REVIEW

Liquorice (*Glycyrrhiza glabra*): A phytochemical and pharmacological review

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In the last years, consumers are paying much more attention to natural medicines and principles, mainly due to the general sense that natural compounds are safe. On the other hand, there is a growing demand by industry for plants used in traditional medicine that could be incorporated in foods, nutraceuticals, cosmetics, or even pharmaceuticals. *Glycyrrhiza glabra* Linn. belongs to the Fabaceae family and has been recognized since ancient times for its ethnopharmacological values. This plant contains different phytocompounds, such as glycyrrhizin, 18β-glycyrrhetinic acid, glabrin A and B, and isoflavones, that have demonstrated various pharmacological activities. Pharmacological experiments have demonstrated that different extracts and pure compounds from this species exhibit a broad range of biological properties, including antibacterial, anti-inflammatory, antiviral, antioxidant, and antidiabetic activities. A few toxicological studies have reported some concerns. This review addresses all those issues and focuses on the pharmacological activities reported for *G. glabra*. Therefore, an updated, critical, and extensive overview on the current knowledge of *G. glabra* composition and biological activities is provided here in order to explore its therapeutic potential and future challenges to be utilized for the formulation of new products that will contribute to human well-being.

KEYWORDS

Glycyrrhiza glabra, pharmacology, phytochemistry, toxicology, traditional use

1 | INTRODUCTION

Since the beginning of human cultivation practices, the role of plants in medicine has been of huge importance. *Glycyrrhiza glabra* is one of the most popular medicinal plants belonging to the Fabaceae family (also known as Leguminosae), and its members are now commonly used as feed and food. The genus *Glycyrrhiza* is derived from the Greek words *glykos* (sweet) and *rhiza* (root). It is also called licorice, liquorice, glycyrrhiza, sweet wood, and *Liquiritiae radix* (in English); *süssholz* and *lakritzenwurzel* (in German); *reglisse* and *bios doux* (in French); *shirin bayan* and *mak* (in Persian); and *liquirizia* and *regaliz* (in Italian and Spanish, respectively). This species is a native of Mediterranean areas, but it is now also present in India, Russia, and China. The extracts are currently used in pharmaceutical and food industries,

as well as in the manufacture of functional foods and food supplements (Hayashi & Sudo, 2009; Herrera, Herrera, & Ariño, 2009).

The use of liquorice predates the Greek and Roman empires, having a long history of traditional medicines and folk remedies. In fact, different geographical areas and periods are linked to different uses (Armanini, Fiore, Mattarello, Bielenberg, & Palermo, 2002). The first documents can be traced back to ancient Assyrian, Egyptian, Chinese, and Indian cultures. Theophrastus and Pedanius Dioscorides wrote about liquorice as a medicinal plant and described its therapeutic effects (Armanini et al., 2002). In traditional Chinese medicine, for example, the plant is recommended as a common remedy for gastrointestinal problems, cough, bronchitis, and arthritis. In particular, it is still widely used to treat gastritis, peptic ulcers, respiratory infections, and tremors in folk medicine. Commonly, *G. glabra* root is employed to

prepare a tea that is an excellent thirst quencher. The dried root has been described as a tooth cleanser (Armanini et al., 2002). Actually, the most important industrial use of *G. glabra* is the production of food additives, such as flavours and sweetening agents (Mukhopadhyay & Panja, 2008). In particular, the root is used as a flavouring agent for American-type tobacco, chewing gum, candies, baked goods, ice cream, and soft drinks (Rizzato, Scalabrin, Radaelli, Capodaglio, & Piccolo, 2017). In beers and fire extinguishers, the root extracts are used as foaming agents, whereas the root fibbers are used in insulation, wallboard, and boxboard materials, after removal of the medicinal and flavouring constituents. In the cosmetic field, *G. glabra* is described as a skin depigmentation agent and is being incorporated in topical products for that purpose.

With regard to government approval, liquorice extract and glycyrrhizin have been allowed for use in foods by the United States Food and Drug Administration, the Council of Europe, and the Joint FAO/WHO Expert Committee on Food Additives (FAO, 2005). Indeed, the U.S. Flavor and Extract Manufacturers Association has recognized it as generally safe.

To the best of our knowledge, a limited number of reviews have been published on this plant, particularly in what concerns to pharmacological aspects (Asl & Hosseinzadeh, 2008; Fiore, Eisenhut, Ragazzi, Zanchin, & Armanini, 2005). The objective of this review was to examine the bioactive compounds of *G. glabra* and the biological activities associated with these compounds.

2 | BOTANICAL DESCRIPTIONS

G. glabra is a typical herbaceous perennial, growing to 1 m in height, presenting pinnate leaves with a length of 7 to 15 cm. The flowers are purple to pale whitish blue, being arranged in a hermaphrodite inflorescence, whereas the fruit is an oblong legume with 2 to 3 cm of length and containing several seeds.

The genus *Glycyrrhiza* (Fabaceae) consists of about 30 species, such as *G. glabra*, *G. uralensis*, *G. inflata*, *G. aspera*, *G. korshinskyi*, or *G. eurycarpa*. Like the other plants of Fabaceae, *G. glabra* is able to fix nitrogen, due to symbiosis with bacteria of the genus *Rhizobium*, at the root level, being suitable for sandy and clay soils, though preferring humid soils. Since the Egyptian age, the therapeutic properties of *G. glabra* are well documented (Fiore et al., 2005). The roots are the most used parts whereas leaves are considered an agrochemical waste. However, in the last years, different authors studied the phytochemical composition of *G. glabra* leaves, demonstrating that certain compounds present in the roots are also identified in leaves, although in smaller quantities (Hayashi & Sudo, 2009; Siracusa et al., 2011).

