]
Cervical	SiHa, HeLa, HK 2	Induced autophagy and apoptosis	↓Viability of cancer cells, ↑cleaved-caspase-3, ↑cleaved caspase-9, ↑cleaved-PARP, ↓Bcl-2, ↑LC3-II, ↑Beclin1, ↑Atg5, ↑Atg7 ↑ Atg12, ↓PI3K (p85), ↓p-Akt (ser473), ↓p-mTOR (ser2448), ↓p-mTOR (ser2481)	10, 30, and 50 μM	[252]

(*Continued*)

Table 3 (Continued).

Type of Cancer	Cell Lines	Anticancer Effects	Mechanisms	Concentration	Reference
Osteosarcoma	Saos-2	Induced apoptosis	↓Proliferation, ↓cell migration, ↓cyclin D1, ↑p53, ↑p21, ↑p27, ↓Bcl-2, ↑Bax, ↓level of ATP-synthesis, ↓ PI3K/Akt signaling, ↓MMP2, ↓MMP9	0,3,10,30, and 100 μM	[253]
Osteosarcoma	U2OS	Induced apoptosis	↓Proliferation, ↓invasion and migration, ↑apoptosis, ↑Bax, ↑active caspase-3, ↓Bcl- 2, ↓p-Akt, ↓p-mTOR, ↓PI3K/Akt signaling pathway	5, 10 and 20 μM	[254]

Abbreviations: AMBRA1, activating molecule in Beclin-1-regulated autophagy protein 1; AP-1, activator protein 1; Apaf-1, apoptotic protease activating factor-1; ARHGDIA, Rho GDP dissociation inhibitor alpha; Atg, autophagy related; ATP, adenosine triphosphate; Bax, BCL2 associated X; BCL-2, B-cell lymphoma 2; CD31, cluster of differentiation 31; CDK, cyclin dependent kinase; CDKN1A, cyclin dependent kinase inhibitor 1A; CHOP, CCAAT/enhancer-binding protein (C/EBP) homologous protein; CIDEA, cell death activator; COX-2, cyclooxygenase-2; CTMP, carboxyl-terminal modulator protein; CTSD, cathepsin D; CXCL, chemokine (C-X-C motif) ligand; DNA, deoxyribonucleic acid; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ESR1, estrogen receptor 1; ESRRA, estrogen related receptor alpha; EZH-1, enhancer of zeste 1 polycomb repressive complex 2 subunit; GADD, growth Arrest and DNA damage inducible protein 153; GRP78, glucose-regulating protein; HIF-1α, hypoxia inducible factor 1α; HSP, heat shock protein; IFN-γ, interferon- γ; IL, interleukin; iNOS, inducible nitric oxide synthase; LC3, microtubule-associated protein 1A/1B-light chain 3; lncRNA, long non-coding RNA; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; miR, microRNA; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; mRNA, messenger ribonucleic acid; mTOR, mammalian target of rapamycin; NBR1, neighbour of BRCA1 gene; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NRIP1, nuclear receptor-interacting protein 1; p-Akt, phospho-Akt; PARP, poly (adenosine diphosphate-ribose) polymerase; PDK1, phosphoinositide-dependent kinase 1; p-ERK, phospho-extracellular signal-regulated kinase; p-GSK3β, phospho-glycogen synthase kinase-3β; PI3K, phosphoinositide 3-kinase; p-JNK, phospho-c-Jun N-terminal kinase; PLAA, phospholipase A2-activating protein; PP2A, protein phosphatase 2A; PPARG, peroxisome proliferator-activated receptor gamma; PRAS, proline-rich Akt substrate; PRKACA, protein kinase CAMP-activated catalytic subunit alpha; PRKCD, protein kinase C delta; RIP140, receptor-interacting protein 140; ROS, reactive oxygen species; RPS6KA, p90 ribosomal S6 kinase-3; RSK, ribosomal S6 kinase; RXRB, retinoid X receptor beta; SQSTM1, sequestosome 1; STAT3, signal transducer and activator of transcription 3; TFF1, trefoil factor 1; TP53, tumor protein p53; TSC, tuberous sclerosis complex; ULK1, Unc-51-like autophagy activating kinase 1; VEGF-A, vascular endothelial growth factor A; ΔΨ, mitochondrial membrane potential.

