Glycyrrhiza glabra (Licorice)-Containing Herbs in Cancer Treatment

Subjects: Integrative & Complementary Medicine

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Cancer is one of the leading causes of premature death and a significant barrier to increasing life expectancy in almost every country in the world. Licorice belongs to the genus *Glycyrrhiza*, and *radix glycyrrhizae* (RG) is the dried roots and rhizomes of licorice. Licorice, as well as licorice-purified compounds, has the potential to abrogate the onset and progression of different malignancy cancers, both in vitro and in vivo. Moreover, previous studies also suggest that licorice is a beneficial medicine plant used as a cure for nausea and vomiting.

licorice cancers chemotherapy

1. Utility of Licorice-Containing Herbs in Cancer

1.1. Licorice Introduction

Licorice belongs to the genus *Glycyrrhiza*, and *radix glycyrrhizae* (RG) is the dried roots and rhizomes of licorice. Licorice is commonly used as a natural sweetener and in herbal medicine. It mainly acts as a supplement in Western countries, for products such as herbal teas, soft drinks, and tobacco products. However, it is regarded as a medicine in Asia. Licorice is utilized to relieve pain, phlegm, spasms, cough, and dyspnea. The abundant active ingredients in licorice demonstrate efficacy in many different biological and physiological functions. To date, more than 300 bioactive compounds have been identified in licorice, including ~100 types of triterpenoid saponins and sapogenins, and ~300 kinds of phenolic compounds [1]. However, it has been found that the cultivated geographical area, the state of plant maturity, environmental conditions (including the pH of the soil, temperature, and weather), harvesting, and processing all affect the content of the bioactive compounds in licorice [2]. For example, the triterpenoid saponins in licorice, especially glycyrrhizic acid (GL; approximately 1.84% to 9.82% of licorice, depending on the sources and methods of extraction), are the major constituents and bioactive ingredients of licorice [3][4][5]. Flavonoids (approximately 1.78% to 4.82% of licorice, depending on the sources and methods of extraction) are the other main bioactive compound found in licorice, including isoliquiritigenin (ISL), isoliquiritin, and liquiritigenin, etc. [3][6]. In the 2010 edition of the Chinese Pharmacopoeia, GL and isoliquiritigenin were selected as the biomarkers for licorice, and it is stated that their content should exceed 2% and 0.5%, respectively [7]. Interestingly, researchers found that these two major compounds (GL and ISL) appear in many studies related to chemotherapy, which will be discussed further in a later section.

Licorice can be simply categorized into three Glycyrrhiza species: *Glycyrrhiza uralensis Fisch*., *Glycyrrhiza glabra L*., and *Glycyrrhiza inflata Bat*. [8]. In China, *G. uralensis*, *G. glabra*, and *G. inflata* are considered equivalent, and are combined and utilized as licorice without discrimination in the 2015 edition of the Chinese Pharmacopoeia. However, the morphological characteristics of the three Glycyrrhiza species show differences in the root, rhizome, seed, fruit, and inflorescence, as well as in the leaf and stem height. It is difficult to identify these licorice species accurately based only on their root or rhizome morphology [9].

There are significant differences between the species, which were established by the analytical methods of numerous studies aimed at separating and quantifying the active ingredients in licorice samples. These studies report that different licorice species have species-specific markers (**Table 1**); for example, the content of major flavonoids (liquiritin, liquiritigenin, and isoliquiritin) in *G. uralensis* is higher than that in *G. glabra*, and glycycoumarin only exists in *G. uralensis* [10][11][12][13][14]. Glycyrrhizin, 50 times sweeter than sugar and especially suitable for children, is evenly distributed in the three species [13]. The amount of isoliquiritigenin (2′,4′,4-trihydroxychalcone, ISL), one of the major bioactive compounds in licorice, is higher in *G. uralensis* than in *G. glabra* and *G. inflata*. [15][16].

Table 1. Most common *Glycyrrhiza* species used as medicine.