3 | PHYTOCHEMISTRY AND BIOACTIVE COMPOUNDS

In the last years, the chemical constituents of liquorice have been extensively investigated by different authors (Hayashi et al., 2016;

Siracusa et al., 2011). Nevertheless, few studies were carried out on the nutritional composition of *G. glabra*. Nutritionally, liquorice is a source of proteins, amino acids, polysaccharides and simple sugars, mineral salts (such as calcium, phosphorus, sodium, potassium, iron, magnesium, silicon, selenium, manganese, zinc, and copper), pectins, resins, starches, sterols, and gums (Q. Wang et al., 2015). Oestrogens, tannins, phytosterols (sitosterol and stigmasterol), coumarins, vitamins (B1, B2, B3, B5, E, and C), and glycosides have been reported (Q. Wang, Qian, et al., 2015). A large number of biological compounds have also been isolated, mostly triterpenes, saponins (responsible for the sweet taste), and flavonoids (Rizzato et al., 2017; Q. Wang, Qian, et al., 2015). The liquorice saponins are present as glucuronides, whereas the aglycones are present as oleananes. The triterpene saponins are the major characteristic constituents of liquorice, being responsible for the sweet taste. The contents of these compounds may vary significantly due to geographic sources, harvesting, and processing, affecting the therapeutic effects of liquorice.
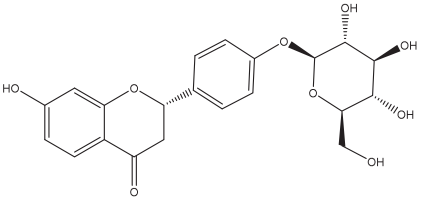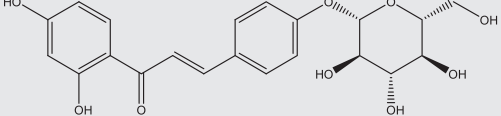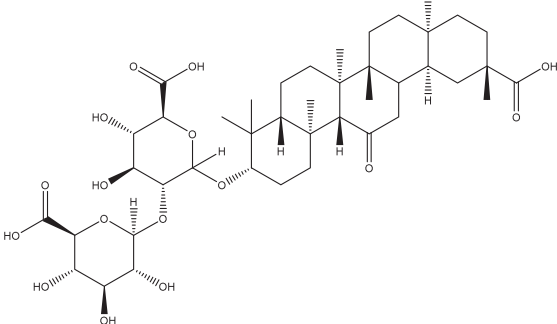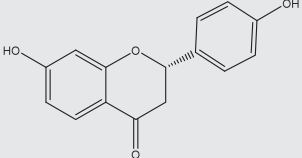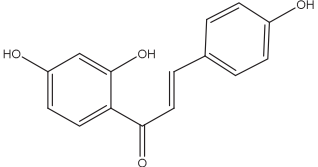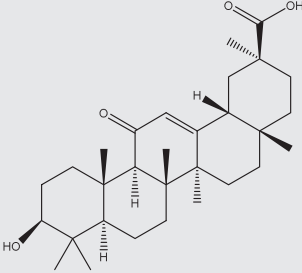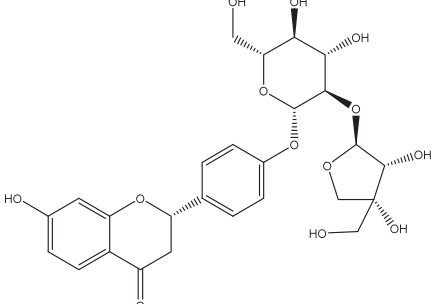
The main constituent of roots is glycyrrhizin, a triterpenoid saponin that is almost 50 times sweeter than sucrose, being the primary active ingredient (J. Y. Yu et al., 2015). Glycyrrhizin represents about 10% of the liquorice root dry weight, being a mixture of potassium, calcium, and magnesium salts of glycyrrhizic acid that varies between 2% and 25% (Rizzato et al., 2017). After oral administration, glycyrrhizin is metabolized to 18-glycyrrhetic acid 3-omonoglucuronide and glycyrrhetic acid by intestinal bacteria (Albermann, Musshoff, Hagemeier, & Madea, 2010).

The yellow colour of liquorice is due to the flavonoid content. The flavonoids identified belong to different classes, including flavanones, flavones, flavanonols, chalcones, isoflavans, isoflavenes, isoflavones, and isoflavanones. The major flavonoids are glycosides of liquiritigenin (4′,7-dihydroxyflavanone) and isoliquiritigenin (2′,4,4′-trihydroxychalcone), such as liquiritin, isoliquiritin, liquiritin apioside, and licuraside (Rizzato et al., 2017). Five new flavonoids have been isolated from dried roots: glucoliquiritin apioside, shinflavanone, shinpterocarpin, prenyllicoflavone A, and 1-methoxyphaseolin. Pinocembrin and licoflavanone were also isolated from the leaves (Fukui, Goto, & Tabata, 1988). Glabridin is the principal isoflavone identified, ranging between 0.08% and 0.35% of roots' dry weight (Simmler, Pauli, & Chen, 2013). The minor phenolic compounds are isoprenoid-substituted flavonoids, chromenes, coumarins, dihydrostilbenes, coumestans, benzofurans, and dihydrophenanthrenes. Furthermore, many volatile components are present in roots, such as geraniol, pentanol, hexanol, terpinen-4-ol, and α-terpineol, conferring the characteristic odour. The essential oil obtained from *G. glabra* is also rich in propionic acid, benzoic acid, furfuraldehyde, 2,3-butanediol, furfuryl formate, maltol, 1-methyl-2-formylpyrrole, and trimethylpyrazine (Chouitah, Meddah, Aoues, & Sonnet, 2011). Table 1 summarizes the chemical structure of the most important compounds identified in *G. glabra*.

4 | PHARMACOLOGICAL PROPERTIES

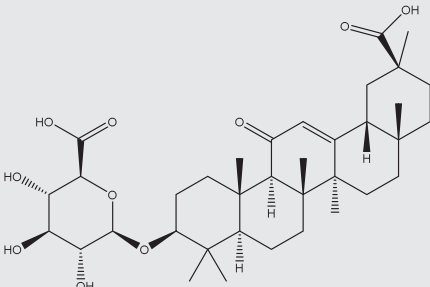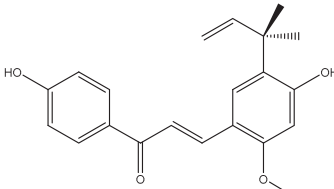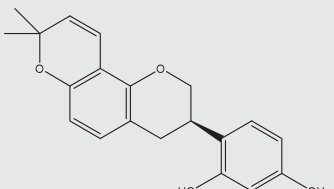Liquorice is one of the oldest and most popular herbal medicines in the world. Many of the liquorice historical uses are still practised

TABLE 1 Chemical structure of the most important compounds of *Glycyrrhiza glabra*

Compounds	Chemical structures
Liquiritin	
Isoliquiritin	
Glycyrrhizin	
Liquiritigenin	
Isoliquiritigenin	
18β-Glycyrrhetinic acid	
Liquiritin apioside	

TABLE 1 (Continued)

Compounds	Chemical structures
Glycyrrhetic acid	
Licochalcone A	
Glabridin	

today. Table 2 summarizes the most important pharmacological activities reported for *G. glabra* as well as the individual compounds related to them.