Table 4 In vivo Anticancer Effects and Mechanistic Insight of Licorice Bioactive Phytocompounds

Type of Cancer	Animal Models	Antitumor Effects	Observed Changes	Dosage	Duration	Reference
Melanoma	BALB/c nu/nu mice xenografted with SK-MEL-28 cells	Induced apoptosis	↓Tumor growth, ↓tumor volume, ↓tumor weight	2 or 10 mg/kg	35 days	[46]
Adenoid cystic carcinoma	BALB/c nude mice xenografted with ACC-M cells	Induced autophagic and apoptotic cell death	↓Tumor frequency, ↑LC3, ↑autophagic responses, ↑apoptosis, ↓mTOR, ↑Atg5 expression	0.5 g/kg or 1 g/kg/	30 days	[235]
Colon	Male BALB/c mice injected with CT-26 cells	Inhibit tumor metastasis	↓Tumor weight, ↑spleen index, improve the physical condition of the tumor bearing mice, ↑formation of tumor necrotic foci through recruiting inflammatory cells, no infiltrated cancer cells were found in the lungs, ↑gut friendly bacteria	500 mg/kg	15 days	[238]
Colon	BALB/c mice bearing CT-26 cells	Induces apoptosis	↓Tumor growth, ↑immune organ index, ↑CD4+, ↑CD8+ immune cells population, ↑IL 2, ↑IL 6, ↑IL 7, ↓TNFα	500 mg/kg	14 days	[255]
Colon	CT 26	Induces apoptosis	↓Proliferation of cancer cells, ↑IL-7 gene,↓tumor growth, ↑CD4+ and CD8+ immune cells population, ↑IL 2, IL 6, IL 7, ↓TNFα	1–100 μg/mL 500 mg/kg once daily	14 days	[255]
Non-small cell lung	C57BL/6 mice injected with LLC cells	Anti-metastatic	↑PD-L1, ↑CD8+,↑antigen presentation	200 mg/kg	19 days	[237]

(*Continued*)

Table 4 (Continued).

Type of Cancer	Animal Models	Antitumor Effects	Observed Changes	Dosage	Duration	Reference
Hepatocellular	BALB/c-nu/nu mice xenografted with Hep3B cells	Inhibit metastasis and induces apoptosis	↓Cyclin D1, ↓PI3K/Akt signaling pathway, ↓Vimentin, ↓N-cadherin,↓Bcl-2	50 mg/kg,	18 days weeks	[256]
Hepatocellular	Hep3B	Inhibit metastasis and induces apoptosis	G1/S cell cycle arrest, ↓migration and metastasis of cancer cells, ↓cyclin D1, ↑p21, ↑p27, ↓cell cycle transition, ↓PI3K/Akt pathway, ↑E-cadherin, ↓Vimentin, ↓N-cadherin,↓Bcl-2,	30,40,50,60 µM 50 mg/kg	3 weeks	[256]
Hepatocellular	BALB/c nude mice xenografted with SMMC7721 cells	Induces apoptosis and autophagy	↓Tumor growth, ↓tumor volume, ↓body weight, ↓tumor weight, ↑cleaved-PARP, ↑cleaved-Caspase-3, ↑Bax, ↑ LC3II, ↓ mTOR, ↓p-Akt, ↓ p-mTOR, ↓Bcl-2	50 mg/ Kg	24 days	[235]
Breast	Nude-Foxn1nu mice xenografted with MDA-MB-231cells	Induce apoptotic and autophagic-mediated apoptosis	↓Tumor weight, ↓volume, ↑caspase-3, ↑ Ki-67, ↑ p62, ↓ VEGF	2.5 and 5.0 mg/kg	14 days	[237]
Breast	Athymic nu/nu mice xenogarfted with MDA-MB-231 cells	Anti-inflammatory and anti-tumorigenic	↓Tumor weight, ↓tumor outgrowth, ↓ iNOS, ↓3-NT, ↓inflammation, ↓JAK2/STAT3	10 mg/kg	28 days weeks	[239]
Endometrial	Nude mice (CAnN. Cg-Foxn1nu/CrlNarl xenografted with HEC-1A-LUCcells	Inhibit metastasis	↓Cancer cell migration, ↓tumor metastasis, ↓peritoneal dissemination and serum level of TGF-β1, ↓N-cadherin, ↓p-Smad2/3, ↓TWIST1/2, ↑E-cadherin	10 mg/k	28 days	[182]
Murine mammary	BALB/c mice xenografted with 4T1 cells	Inhibits metastasis	↓p-p65NFκB, ↓MMP-9, ↓ICAM-1, ↓VCAM-1, ↓VEGF-A, ↓metastatic lung nodules, ↓infiltration of macrophages, ↓CD31, ↓VEGF-receptor(r)2, ↓LYVE-1, ↓VEGF-C, ↓VEGF-R3	2 or 4 mg/ kg	21 days	[246]
Endometrial	Athymic nude mice by subcutaneous injection of HEC-1A-LU)	Induces apoptosis and autophagy	↓Tumor growth, ↓PCNA, ↓caspase-7, SQSTM1/p62, ↓LC3B	1 mg/kg	46 days	[249]
Cervical	Athymic BALB/c mice xenografted with SiHa cells	Induces autophagy and apoptosis	↑↓Body weight, ↑cleaved-PARP, ↑cleaved-caspase-3, ↑LC3-II, ↓Ki-67	10 and 20 mg/kg	28 days	[252]
Osteosarcoma	NOD-SCID mice xenografted with Saos-2 cells	Induces apoptosis	↓PCNA, ↓MMP2, ↓ MMP9, ↑caspase-3, ↓p-PI3K, ↓p-Akt	50 mg/kg	56 days	[253]