Glycyrrhiza Species	Region	Specific Content	Ref
Glycyrrhiza uralensis (Glycyrrhiza radix)	China Northeastern Far east Russia	Owning the highest content of flavonoids (liquiritin, liquiritigenin, and isoliquiritin). Glycycoumarin only represented in *G. uralensis*.	[10][11][12] [13][14][17]
		Isotrifloliol, licoricone, neoglycyrol, glycyrin, and licorisoflavan A in *G. uralensis* are higher.	[10]
		Glyinflanin D/G and licoflavone B are absent.	[18]
Glycyrrhiza glabra	Italy Spain China Russia Iran Central Asia	Owning the highest content of 18α-glycyrrhizic acid and 18β-glycyrrhizic acid.	[19]
		Higher content of saponins–licorice saponin K2/H2, licorice saponin B2, and licorice saponin G2/yunganoside K2. Quercetin absent in *G. glabra*.	[18][20][21]
		The highest content of apiosides (liquiritin apioside, isoliquiritin apioside, licuraside).	[14]
		Abundant 8-cyclized isoprenyl isoflavanes (e.g., glabridin and 4′-O-methylglabridin).	[13]
		Polysaccharide content in *G. glabra* is the highest.	[22][23]
Glycyrrhiza	China, Asia	Highest content of triterpene saponins.	[9][13]

Glycyrrhiza Species	Region	Specific Content	Ref
inflata		Chalcone derivatives such as licochalcone (A, B, C, E), kanzonol C, and echinatin in *G. inflata* are higher.	[13][18][24]
		The content of quercetin is higher than that in *G. uralensis*.	[18][20][21]
		Highest content of prenylated chalcones.	[18]

tential as
d allergic responses, as well as preventing liver damage [8][25][26]. Licorice extract also acts as a moderate hypocholesterolemic nutrient, and a potent antioxidant agent, to prevent cardiovascular disease [27]. Clinical data suggest that licorice, or its bioactive components, prevent dyspepsia and hyperlipidemia [28][29]. When taken concurrently with a glycyrrhizin-containing product, licorice is shown to afford hepatoprotection during alcohol consumption [30]. Three randomized clinical trials claim that Glycyrrhiza acts as a mucoadhesive film, improving oral mucositis during radiotherapy [31][32][33]. Moreover, preoperative gargling with a licorice solution reduces postoperative sore throat, thus, revealing its analgesic properties [34]. The clinical trials of licorice are summarized in **Table 2**.

Table 2. Licorice and its components applied in chemopreventive clinical trials.

Name	Disease/Disorder	Dose/Duration	Patient (*n*)	Trial Experiment Group	Trial Control Group	Outcome	Location/ Identifier No.	Ref
Extract of *G. glabra*	Radiotherapy Head or neck	Oral 100 c.c/Bid 2 weeks	*n* = 37	Extract of *G. glabra*	Placebo (radiotherapy)	Prevent oral mucositis	IRCT201203012464N4 Iran Tehran University of medical science	[31]
G. glabra (yashtimadhu)	Radiotherapy Head or neck	Oral 5 g/Bid 6 weeks	*n* = 127	*G. glabra*	Placebo (radiotherapy)	Prevent oral mucositis	Himalayan Institute of Medical Sciences, Dehradun, India	[32]
Licorice	Radiotherapy Head or neck	Mouth wash	*n* = 60	Licorice mucoadhesive film	Placebo mucoadhesive film	Prevent oral mucositis	Isfahan University of Medical Sciences, Isfahan, Iran	[33]
Licorice extract	Randomized Double-blind	Oral 1 g/Tid	*n* = 236	+licorice extract	Sugar water	Pain relieving	NCT02968823	[34]
Licorice	Dyspepsia	380 mg/Bid 4 weeks	*n* = 120	+licorice	N.A.	Improved *H. pylori* eradication	IRCT2014061718124N	[28] [29]
Glycyrrhizin	Alcohol consuming	Oral 0.1–0.3% 12 days	*n* = 24	+Licorice	Placebo (alcohol)	Hepato-protection	N.A.	[30]

2. Bioactive Components of Licorice

Licorice root contains a variety of bioactive components, including alkaloids, polysaccharides, polyamines, triterpenes, phenolic acids, flavones, flavans, chalcones, flavonoids, and isoflavonoids. Among them, only a few can be characterized and isolated from licorice. Only the components studied for chemoprevention are discussed (See **Table 3**), such as glycyrrhetic acid (GA) and chalcone-type derivative isoliquiritigenin (ISL) (**Figure 1**).