4.1 | Antioxidant activity

The antioxidant activity of *G. glabra* is one of the major reasons for its uses. The phenolic content is probably responsible for the powerful antioxidant activity observed (Rackova et al., 2007). Varsha and Sonam (2013) attributed this activity to flavonoids, whereas Singh et al. (2015) reported that mostly isoflavones, such as glabridin, hispaglabridin A, and 30-hydroxy-4-O-methylglabridin, are the responsible compounds. Biondi, Rocco, and Ruberto (2003) reported a huge antioxidant activity of the dihydrostilbene derivates present in *G. glabra* leaves. Also, licochalcones B and D are present in *G. glabra*, showing a strong scavenging activity on DPPH radical and the ability to inhibit the microsomal lipid peroxidation (Biondi et al., 2003; V. Sharma, Katiyar, & Agrawal, 2016). These phenolic compounds are effective in the protection of biological systems against oxidative stress, being able to inhibit the onset of skin damages (Haraguchi et al., 1998). According to Castangia et al. (2015), the topical application of liquorice extract formulations may be of value in innovative dermal and cosmetic products as it counteracts oxidative stress damage, maintaining the skin homeostasis due to its high antioxidant content. Table 1 summarizes the most important studies of antioxidant activity.

4.2 | Anti-inflammatory activity

The anti-inflammatory activity of *G. glabra* and its use in the treatment of inflammatory diseases have been documented since ancient

times (R. Yang, Yuan, Ma, Zhou, & Liu, 2017). Shalaby, Ibrahim, Mahmoud, and Mahmoud (2004) evaluated the anti-inflammatory activity of *G. glabra* in male rats after 4 weeks of food intake. The authors observed a significant decrease in the total cholesterol and triglyceride levels as well as in the levels of serum liver enzymes. Harwansh, Patra, Pareta, Singh, and Biswas (2011) reviewed the positive effects of *G. glabra* on the treatment of the upper respiratory tract and gastric system diseases. These pharmacological effects were due to an increase in the secretion of serotonin and prostaglandins in the stomach that led to a decrease of gastric inflammation (Bahmani et al., 2014). Different authors described that the anti-inflammatory action is primary mediated by glycyrrhizin, which in vitro could inhibit factors responsible for inflammation as well as promote the healing of stomach and mouth ulcers (Rackova et al., 2007; Yin et al., 2017). In fact, the anti-inflammatory effects of glycyrrhizin were described as similar to those of glucocorticoids and mineralocorticoids (Kageyama, Suzuki, & Saruta, 1994). Furthermore, *G. glabra* is used in renal and liver complications on the basis of its strong anti-inflammatory effects (Y. Xiao et al., 2010). Y. Xiao et al. (2010) reported the inhibition of liver granuloma formation and the inflammatory cytokine production by glycyrrhizin, whereas X. R. Wang, Hao, and Chu (2017) described the anti-inflammatory effects on endometriosis. Moreover, Liu et al. (2017) proved the anti-inflammatory activity of glabridin on RAW cells.

4.3 | Antitussic and expectorant activity

The antitussic and expectorant effects of liquorice have been reported by different authors, particularly its useful effects on the treatment of sore throat, cough, and bronchial catarrh (Damle, 2014; Fiore et al.,

TABLE 2 Summary of the key studies conducted with liquorice-derived compounds or extract

Property	Compound	Concentration	Method	Major findings	Reference
Neuroprotective activity	Glabridin	5–50 mg/kg	In vivo—oral administration to mice	Improvement of learning and memory in nondiabetic rats; it reversed learning and memory deficits of diabetic rats. Low-dose glabridin did not alter cognitive function	(Hasanein, 2011)
	Glycyrrhiza glabra extract	75–300 mg/kg, 7 days	In vivo—oral administration to Swiss young male albino mice	Production of antidepressant-like effect in mice in forced swim test and tail suspension test, probably by interaction with adrenergic and dopaminergic system	(Dhingra & Sharma, 2006)
	G. glabra aqueous extract	75–300 mg/kg, 7 days	In vivo—oral administration to mice	Dose of 150 mg/kg significantly improved learning and memory of mice	(Parle, Dhingra, & Kulkarni, 2004)
Sedative activity	Glabridin	$10^{-12}–10^{-8}$ M	In vivo—acutely isolated dorsal raphe neurons of a rat	Sedative and hypnotic effects by potentiating GABAergic inhibition in dorsal raphe neurons by GABA$_A$ receptor	(Jin et al., 2013)
		30 µM	In vitro—Xenopus laevis oocytes expressing recombinant GABA$_A$ receptors	Strong potentiating effect on GABA$_A$ α1β(1–3)γ2 receptors	(Cho et al., 2010)
Antidepressive activity	G. glabra aqueous extract	75–300 mg/kg	In vivo—forced swim test and tail suspension test applied to mice	Antidepressant-like effect of liquorice extract seems to be mediated by increase of brain norepinephrine and dopamine, but not by increase of serotonin	(Dhingra & Sharma, 2006)
Oestrogenic activity	18β-Glycyrrhetinic acid	0–200 µM	In vitro—human breast cancer cells (MCF-7)	Induction of apoptosis in human breast carcinoma MCF-7 cells via caspase activation and modulation of Akt/FOXO3a pathway	(Sharma, Kar, Palit, & Das, 2012)
	Glabridin	1 nM–10 µM	In vitro—endometrial cell line (Ishikawa cells)	Activation of ER-α-SRC-1-co-activator complex, which displays a dose-dependent increase in oestrogenic activity	(Su Wei Poh, Voon Chen Yong, Viseswaran, & Chia, 2015)
		1 nM–25 µM	In vitro—human breast cancer cells (T-47D, MCF-7, and MDA-MB-468)	Inhibition of the growth of breast cancer cells	(Su Wei Poh et al., 2015)
		50 µg, 3–14 days	In vivo—daily feeding of prepubertal female Wistar rats	Stimulation of creatine kinase specific activity	(Tamir, Eizenberg, Somjen, Izrael, & Vaya, 2001)
	Liquorice root extract	25 µg/day, 2 weeks	In vivo—oral administration to female rats	Increase in creatine kinase activity	(Tamir et al., 2000)
	Liquiritigenin	2–10 µg/ml	In vitro—MCF-7 and T47D cells	Induction of oestrogen responsive alkaline phosphatase activity in endometrial cancer cells, oestrogen responsive element luciferase in MCF-7 cells and Tff1 mRNA in T47D cells	(Somjen et al., 2004)
	Isoliquiritigenin	0–0.04 mg/ml	In vivo—intraperitoneal injection of female ICR mice	Improvement of IVF rate	(Tung, Shoyama, Wada, & Tanaka, 2014)
Skin effects	Glycyrrhizinic acid	20%, 2 weeks	In vivo—double-blind clinical trial in human patients	Reduction of erythema, oedema, and itching scores	(Halder & Richards, 2004)
		—	In vitro—topical treatments in human patients during 4 weeks	Lighten hand solar lentigines	(Nerya et al., 2003)
	Glycyrrhetinic acid; glabridin	0–120 µM	In vitro—human keratinocyte culture	Prevention of oxidative DNA fragmentation and activation of apoptosis-associated proteins in human keratinocyte	(Grippaudo & Di Russo, 2016)