Abbreviations: Atg, autophagy related; Bax, BCL2 associated X; BCL-2, B-cell lymphoma 2; CD, cluster of differentiation; ICAM, intercellular adhesion molecule; IL, interleukin; iNOS, inducible nitric oxide synthase; JAKL, Janus Kinase 1; LC3, microtubule-associated protein 1A/1B-light chain 3; LC3, microtubule-associated protein 1A/1B-light chain 3; LYVE-1, lymphatic vessel endothelial hyaluronan receptor 1; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; PARP, poly (adenosine diphosphate-ribose) polymerase; PCNA, proliferating-cell nuclear antigen; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; p-Smad 2/3, phosphorylated small mothers against decapentaplegic 2/3; SQSTM1, sequestosome 1; STAT-3, signal transducer and activator of transcription 3; TGF-β1, transforming growth factor-β; TNF-α, tumor necrosis factor-α; TWIST ½, Twist family basic helix-loop-helix transcription factor 2; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

formation by endothelial cells as well invasion and migration via modulating the expression of MMP-9, VEGF-A and plasminogen activators.[155] In a study, Jiang et al[156] reported that glabridin, a potent constituent of *G.glabra*, has anticancer potential as it inhibits the migration, invasion and angiogenesis of human breast cancer cells by modulating the FAK/Rho signaling pathway. The aqueous extract of *G. glabra* blocks the in vitro and in vivo proliferation of Ehrlich ascites tumor cells.

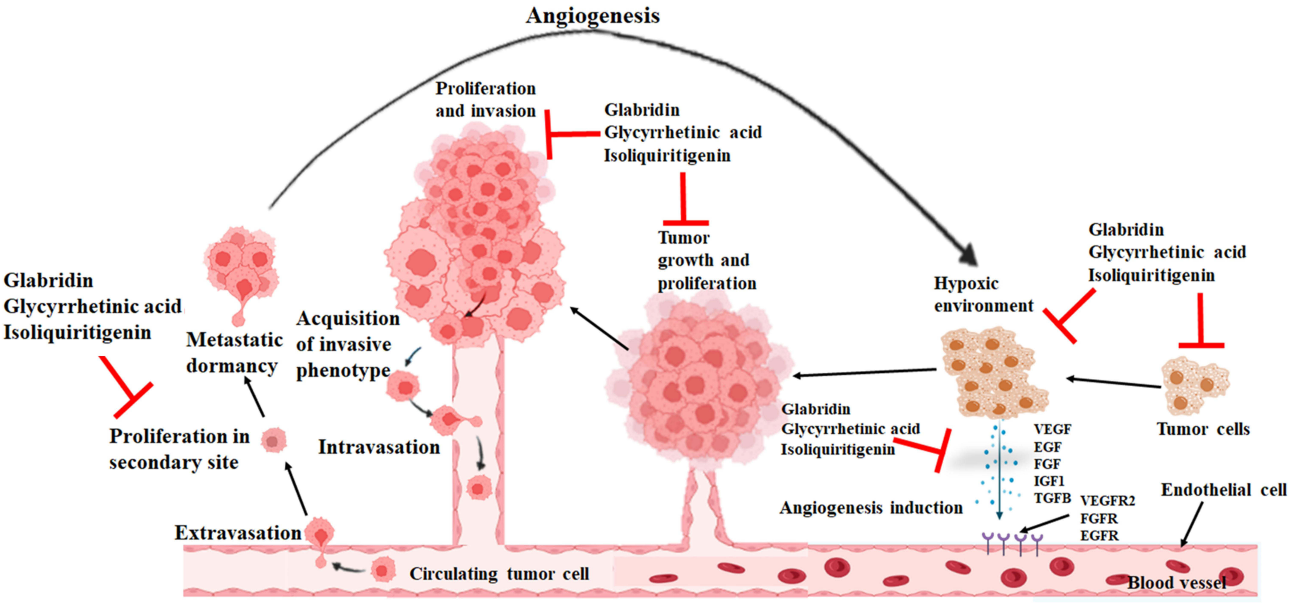


Figure 4 Tumor angiogenic processes and growth of cancer progression are inhibited by phytoconstituents isolated from licorice.

Abbreviations: EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; IGF1, insulin-like growth factor-1; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factors; VEGFR2, vascular endothelial growth factor receptors 2.