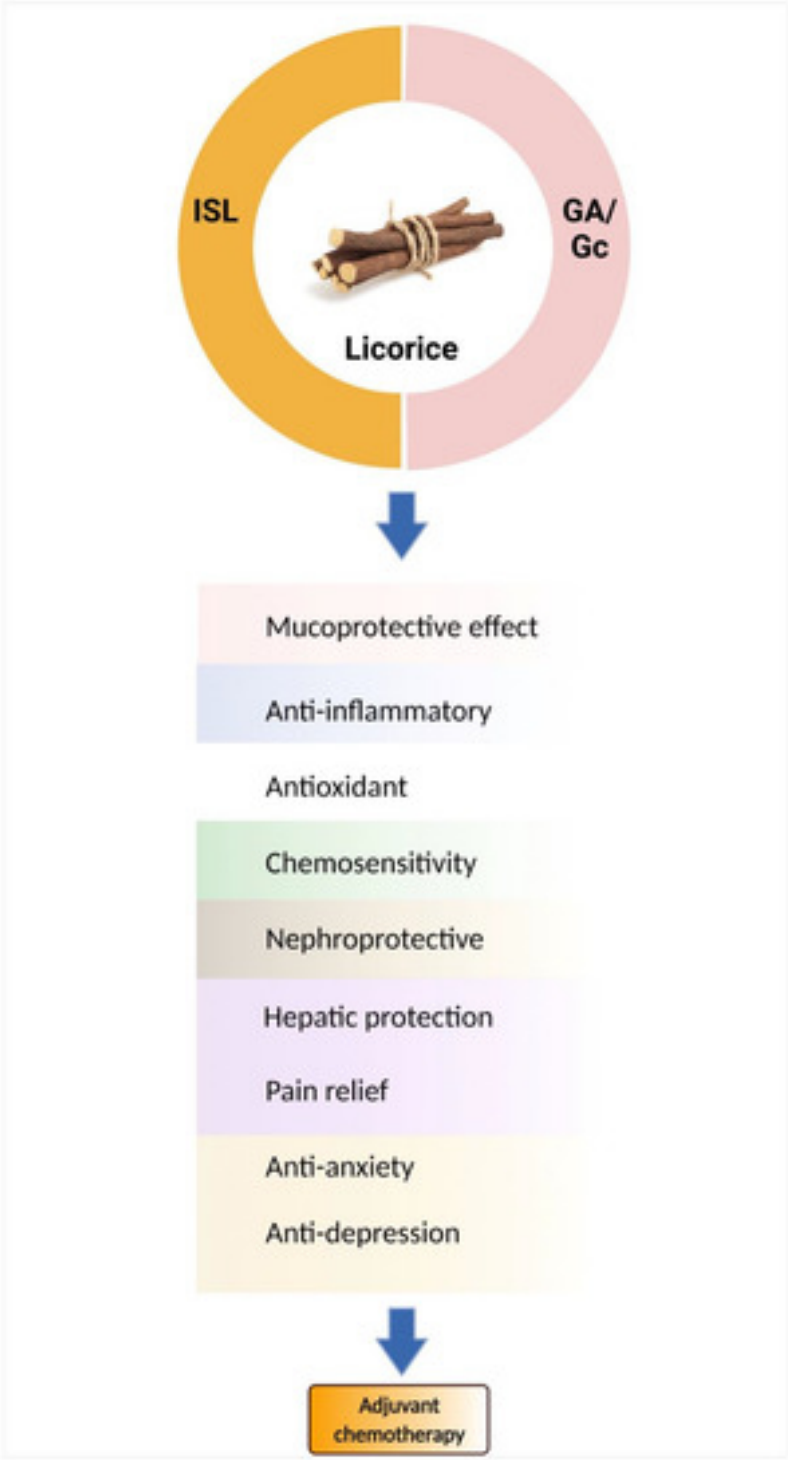

Figure 1. Licorice and its active components are candidates for chemo-combinations. *Glycyrrhizin* (Gc)/*glycyrrhetic* acid (GA) and isoliquiritigenin (ISL) mediate many mechanisms to improve chemotherapy-induced adverse effects.

Glycyrrhizin demonstrates immunomodulatory actions in vitro, stimulating T lymphocytes for IL-2 production [35]. An anti-inflammatory effect is associated with glycyrrhizinic and glycyrrhetic acid, via an inhibition of corticosteroid metabolism and production [36]. To extend the corticosteroid effects, it is broadly classified into immunological and metabolic effects [37]. From a metabolic perspective, the active form of glycyrrhizin, glycyrrhetic acid, influences

energy metabolism and fat distribution by mediating fatty acid oxidation–related genes [38][39]. To emphasize the role of antioxidants, pretreatment with glycyrrhizinic acid could decrease free radicals and increase the level of reduced glutathione (GSH) [40][41]. Licorice extract and glycyrrhizic acid could reduce ROS-mediating p53 activation, and promote p21 expression against cisplatin-induced nephrotoxicity in vitro [42]. In an animal model, glycyrrhizic acid (GA) and 18β-glycyrrhetinic acid (18βGA) are represented as chemoprotectants, through the modulation of the NF-κB and Nrf2 pathways to reduce cisplatin-induced nephrotoxicity [43]. Overall, glycyrrhizin has been widely studied for combination chemotherapies involving cisplatin, 5-Fluorouracil, radiation, doxorubicin, paclitaxel, etc. [43][44][45][46][47][48][49][50][51][52][53].