(Continues)

TABLE 2 (Continued)

Property	Compound	Concentration	Method	Major findings	Reference
	Glabridin; glabrene; isoliquiritigenin	0.7 μM (glabridin), 7 μM (glabrene), and 26 μM (isoliquiritigenin)	In vitro—human melanocyte (G361)	Inhibition on tyrosinase-dependent melanin biosynthesis	(Parvez, Kang, Chung, & Bae, 2007)
	Liquorice hydro-alcoholic extract	1–2%	In vivo—Wistar albino rats	Potentiation of hair growth activity	(Veratti et al., 2011)
Antiviral activity	Glycyrrhizin	10 mg/kg (compound)	In vitro—Vero cells; In vivo—ducks	Stimulation of immune and antiviral effect against DHV	(Soufy et al., 2012)
		0.1 μg/ml (extract)	In vitro—human foreskin cell line	Protection of host cells against EV71 infection	(Kuo, Chang, Wang, & Chiang, 2009)
		316–625 mg/L (compound)	In vitro—Vero cells	Protection against coronavirus	(Cinatl et al., 2003)
		100 μg/ml (compound)	In vitro—peripheral blood mononuclear cells	Inhibition of nonsyncytium-inducing variant of HIV replication	(Sasaki, Takei, Kobayashi, Pollard, & Suzuki, 2002)
		400–1,600 mg/day (compound)	In vitro—human immunodeficiency virus type 1 (HIV-1) P24 antigen	Inhibition of HIV-1 replication	(Hattori et al., 1989)
		80, 160, 240 mg 3× per week or 200 mg 6× per week	In vivo—human patients (intravenous)	Treatment of chronic hepatitis C infection	(van Rossum, Vulto, Hop, & Schalm, 1999)
		100 mg/day		Prevention of autoimmune hepatitis progression	(Yasui et al., 2011)
		25–200 μg/ml	In vitro—lung epithelial A549 cells	Reduction of pathogenic H5N1 influenza A virus replication	(Michaelis et al., 2011)
Anticarcinogenic activity	Glabridin	0–10 μM, 24, 48, and 72 hr; 0–20 mg/kg, 4 weeks	In vitro—cancer stem cells (CSCs); In vivo—BALB/c nude mice	Reduction of CSC-like properties, enhancing the effectiveness of breast cancer therapy	(Jiang et al., 2016)
		0–100 μM (compound)	In vitro—human hepatic cell lines (Huh7, HepG2, Sk-Hep-1)	Induction of apoptosis in Huh7 cells	(Hsieh et al., 2016)
	Licochalcone E	12.5–50 μM (compound)	In vitro—human oral keratinocytes and human pharyngeal squamous carcinoma cell line	Induction of FaDu cell death	(Yu et al., 2017)
	Licochalcone A	0–500 μM (compound)	In vitro—human gastric cancer cell lines (MKN-28, AGS, MKN-45)	Induction of apoptosis of gastric cancer cell via the caspase-dependent mitochondrial pathway	(Xiao et al., 2011)
Antimicrobial activity	Glabridin	3.12–25 μg/ml; 3.13–12.5 μg/ml	MIC; MIC	Inhibition of the growth of clinical isolates of multidrug-resistant Staphylococcus aureus	(Fukai et al., 2002a; Singh, Pal, & Darokar, 2015)
	Glycyrrhetinic acid	29.16 μg/ml; 62.5–1.024 mg/L	MIC; MIC	Decrease of Mycobacterium tuberculosis; Inhibition of the growth of clinical isolates of multidrug-resistant S. aureus	(Gupta et al., 2008); (Oyama et al., 2016)
		100–400 μg/ml	MIC, MBC	Decrease of Pseudomonas aeruginosa	(Chakotiya, Tanwar, Narula, & Sharma, 2016)
		≤50 μg/L	MIC	Decrease of Helicobacter pylori	(Krausse, Bielenberg, Blaschek, & Ullmann, 2004)
Antioxidant activity	Glabridin	3.12–25 μg/ml; 60 mg	DPPH, FRAP, SOD; In vivo—oral administration to humans (LDL isolation)	Protection of low-density lipoprotein from oxidation	(Singh et al., 2015); (Carmeli & Fogelman, 2009)
	Licochalcone	2–20 μg/ml	DPPH, superoxide anion, lipid peroxidation, red blood cells	Inhibition of the microsomal lipid peroxidation	(Haraguchi, Ishikawa, Mizutani, Tamura, & Kinoshita, 1998)
Hepatoprotective activity	Liquorice aqueous extract	100–300 mg/kg 15 days	In vivo—oral administration to Wistar rats	Stimulation of the antioxidant enzymes and arrest of inflammatory cytokine production	(Huo, Wang, Liang, Bao, & Gu, 2011)
	G. glabra aqueous root extract	2 g/day, 2 months	In vivo—humans	ALT and AST decrease	(Hajiaghamohammadi, Ziaee, & Samimi, 2012)
		10, 30, 100 mg/kg	In vivo—BALB/c mice	Protection against LPS fulminant hepatic failure	(Yin et al., 2017)
	Glycyrrhetinic acid	0.5–20 μM	In vivo—RAW 264.7 macrophages; Metabolomics	Decrease of inflammation in RAW 264.7 cells	(Liu et al., 2017)