According to Kim et al.[157] Glycyrrhizin isolated from the roots of *G. glabra* inhibited the metastasis and survival of tumor by modulating the levels of onco-suppressor p53 gene, MAPK, ERK and EGFR which led to apoptosis and showed antiangiogenetic effect.

Antimetastic Activities

Metastasis is a multistep process that contributes to the spread of cancer cells to distant organs of the body through blood or the lymphatic system, resulting in death in cancer patients.[158–163] Targeting metastasis is an attractive strategy in the management of progression and development of cancer (Figure 5).[164–166] According to literature, various in vitro and in vivo models

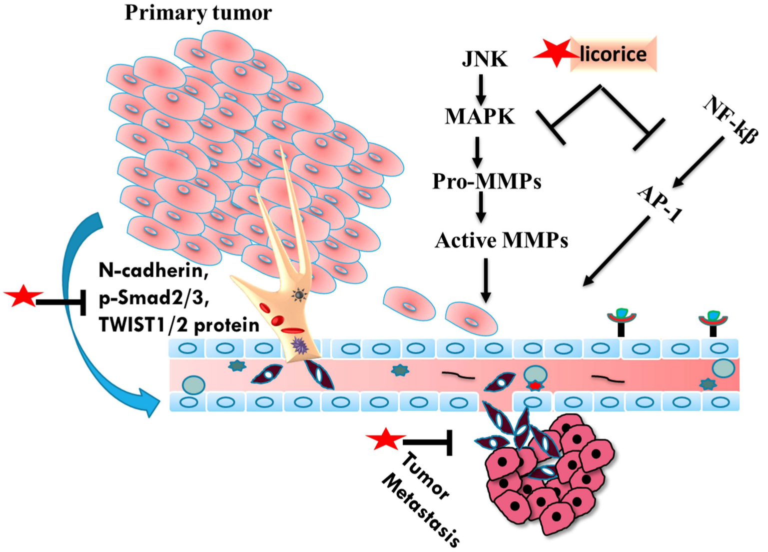


Figure 5 Antimetastatic actions governed by bioactive metabolites of licorice. It has been observed that metabolites of licorice suppress the expression of MMPs via JNK/MAPK and AP-1 signaling.

Abbreviations: AP-1, activator protein 1; JNK, c-Jun N-terminal kinases; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B; p-Smad 2/3, phosphorylated small mothers against decapentaplegic 2/3, TWIST ½, Twist Family basic helix-loop-helix transcription factor 2.

showed that natural bioactive compounds, including those from *G. glabra*, have antimetastasis potential[167] including Matrix metalloproteinases (MMPs), such as MMP-2, and MMP-9, and urokinase plasminogen activator (uPA) play a significant role in the metastasis process by degrading extracellular matrix (ECM) of cancerous cells as well as modulating the mechanism of angiogenesis in the maintenance of tumor cell survivability.[168,169] MMPs are degradation enzymes that modulate numerous physiological processes, such as cell growth, differentiation and apoptosis. However, overexpression of MMP-2 and MMP-9 is linked with prooncogenic events, such as neoangiogenesis, tumor cell proliferation, and metastasis.[170–172] In addition to MMPs, ERK1/2, p38, MAPK and JNK/SAPK play a central role in the regulation of cancer metastasis expression.[173–176] Furthermore, once cancer cells develop a more invasive nature, they can enter blood and spread to distant regions, resulting in metastasis. Tumor cells that have moved to a secondary site can either go into metastatic dormancy or stimulate angiogenesis and start growing new blood vessels.[177] Hence, to control the mechanism of metastasis, targeting oncogenic molecular pathways by natural phytoconstituents is an important therapeutic approach.[178,179]

Glabridin, a major chemical constituent of licorice, significantly blocks the migration/invasion of various HCC cells, namely Huh7 and Sk-Hep-1, by modulating the expression levels of MMP-9 and the phosphorylation processes of ERK1/2 and JNK1/2 markers. This inhibitory effect was linked with an upregulation of tissue inhibitor of MMP-1 and a downregulation of the transcription factors NF-κB and activator protein 1 signaling pathways.[180] Wang et al[181] reported that GA has the potential to suppress breast tumor outgrowth and pulmonary metastasis by modulating the p38 MAPK-AP1 signaling pathway. In vitro experimentation revealed that LicE decreased the expression of specificity protein 1 (Sp1) in MCF-7 and MDA- MB-231 cell lines, resulting in regulation of the cell cycle as well as inhibiting the process of carcinogenesis and tumor metastasis. Isoliquiritigenin, an isolated component of licorice, inhibited the process of tumor metastasis via upregulating E-cadherin and downregulating the N-cadherin, p-Smad2/3, and TWIST1/2 protein expression in HEC-1A, Ishikawa, and RL95-2 xenograft animal model.[182]