Isoliquiritigenin, one of the major bioactive compounds found in licorice, shares the same basic pharmacologic effects as *Glycyrrhiza* and exerts more biological activity, especially in its anti-tumor effects [54]. In a CT-26 murine colon animal model, ISL suppresses cisplatin-induced kidney/liver damage by mediating nitric oxide, lipid peroxidation, and GSH levels [55]. Based on the antioxidant properties of ISL, it shows a protective effect on cisplatin-induced toxicity, through regulating the oxidative ER stress hormesis. [56]. In addition, to target the anti-inflammatory effects, ISL also inhibits IL-6, IL-12, and TNF-α production [57]. Many studies suggest that licorice extract or licorice-derived active components benefit chemotherapy (**Figure 1**). **Table 3** summarizes the licorice components associated with chemopreventive activities, mainly focusing on glycyrrhizin and ISL. However, some components of licorice present unwanted side effects; therefore, Kampo medicine is another option to improve chemotherapy-induced adverse effects.

Table 3. Licorice compounds, mechanisms of action and potential chemopreventions.

Compounds	Pharmacological Group	Chemotherapy	Therapeutic Actions/Mechanism	Ref
Glycyrrhizinic acid	Triterpenoid saponin	5-Fluorouracil	• Mucoprotective effects, anti-inflammatory, and antioxidant (suppresses inflammatory mediators and oxidative stress via NF-κB and Nrf2 pathways) • Enhances chemosensitivity (nitric oxide regulator)	[44] [45]
		Cisplatin	• Nephroprotective effect (inhibition of HMGB1)	[43]
		Cisplatin/radiation	• Enhances chemosensitivity (1. decreases the expression of MRP2,	[46] [47] [48]

Compounds	Pharmacological Group	Chemotherapy	Therapeutic Actions/Mechanism	Ref
			MRP3, MRP4, and MRP5; 2. inhibition of HMGB1)	
		Erlotinib/cisplatin	• Enhances chemosensitivity (inhibition of progesterone receptor membrane component 1 (PGRMC1))	[49]
		Doxorubicin	• Anti-inflammatory (decreasing phagocytosis of macrophage) • Enhances chemosensitivity (mediates cell apoptosis via Bax/Bcl-2 ratio and caspase-3 activity) • Cardioprotective (inhibition of HMGB1via HMGB1-dependent Akt/mTOR downregulating phospho-Akt, phospho-mTOR, p62, and LC3 II)	[51] [52] [58]
		Paclitaxel	• Enhances chemosensitivity (via HMGB1/c-Myc inhibition)	[50] [59]
			• Anti-inflammatory (inhibition of NF-κB activation and IL-6 production)	[53]
		N.A.	• Anti-anxiety and anti-depression (inhibition of HMGB1)	[60] [61]
Glycyrrhizin		Cyclosporine (CsA)	• Combined glycyrrhizin can reduce CsA-related liver injury, and attenuation of the severity of nausea and other adverse events	[62]
Isoliquiritigenin	Trans-chalcone (flavonoid)	Cisplatin	• Antioxidant effects, and enhances chemosensitivity (enhances ER stress	[56] [63]

Compounds	Pharmacological Group	Chemotherapy	Therapeutic Actions/Mechanism	Ref
			and oxidative stress) • Enhances chemosensitivity (via HO-1 and GRP78/ABCG2)	[64] [65]
			• Nephro and hepatic protection (increases nitric oxide and tissue lipid peroxidation levels, and depletes GSH levels). • Anti-inflammatory (inhibition of FPR2 in macrophage)	[55] [66]
		5-Fluorouracil	• Enhances chemosensitivity (induces p62/SQSTM1 by reducing caspase-8 activation)	[67]
			• Immuno-protector (activation of macrophages and lymphocytes)	[68]
		Doxorubicin	• Antioxidant effect, hepatic protection (via SIRT1/Nrf2 pathway)	[69]
			• Enhances chemosensitivity	[70] [71]

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