(Continues)

TABLE 2 (Continued)

Property	Compound	Method	Concentration	Major findings	Reference
Anti-inflammatory activity	Glabridin	In vivo—oral administration to mice	75 mg/kg	Decrease of MIP 1α expression	(Xiao et al., 2010)
	Glycyrrhizin	DPPH, AAPH	1–100 μM	Protection against lipid peroxidation of liposomal membrane; Inhibition of ROS	(Rackova et al., 2007)
		LPS inflammatory mediators production (TNF-α, IL-1β, COX-2, PG2)	50–200 μg/ml	Decrease of endometriosis	(X. R. Wang, et al., 2017)
		In vivo—mice	10, 20, 100 mg/kg	Decrease of LPS inflammatory mediators	(Yin et al., 2017)

Note. ALT: alanine aminotransferase; AST: aspartate aminotransferase; DHV: duck hepatitis virus; FRAP: ferric reducing antioxidant potential; ICR: Institute of Cancer Research; IVF: in vitro fertilization; LDL: low-density lipoprotein; LPS: lipopolysaccharide; MBC: minimum bactericidal concentration; MIC: minimum inhibitory concentration; ROS: reactive oxygen species; SOD: superoxide dismutase.

2005). These effects are associated with the presence of glycyrrhizin that helps to expel congestion in the upper respiratory tract and accelerates tracheal mucus secretion (V. Sharma et al., 2016). Likewise, liquiritin apioside, an active compound reported in the methanolic extract of liquorice, has the ability to inhibit capsaicin, a compound that induces cough (Kamei, Nakamura, Ichiki, & Kubo, 2003). The effect on sore throat has been compared with that of carbenoxolone, a glycyrrhetinic acid derivative with a steroid-like structure, which stimulates gastric mucus secretion (Damle, 2014).

4.4 | Antiulcerative activity

The use of *G. glabra* extract as antiulcerative is widely known. For the gastrointestinal system, it is used in gastric and duodenal ulcers (Bardhan, Cumberland, Dixon, & Holdsworth, 1978), whereas for the treatment of spasmodic pains of chronic gastritis, it is employed as an adjuvant (Armanini et al., 2002). The benefits of *G. glabra* in the treatment of duodenal and peptic ulcers have been reported since the 1970s, and this traditional use is related to the presence of anti-inflammatory saponins (Krausse et al., 2004). The major compound responsible for this activity is glycyrrhizin, which can raise the concentration of prostaglandins in the digestive tract, promoting stomach mucus secretion (Jafarian & Ghazvini, 2007). In addition, liquorice prolongs the lifespan of stomach surface cells, demonstrating an antipepsin effect (Ram, Lachake, Kaushik, & Shreedhara, 2010). Furthermore, deglycyrrhizinated liquorice has shown some effects in the treatment of gastrointestinal ulcers, suggesting the presence of other active ingredients (Zadeh, Kor, & Goftar, 2013). Indeed, carbenoxolone, a glycyrrhetinic acid analogue, is reported to inhibit two important enzymes for the metabolism of prostaglandin, 15-hydroxyprostaglandin dehydrogenase and Δ^{13} prostaglandin reductase, raising prostaglandin levels and leading to positive effects in clinical trials for gastric and duodenal ulcers (Damle, 2014). In fact, prostaglandins stimulate mucous secretion and cell proliferation leading to ulcer healing. Nevertheless, the glycyrrhetic acid derivative carbenoxolone presents secondary effects such as the potential development of pseudo aldosteronism, which limits its use. In a clinical trial, Bardhan et al. (1978) studied the effect of liquorice by oral administration in 96 patients with gastric ulcer. The patients were randomly allocated to the treatment either with deglycyrrhizinated liquorice or with placebo. However, after 4 weeks, no differences were observed between groups in the percentage of ulcer area reduction or clinical improvements (Bardhan et al., 1978).

4.5 | Antimicrobial activity

Multidrug-resistant microorganisms represent a serious problem in clinical medicine leading to the search of new active principles. Different authors reported the antimicrobial properties of *G. glabra*, particularly on Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Bacillus subtilis* (Gupta et al., 2008; L. Wang, Yang, Yuan, Liu, & Liu, 2015). The antibacterial activity observed is due to the presence of secondary metabolites, namely, saponins, alkaloids, and flavonoids (Fukui et al., 1988; L. Wang, Yang, et al., 2015). In

particular, glabridin, glabrol, glabrene, hispaglabridin A, hispaglabridin B, 40-methylglabridin, and 3-hydroxyglabrol, isolated from *G. glabra*, are responsible for this activity (L. Wang, Yang, et al., 2015). The mechanism behind this could be the decrease of bacterial gene expression, the inhibition of bacterial growth, and the reduction of bacterial toxin production (Gupta et al., 2008; L. Wang, Yang, et al., 2015). In 2014, S.-J. Ahn, Song, Mah, Cho, and Kook (2014) demonstrated that liquorice prevents bacterial caries caused by *Streptococcus mutans* and *Streptococcus sobrinus*. Likewise, in vitro studies proved that aqueous and ethanolic extracts of liquorice have an inhibitory activity on *Streptococcus pyogenes* (Fukai et al., 2002a, 2002b; L. Wang, Yang, et al., 2015). On the other hand, the ability to inactivate methicillin-resistant *S. aureus* (MRSA) by decreasing the expression of SaeR and Hla, the key virulence genes of MRSA, have also been reported by different authors (Fukai et al., 2002a, 2002b; L. Wang, Yang, et al., 2015). It is also suggested that licochalcone E could be used for chemical synthesis of novel anti-*S. aureus* compounds, reducing the production of α-toxin in both methicillin-sensitive *S. aureus* and MRSA (L. Wang, Yang, et al., 2015).