Synergistic Actions of Licorice Phytochemicals with Anticancer Agents

Licorice is extensively used as an herbal medicine in traditional Chinese as well as Indian medicine to treat gastric, liver, and respiratory problems and different types of cancers, and to reduce the toxicity caused by other herbs. Licorice and its flavonoids show more potential effect against various cancers when used in conjunction with other anticancer drugs. Numerous studies have been conducted to investigate the role of licorice and other anticancer drugs individually in various cancers. These chemotherapeutic drugs showed great potential in the treatment of a diverse range of cancers, on the other hand, they also exert side effects to the normal cells and induce toxicity.[183–185] But when the researchers used anticancer drugs, such as paclitaxel, cisplatin, and gemcitabine in combination with licorice, it inhibited the side effects by protecting the normal cells from toxicity along with enhancing anticancer potential. Tables 5 and 6 show the synergistic effects of licorice with other anticancer drugs both in vitro and in vivo.

Table 5 In vitro Synergistic Action of Licorice Phytocompounds with Various Anticancer Drugs

Licorice Metabolites	Anticancer Drugs	Type of Cancer	Cell Lines	Mechanisms	Reference
Liquiritigenin	Cisplatin	Melanoma	B16F10	↓PI3K/Akt, ↓MMP-2, ↓MMP-9	[257]
Glycyrrhizin	Cisplatin	Hepatocellular carcinoma	Huh7	↑MRP2, MRP-3, MRP-4, MRP5 m-RNAs	[258]
Licochalcone-A	Paclitaxel and vinblastine	Leukemia, breast cancer	MCF-7 and HL-60	↓Bcl-2 and Bcl-2/Bax	[258]
Licochalcone-A	Geldanamycin	Ovarian cancer	OVCAR-3 and SK-OV-3	↑Caspase-8- and Bid-dependent pathways and the mitochondria-mediated apoptotic pathway	[259]
Isoliquiritigenin	Cyclophosphamide	Cervical cancer	U14	↓Proliferation	[260]

Abbreviations: Bax, BCL2-associated X; BCL-2, B-cell lymphoma 2; MMP, matrix metalloproteinase; MRP, multidrug resistance associated proteins; PI3K, phosphoinositide 3-kinase.

Table 6 In vivo Synergistic Effect of Licorice with Various Anticancer Drugs

Metabolites of Licorice	Anticancer Drugs	Type of Cancer	Model	Antitumor Effects	Mechanisms	Reference
Liquiritigenin	Cisplatin	Melanoma	Female C57 BL/6 black mice	Suppressed cell migration and cell invasion	↓PI3K/Akt	[257]
Licoricidin	Gemcitabine	Osteosarcoma	Female BALB/c nude mice	Enhanced cytotoxicity	↓Akt and NF-κB	[261]
Licochalcone A	Cisplatin	Colon carcinoma	BALB/c mice	Suppressed cell proliferation	↓DNA synthesis	[262]
Isoliquiritigenin	Cyclophosphamide	Cervical Cancer	KM mice	Suppressed cell proliferation	DNA strand break	[260]

Abbreviations: NF κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase.

Nanotechnology Studies of Bioactive Constituents of Licorice in Cancer

Nanotherapeutics (1–100 nm) have been shown to overcome the shortcomings of conventional treatments,[185] such as unwanted side effects on rapidly growing healthy cells, non-specific targeting and distribution, dose-dependent toxicity, and multi-drug resistance.[185–187] They possess enhanced target-specificity, increased permeability and retention time of the drug in the cancer cells, improved biocompatibility, and decreased dose of the drug which together contribute to reduced toxicity.[185,188,189] Romberg et al[190] and Cheng et al[191] pointed out that recently developed nanoparticles possess various limitations, thereby shifting the focus of formulation sciences to natural compounds-based nanoparticles which would increase targeting efficiency to cancer cells and lower the rate of clearance. This is further supported by various advantages, such as increased patient compliance (with peroral administration), less extensive metabolic by-products and subsequent higher bioavailability.[192] As summarized in Tables 7 and 8, various nanoformulations containing licorice and its bioactive compounds were developed and tested against specific cancer types and results from these studies have been listed. Various cell line studies, as evidenced by Table 7, have focused on hepatic carcinoma due to the abundance of glycyrrhetinic acid receptors which are over-expressed on hepatocytes making it a viable targeting options.[193] These have been explored due to the limitations of conventional therapies as mentioned above. The results from cell line studies need to be tested in animal models to confirm the efficacy and safety of the drug or formulation under study. The studies listed

Table 7 In vitro Studies of Nanoformulations of Bioactive Compounds of Licorice

Formulation Type	Drug Used	Cell Line	Main Results	Reference
GA-alginate nanogel	Doxorubicin + Glycyrrhizin (20 mg/mL)	Murine macrophage cell line (RAW 264.7)	Activation and invasion by macrophages averted due to the presence of glycyrrhizin Cells retained the normal morphology, less nitric oxide production Reduced IL-6 and tumor necrosis factor-α expression Reduced phagocytosis of drug	[263]
		Hepatocellular carcinoma HepG2 cells	Confirmed pathway of endocytosis and active liver targeting which increased nanogel particle phagocytic intake Decreased cell viability and increased cell toxicity, apoptosis due to reduced efflux activity of p-glycoprotein, upregulation of caspase-3 mRNA and a high Bax/Bcl-2 ratio	

(*Continued*)

Table 7 (Continued).