Besides, α-haemolysin is an important exotoxin in the pathogenesis of *S. aureus* infections (Berube & Bubeck Wardenburg, 2013). Such infections are associated with a broad spectrum of diseases, ranging from endocarditis to minor skin infections, toxinoses, and lethal pneumonia. Liquiritigenin, one of the most active compounds of liquorice, demonstrated the capacity to prevent human lung cells (A549) from α-haemolysin-mediated injuries, by decreasing α-haemolysin production (L. Wang, Yang, et al., 2015). Similarly, glabrin and glycyrrhetinic acid have shown antibacterial activity against *S. aureus* (Singh et al., 2015).

Different authors reported the antibacterial action of *G. glabra* against *Mycobacterium tuberculosis* (Gupta et al., 2008), demonstrating that glabridin is the responsible compound for this activity, instead of hispaglabridin B (Simmler et al., 2013). The antitubercular phenolic compounds were previously identified as licoisoflavone and licochalcone A (Chakotiya, Tanwar, Srivastava, Narula, & Sharma, 2017).

In a mice lung infection model, *G. glabra* was therapeutically active against multidrug-resistant strain of *P. aeruginosa* (Chakotiya et al., 2016), and the hydro-alcoholic extract led to a reduction of the microbial load in the blood, mainly due to the presence of stigmasterol, ergosterol, licochalcone, and glabridin (Chakotiya et al., 2017).

The activity of *G. glabra* against *Helicobacter pylori* has been also reported, as mentioned in the previous subsection (Krausse et al., 2004). According to Krausse et al. (2004), the compounds responsible for this activity are glabridin and glabrene. Cao et al. (2016) also reported that 18β-glycyrrhetinic acid significantly attenuated the gastritis infection caused by *H. pylori*. Asha et al. (2013) found that the flavonoid glabridin exhibits activity against *H. pylori* whereas glycyrrhizin did not present activity even at a concentration of 250 μg/ml. These flavonoids also showed activity against *H. pylori* strains resistant to clarithromycin and amoxicillin (Fukai et al., 2002a, 2002b). The probable mechanism behind these action is the inhibition of the protein synthesis, DNA gyrase, and dihydrofolate reductase (Fukai et al., 2002a, 2002b). Moreover, the liquorice polysaccharides also present activity against *Porphyromonas gingivalis* adhesion, which is of huge importance because no specific adhesion inhibitors have been described (Chinsembu, 2016).

The antifungal activity of *G. glabra* is also detailed (Sato, Goto, Nanjo, Kawai, & Murata, 2000). Sato et al. (2000) reported that the methanolic extract of liquorice presents fungicidal activity against *Arthrinium sacchari* and *Chaetomium funicola*, whereas glabridin was found to be the active compound responsible for the observed effects (Sato et al., 2000). In fact, isoflavonoids, such as glabridin, glabrol, and their derivatives, are responsible for the in vivo inhibition of *Mycobacterium smegmatis*, *Shigella*, *Salmonella*, *E. coli*, *S. mutans*, and *Lactobacillus acidophilus* (Ajagannanavar et al., 2014). Recently, Chandra and Gunasekaran (2017) also proved the antifungal activity of crude methanolic extract of *G. glabra* against *Aspergillus niger*.

Different authors reported that *C. albicans* is susceptible to liquorice extracts due to their richness in liquiritigenin, liquiritin, licochalcone A, and glabridin (Chandra & Gunasekaran, 2017; J. Y. Lee et al., 2009; Singh et al., 2015). Nevertheless, according to Karahan, Avsar, Ozyigit, and Berber (2016), the antimicrobial activity could be influenced by the environmental conditions that may affect the chemical compound contents and the biological activity.

According to Messier et al., licochalcone A and glabridin present a therapeutic potential against *C. albicans* oral infections, whereas glycyrrhizic acid had no effect (Messier & Grenier, 2011; Moazeni et al., 2017). Fukui et al. (1988) isolated licoflavanone from the leaves of *G. glabra*, demonstrating its antimicrobial activity. Indeed, Chen et al. (1993) reported that licochalcone A is an antiparasitic compound with potential activity against human pathogenic protozoan *Leishmania* species.

4.6 | Antiviral activity

The antiviral activity of *G. glabra* extracts against different viruses has been reported, including herpes simplex, *Varicella zoster*, Japanese encephalitis, influenza, and vesicular stomatitis virus (L. Wang, Yang, et al., 2015). Different studies have demonstrated that two triterpenoids are responsible for the antiviral activity reported: glycyrrhizin and 18β-glycyrrhetinic acid (L. Wang, Yang, et al., 2015). These compounds have the ability to inhibit virus gene expression and replication, decreasing the adhesion force and stress and reducing HMGB1 binding to DNA (L. Wang, Yang, et al., 2015). Also, they can enhance host cell activities by blocking the degradation of IκB enzyme involved in the propagation of the cellular response to inflammation, activating T lymphocyte proliferation, and suppressing host cell apoptosis (L. Wang, Yang, et al., 2015). The antiviral mechanisms of both compounds are similar, inhibiting the adsorption and penetration of the virus in the early steps of the replicative cycle. Nevertheless, Cinatl et al. (2003) reported that these active principles are less effective if added during the adsorption period than after virus adsorption. On the other hand, Soufy et al. (2012) found that glycyrrhizin has excellent immunostimulant properties and induces a synergistic effect with duck hepatitis virus (DHV) vaccine by activating T lymphocyte proliferation. Thus, the treatment with glycyrrhizin alone or in combination with DHV vaccine could lead to an immune stimulation and antiviral effect against DHV (Soufy et al., 2012).