Formulation Type	**Drug Used**	**Cell Line**	**Main Results**	**Reference**
PEGylated nano-liposomes	Silibinin (25% w/v) + GA (75% w/v) (IC_{50} = 48.67 µg/mL)	Human hepatocellular carcinoma HepG2 cells and fibroblast cells	Decreased IC50 value and increased cytotoxicity (10x) than respective free drugs Synergistic action of silibinin in presence of GA	[264]
Nano-micelles formulated as solid dispersion using tannic acid and disodium glycyrrhizin	Camptothecin (0.0145 µg/mL)	Human hepatocellular carcinoma HepG2 cells	Increased cell inhibition and cell apoptosis activity compared to free drug Tannic acid inhibited P-gp glycoprotein efflux activity thereby increasing cellular drug uptake	[265]
Glycyrrhizin Conjugated Dendrimer and Multi-Walled Carbon Nanotubes	Doxorubicin (Dendrimer IC_{50} = 2 µM) (Nanotubes IC_{50} = 2.7 µM	Human hepatocellular carcinoma HepG2 cells	Reduction in IC_{50} value of the drug compared to formulations without glycyrrhizin and free drug Increased cytotoxicity due to increased drug intake via receptor mediated endocytosis Dendrimers (more apoptotic cells) are more effective carriers than nanotubes (more necrotic cells) when attached with glycyrrhizin	[266]
GA-conjugated human serum albumin nanoparticles	Resveratrol (IC_{50} = 62.5 µg/mL)	Hepatocellular carcinoma HepG2 cells	Concentration dependent uptake	[267]
Valerate- conjugated chitosan nanoparticles surface modified with glycyrrhizin	Ferulic acid (IC_{50} = 60 µg/mL)	Hepatocellular carcinoma HepG2 cells	Increased cytotoxicity due to glycyrrhizin receptor mediated intake of drug	[268]
Glycyrrhetinic acid-modified hyaluronic acid nanoparticles	Adenine (0.25 mg/mL)	Human HepG2 cells, L02, Bel-7402 and MCF-7 cells	Absorption into HepG2 in a time dependent manner Targeting efficiency: HepG2>L02>MCF-7 Inhibition of colony formation in time and dose dependent manner Induced apoptosis in cancer cells thus inhibiting proliferation of cancer cells	[269]
Glycyrrhetinic acid-modified hyaluronic acid nanoparticles	Docetaxel (IC_{50} = 1.6 µg/mL)	HepG2 cells and Human breast cancer MCF7 cells	More uptake by HepG2 than MCF7 cells Decrease in IC50 values and cell viability compared to free drug Inhibition of colony formation of HepG2 cells in time and dose dependent manner Increased apoptosis and deformed morphology	[270]
Hyaluronic acid-glycyrrhetinic acid conjugated nanoparticles	Doxorubicin (IC_{50} = 5.75 µg/mL)	Hepatocellular carcinoma HepG2 cells	Increased cleavage in presence of glutathione Rapid intracellular release and nuclear delivery of drug compared to standard of care conventional formulations	[271]

(*Continued*)

Table 7 (Continued).