Herpes simplex virus (HSV) is one of the most common viruses infecting humans and animals. During HSV infection, the cellular adhesion is increased, playing a key role in inflammatory response. W. Huang et al. (2012) reported that the adhesion force and stress between the cerebral capillary vessel endothelial cells and the polymorphic nuclear leukocytes were amplified during HSV infection. Glycyrrhizin stimulates the mouse defence system against HSV-1 infection (Sekizawa, Yanagi, & Itoyama, 2001). Furthermore, glycyrrhizic acid was found to have a distinctive effect against Kaposi sarcoma-associated herpes virus (KSHV). It was proved that glycyrrhizic acid could terminate the latent infection of KSHV when all current drugs are ineffective (Damle, 2014). Also, glycyrrhizic acid down-regulates the expression of latency-associated nuclear antigen in B lymphocytes leading to natural cell death (apoptosis) of the KSHV-infected cells (Damle, 2014). Recently, the antiviral activity of glycyrrhizin against severe acute respiratory syndrome virus was evaluated (Cinatl et al., 2003). Glycyrrhizin affects the cellular signalling pathways such as protein kinase C, casein kinase II, and transcription factors, namely, activator protein 1 and nuclear factor κB (Cinatl et al., 2003). Furthermore, glycyrrhizin and its aglycone, 18β-glycyrrhetinic acid, up-regulate the expression of inducible nitric oxide synthase and the production of nitric oxide in macrophages (Cinatl et al., 2003). Zhang et al. also reported that glycyrrhizin reduces the expression of proinflammatory cytokines affecting coxsackievirus B3-induced myocarditis (L. Wang, Yang, et al., 2015; Zhang, Song, & Zhang, 2012). Also, the activity against human immunodeficiency virus (HIV) was evaluated (Sasaki et al., 2002). Glycyrrhizin has been used to treat patients with HIV-1 (L. Wang, Yang, et al., 2015). The results revealed a low concentration of P24 antigen in patients, probably due to the up-regulation of chemokines (Sabde et al., 2011).

Intravenous glycyrrhizin has been employed for more than 20 years in Japan for the treatment of chronic hepatitis (van Rossum et al., 1999). Glycyrrhizin, when compared with the placebo, presents clinical interest for the possible treatment of chronic hepatitis C, inducing a significant reduction of the serum aminotransferases and an improvement in the liver histology (Ploeger et al., 2001). Also, it prevents the development of hepatocellular carcinoma in chronic hepatitis C (van Rossum, Vulto, de Man, Brouwer, & Schalm, 1998). Intravenous glycyrrhizin can be also used for the treatment of acute-onset autoimmune hepatitis (Yasui et al., 2011). Another study shows that glycyrrhizin interferes with highly pathogenic H5N1 influenza A virus replication (Michaelis et al., 2011).

Glycyrrhizin can also be used as a novel therapeutic method to control porcine epidemic diarrhoea virus (PEDV) infection, inhibiting the infection of Vero cells (namely, the entry and replication of PEDV) and decreasing the mRNA levels of proinflammatory cytokines (Huan et al., 2017).

4.7 | Hepatoprotective activity

The hepatoprotective activity of glycyrrhizin and 18β-glycyrrhetic acid by inhibition of free-radical generation and lipid peroxidation has been extensively reported (Huo et al., 2011). One of these studies indicated that the hydromethanolic root extract of G. glabra exhibits a significant protection against hepatotoxicity induced by carbon tetrachloride in the liver tissue of mice (V. Sharma & Agrawal, 2017). The effects of liquorice on nonalcoholic fatty liver disease have also been investigated (Hajiaghamohammadi et al., 2012). According to Rizzato et al. (2017), glycyrrhizin and glycyrrhetinic acids prevent drug-induced liver injury and ensure the disruption of bile acid metabolism in humans. Indeed glycyrrhetinic acid has been reported as anti-inflammatory and hepatoprotective compound (Yin et al., 2017), whereas glycyrrhizin, when compared with the placebo, induced a significant reduction in the serum aminotransferases and improved the liver histology (van Rossum et al., 1998). It has also been reported that the long-term use of glycyrrhizin prevents the development of hepatocellular carcinoma in chronic hepatitis C (van Rossum et al., 1998). In vitro studies have shown that glycyrrhizin modifies the intracellular transport and suppresses the hepatitis B virus surface antigen (Sato et al., 1996). In addition, it prevents the oxidative and hepatic damage caused by aflatoxins through increasing CYP1A1 and glutathione-S-transferase activity, contributing to the anticarcinogenic activity by metabolic deactivation of the hepatotoxin (Y. Yang et al., 2017). Mahmoud, Hussein, Hozayen, and Abd El-Twab (2017) reported that the treatment with 18β-glycyrrhetinic acid significantly reduced the serum enzymes, bilirubin, and proinflammatory cytokines in the liver, decreasing the expression of P450 E1.

4.8 | Anticarcinogenic and antimutagenic activity

Different studies suggest that the extract of G. glabra may be a potential supplemental source for different cancer treatments (C. S. Lee, Kim, Lee, Han, & Lee, 2008; Ohtsuki, Oh-Ishi, & Nagata, 1992). This activity is due to the 18β-glycyrrhetinic and glycyrrhizic acids that induce mitochondrial permeability transition, leading to the apoptosis of tumour cells (C. S. Lee et al., 2008). C. S. Lee et al. (2008) demonstrated the toxic effect of G. glabra against the human cervix and uterus tumour cell line SiHa cells. Ohtsuki et al. (1992) reported the in vivo inhibition of Ehrlich ascites tumour cell growth by the aqueous and methanolic extracts of G. glabra, with the corresponding reduction in cell number, body weight, and ascites volume. The hydromethanolic root extract of G. glabra also exhibited antimutagenic potential by suppressing micronuclei formation and chromosomal aberration in bone marrow cells of albino mice (V. Sharma, Agrawal, & Shrivastava, 2014). Glycyrrhizin and glycyrrhetinic acids are effective compounds in gastric cancer treatment, whereas glycyrrhizin suppresses thromboxane A2 in lung cancer cell with low toxicity (Deng, Wang, Zeng, Chen, & Huang, 2017). According to S. Wang et al. (2017), 18β-glycyrrhetinic acid has antitumour activities in breast and ovarian cancer, gastric tumours, and leukaemia. In liver cancer, the compound inhibits the proliferation of HepG2 cells without affecting the normal liver cell line. In particular, 18β-glycyrrhetinic acid increases the formation of reactive oxygen species, nitric oxide production, and loss of the mitochondrial membrane potential (Hasan et al., 2016).

Glycyrrhetinic acid derivatives have also presented promising cytotoxicity on human breast cancer cell lines (MCF-7, MDA-MB-231; Li, Feng, Song, Li, & Huai, 2016). Also, the anticancer activity in human leukaemia, by inducing the apoptosis of HL-60 cells through the activation of extrinsic and intrinsic apoptotic pathways, was proved by Y. C. Huang et al. (2016). Recently, licochalcone E, when

compared with well-known antitumour agents, licochalcone A and isoliquiritigenin, exhibited the most potent cytotoxic effect (X. Y. Xiao et al., 2011; S. J. Yu et al., 2017). Xiao et al. explored the licochalcone A mechanism of action in MKN-28, AGS, and MKN-45 gastric cancer cells and human gastric epithelial immortalized cells (Park et al., 2015; X. Y. Xiao et al., 2011). The results indicated that licochalcone A inhibits gastric cancer cells growth in a dose-dependent way, by blocking cell cycle progression at the G2/M transition, inducing apoptosis. In addition, licochalcone A induced apoptosis by its effects on the expression of PARP, caspase-3, Bcl-2, and Bax (X. Y. Xiao et al., 2011). Kanazawa et al. (2003) and Jung et al. (2006) showed that isoliquiritigenin inhibits the cell growth by G2/M cell cycle arrest in breast and prostate tumour cells.