Formulation Type	Drug Used	Cell Line	Main Results	Reference
Glycyrrhetinic acid-modified curcumin supramolecular hydrogel	Curcumin (IC_{50} = 10.7 μM)	Hepatocellular carcinoma HepG2 and Mouse fibroblast 3T3 cells	Reduced IC50 values Greater targeting efficiency Higher cellular uptake due to pro-gel formulation approach	[272]
Glycyrrhetinic Acid Functionalized Graphene Oxide	Doxorubicin (0.5 μg/mL)	Human hepatocellular carcinoma HepG2 cells, normal human hepatic L02 cells, and rat cardiac muscle H9c2 cells	Targeting efficiency: HepG2>L02>H9c2 Taken via endocytosis and delivered to mitochondria Decreased the potential difference of mitochondrial membrane which in turn opened up mitochondrial permeability transition pore to initiate a series of responses and leads to caspase-3 activation necessary for apoptosis	[273]
Glycyrrhetinic acid-functionalized mesoporous silica nanoparticles	Curcumin (2 mg/mL)	Hepatocellular carcinoma HepG2 cells	Higher cytotoxicity compared to curcumin loaded mesoporous silica nanoparticles Receptor mediated endocytosis intake of drug Increased rate of apoptosis	[274]
Dual-functional (modified with glycyrrhetinic acid and L-histidine) hyaluronic acid nanoparticles	Doxorubicin (5 μg/mL)	Hepatocellular carcinoma HepG2 cells	Decrease in IC50 values Increased drug distribution in cytoplasm and nuclear regions Receptor mediated endocytosis intake of drug	[275]
Nano-suspension	Isoliquiritigenin (0.18 μM)	A549 lung cancer cells	Increased apoptosis at 7.5 to 10-fold Less cytotoxic to healthy cells	[276]
Isoliquiritigenin-iRGD nanoparticles	Isoliquiritigenin (50 μM)	Human breast cancer cell lines (MDA-MB231 and MCF7) and mouse breast cancer cell line (4T1)	MCF7 cells showed better inhibition than free drug but not better than isoliquiritigenin nanoparticles MDA-MB231 and 4T1 showed better inhibition than isoliquiritigenin nanoparticles formulation and free drug Increased apoptosis compared to free drug and nanoparticles due to high rates of cellular drug uptake	[277]
Isoliquiritigenin loaded nanoliposomes	Isoliquiritigenin (<12.5 μM)	HCT116, SW620 and HT29 colorectal cancer cell lines	Better inhibition compared to free drug Increased rate of apoptosis Decreased uptake of glucose and lactic acid Reduced oxygen consumption led to reduced adenosine triphosphate synthesis Decreased Akt/mTOR expression which is important for tumor progression	[278]

Abbreviations: Bax, BCL2-associated X; BCL-2, B-cell lymphoma 2; GA, glycyrrhizinic acid; IC_{50}, half maximal inhibitory concentration; mTOR, mammalian target of rapamycin; w/v, weight/volume.

in Table 8 represent the intratumor studies conducted thereby helping to uncover the tremendous potential possessed by these nanoformulations in the chemotherapeutic field. Our thorough search revealed that although there were in vitro and in vivo studies carried out for isoangustone A,[194–197] licochalcone A[198–201] and licochalcone E[155,202,203] as anticancer molecules, there were no studies conducted for these molecules in the nanotherapeutics domain. The difficulties

Table 8 In vivo Studies of Nanoformulations of Bioactive Compounds of Licorice

Formulation Type	Drug Used	Model Used	Main Results	Reference
Glycyrrhzic acid-alginate nanogel	Doxorubicin + glycyrrhizin (2.5 mg/kg)	Male Sprague-Dawley rats	Higher blood concentrations of therapeutic agent Increased distribution half-life by 7.5 folds Decreased elimination rate	[263]
		H22 tumor bearing Kunming mice	Glycyrrhzic acid inhibited multidrug resistance protein-1 in hepatoma cells enhancing the availability of drug and subsequently anti-tumor activity Less systemic toxicity with no body weight loss	
Nano-micelles formulated as solid dispersion using tannic acid and disodium glycyrrhizin	Camptothecin (5 mg/kg)	Male Sprague-Dawley rats	Improved bioavailability compared to free drug	[265]
		HepG-2 tumor-bearing BALB/c nude mice	Highest distribution at 8h with maximum amount concentrated at tumor site Increased tumor inhibition activity Maintained body weight Tumor cells displayed increased interstitial spaces, large necrotic area and decreased nuclear chromatin	
GA-conjugated human serum albumin nanoparticles	Resveratrol (5 mg/kg)	H22 tumor bearing male Kunming mice	Better and concentrated biodistribution to liver	[267]
Glycyrrhetinic acid-modified hyaluronic acid nanoparticles	Adenine (10 mg/kg)	Kunming mice	Faster biodistribution within 1 hour in mice compared to free drug Reduced tumor volume effectively compared to control and placebo groups Decreased proliferating cell nuclear antigen levels Increased apoptotic cell count	[267]
Hyaluronic acid-glycyrrhetinic acid conjugated nanoparticles	Doxorubicin (4 mg/kg)	H22 tumor bearing Kunming mice	Improved biodistribution with liver tumor targeting efficiency Decreased tumor volume No significant weight loss	[271]
Glycyrrhetinic Acid Functionalized Graphene Oxide	Doxorubicin (2 mg/kg)	HepG2 cells bearing BALB/c nude mice	Increased Bax:Bcl2 ratio confirmed mitochondrial permeability transition pore opening and activation of caspase 3.7 and 9 Decreased tumor size significantly	[273]
Dual-functional (modified with glycyrrhetinic acid and L-histidine) hyaluronic acid nanoparticles	Doxorubicin (5 mg/kg)	H22 tumor bearing mice	Increased liver targeting capacity Higher tumor inhibition efficiency	[275]
Isoliquiritigenin-iRGD nanoparticles	Isoliquiritigenin (25 mg/kg)	4T1 bearing female nude mice	Mean tumor volume reduced Higher mitotic bodies indicate reduced cell viability	[277]

Abbreviations: Bax, BCL2-associated X; BCL-2, B-cell lymphoma 2.

encountered during the manufacturing of these medications as nanotherapeutics could be one of the factors limiting their usage as anticancer moieties. The findings suggest that these compounds could be developed into viable anticancer nanomedicines in the future. As a result, the findings can be extended, implying that they have a lot of potential for future clinical research. More research is needed to overcome the problems of nanoformulations and generate reliable medicines with few adverse effects.

Safety Studies of Licorice

In general, licorice products are considered to have no hazard to the public and are utilized widely in food (ice cream, candies, chewing gums, and beverages), cosmetics (toothpaste) and tobacco as flavoring and sweetening agents.[7,9] However, before licorice extract or any of its individual components can enter into clinical oncological practice, due to their strong pharmacological activities, their safety must be verified thoroughly and systematically, paying special attention to the dosage and duration of the treatment.[18] Several studies have indeed warranted for the toxicity of licorice depending on its dosage and duration.[18] Actually, chronic licorice intake was shown to induce a condition comparable to that found in primary hyperaldosteronism, while licorice overconsumption resulted in hypermineralocorticoidism characterized by salt and water retention, hypertension, hypokalemia, metabolic alkalosis, and suppression of the renin-aldosterone system.[28,204] Biochemical evidence suggests that licorice and its phytochemicals, particularly glycyrrhizinates, can reversibly block the cortisol-inactivating enzyme, 11β-hydroxysteroid dehydrogenase, thereby producing hypermineralocorticoid-like effects.[205] In addition, based on a case report, excessive consumption of licorice may also lead to toxic consequences in the form of thrombocytopenia.[206] Therefore, health care providers should be aware of the hazardous consequences related to chronic and excessive intake of licorice extracts to be able to prevent worsening of these symptoms when detected early [16]. Furthermore, caution must be exercised when using licorice during pregnancy, as heavy licorice consumption has been associated with lower gestational age and preterm delivery in humans.[207,208] Accordingly, the main challenge in exploiting the promising anticancer activities of licorice constituents in clinical settings primarily lies on its appropriate dosing, besides targeted delivery to malignant sites, inducing minimal adverse reactions in normal healthy tissues. It is highly expected that future experimental studies with nano-sized carriers will provide a strong base for overcoming these challenges by virtue of modern nano-technological methods.

Clinical Trials

Several clinical trials conducted with licorice products have also reported glycyrrhizin-related complications, such as elevated blood pressure due to increasing extracellular fluid volume and large artery stiffness, and reduced serum potassium levels.[209] However, other clinical trials (mostly on the gastrointestinal disorders) have suggested diverse healing properties of licorice preparations without exerting any observable adverse effects.[205,209] A clinical stage II preliminary trial revealed that licorice root extract in combination with docetaxel works in treating patients with hormonal therapy resistant metastatic prostate tumors (NCT00176631). Similarly, licochalcone A and paclitaxel have been shown to increase natural cell death and apoptosis in OSCC tumors (NCT03292822).

Conclusions and Perspectives

Our present review describes anticancer potential of the phytoconstituents of *G. glabra* along with synergistic chemotherapeutic insight. Traditionally, licorice has been utilized as a sweetening and flavoring agent for food items. Roots of licorice are reported to possess strong therapeutic potential to reduce inflammation and cancer progression. Among the reported phytoconstituents, the flavonoids and terpenoids are the major therapeutically active molecules. The in vitro and in vivo data presented in the current review article clearly show the strong potential of licorice-derived phytochemicals from the classes of triterpenes, chalcones and isoflavones in the fight against different types of cancer. Despite potential therapeutic importance of these effects, several obstacles, such as toxic reactions observed with excessive consumption, have impeded moving on with clinical trials. It is highly expected that surpassing these bottlenecks by using modern nanotechnological methods might lead us to expansion of the current anticancer arsenal. In addition, as licorice constituents possess a wide range of molecular targets in cancer, they might be helpful in preventing drug resistance. Therefore, synergistic mechanistic insight of licorice-derived phytoconstituents and conventional chemotherapeutic drugs should be further explored. There are few human studies available and more randomized controlled trials are needed to measure the effectiveness of licorice-based cancer treatment. The story of licorice reflects a fascinating example of how an ancient herbal medicine can be introduced as a drug into clinical settings, after intensive efforts in elucidating its constituents and molecular mechanisms behind their various bioactivities.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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