Different studies demonstrated that isoliquiritigenin suppresses pulmonary metastasis in mice (Yamazaki et al., 2002) and human hepatoma cells (Hsu, Kuo, & Lin, 2005). Apoptosis was primarily mediated through mitochondrial death cascade, as shown by loss of mitochondrial membrane potential, release of cytochrome *c*, and activation of caspase-9. A possible explanation is that cell growth was arrested through up-regulation of p53 and p21 and down-regulation of cdk2, cyclin E, and E2F-1 while apoptosis was induced by increasing Bax protein expression and activating caspase-7 (G. Sharma et al., 2012). Glabridin exhibited antitumour properties in various human cancer cells (Jiang et al., 2016). The results revealed that glabridin induced apoptosis in dose dependently in Huh7 cells through caspase-3, caspase-8, and caspase-9 activation and PARP cleavage (Hsieh et al., 2016).

4.9 | Neuroprotective activity

The effects of *G. glabra* on learning and memory were investigated in mice (Dhingra & Sharma, 2006; Parle et al., 2004). In 2004, Parle et al. (2004) administered the extract of *G. glabra* orally to mice during 7 days at different concentrations (75–300 mg/kg). Chakravarthi and Avadhani (2013) and Dhingra and Sharma (2006) studied the effects of *G. glabra* root aqueous extract on the learning and memory of 1-month-old male Wistar albino mice at doses between 75 and 300 mg/kg, orally administered during six successive weeks. Both studies demonstrated a significant improvement of learning and memory in mice, but the exact mechanism behind this action remains unknown (Chakravarthi & Avadhani, 2013; Dhingra & Sharma, 2006). These findings suggest a possible neuroprotective role of liquorice in the prevention of diseases such as Alzheimer. The basis of Alzheimer is the chronic inflammation of certain brain regions. Thus, the anti-inflammatory activity of liquorice might contribute to the observed memory-enhancing effects (Yokota, Nishio, Kubota, & Mizoguchi, 1998). Also, oxygen free radicals are implicated in the process of aging and could be responsible for the development of Alzheimer's disease in elderly persons. The protective role of liquorice extract may be attributed to its antioxidant properties, resulting in reduced brain damage and improvement of neuronal function and memory. The combination of anti-inflammatory and antioxidant activities with neuroprotective role could lead to memory-enhancing effects. Hasanein (2011) investigated the effect of chronic treatment with glabridin on the cognitive function of diabetic rats. The results showed

an improvement of learning and memory in nondiabetic rats and a reversal of learning and memory deficits in diabetic rats. The effect was attributed to the combined antioxidant, neuroprotective, and anti-cholinesterase properties of glabridin, suggesting a potential use in the management of dementia diabetic patients (Hasanein, 2011).

4.10 | Sedative activity

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system, being GABA$_A$ receptors a target for anaesthetics and neuroleptic, anxiolytic, and anticonvulsant compounds (Simmler et al., 2013). *G. glabra* acts as a modulator of GABA$_A$ receptors (Hoffmann, Beltrán, Ziemba, Hatt, & Gisselmann, 2016), being able to induce sedative and anxiolytic effects. Glabridin was evaluated by examining GABA responses in acutely isolated dorsal raphe neurons of a rat (Jin et al., 2013). According to the authors, glabridin potentiated GABA-induced responses by positive modulation of GABA$_A$ receptors, exhibiting sedative and hypnotic effects (Jin et al., 2013). Glabridin potentiation is not sensitive to flumazenil and uses a similar mechanism of the general anaesthetics involving the amino acids N265 and M286, which are located in the second and third transmembrane domains on the β-subunit of GABA$_A$ receptors (Hanrahan, Chebib, & Johnston, 2011). Also, glabridin could contribute to the hypnotic effect, as it is able to cross the blood–brain barrier (Simmler et al., 2013).

4.11 | Antidepressive activity

Liquorice extract may have potential therapeutic value for the treatment of depressive disorders. Recent studies have shown that liquorice extract produces significant antidepressant effects in mice during forced swim test (FST) and tail suspension test (TST; Dhingra & Sharma, 2006). In the FST model, mice were forced to swim in a restricted space and induced to a characteristic behaviour of immobility. This situation reflects a state of depression. The TST model also induces a state of immobility that is claimed to reproduce a condition similar to human depression. Both models are widely used to screen antidepressant drugs. The precise mechanisms by which liquorice extract produced this effect are not completely understood. However, it is suggested that the extract may interact with α1-adrenoceptors and dopamine D2 receptors, increasing the levels of norepinephrine and dopamine in the mice brain (Dhingra & Sharma, 2006). Besides, p-CPA (a serotonin synthesis inhibitor) did not attenuate the antidepressant effect of liquorice extract, suggesting that this is not mediated by the serotonergic system. On the other hand, p-CPA reversed the antidepressant effect of fluoxetine, suggesting that fluoxetine acts in the serotonergic system. Reserpine produces a significant depression by depleting biogenic amines in the brain of rodents. As liquorice extract reversed reserpine-induced depression, its antidepressant effect can be associated with the restoration of brain monoamines, such as norepinephrine and dopamine.

4.12 | Oestrogenic and androgenic effects

Since ancient times, the influences of liquorice on the action of cortisol, reduction of testosterone synthesis, and the influence on

oestrogen activity are well known (Armanini et al., 2002). S. H. Kim and Park (2012) reported that isoflavones can influence sexual development and impair oestrous cycling and ovarian and hypothalamus and pituitary glands function (S. H. Kim & Park, 2012). The oestrogenic effect of liquorice ethanolic extract could be explained by its agonist activity on MCF-7 breast cancer cells, being this action mediated by 18β-glycyrrhetinic acid (G. Sharma et al., 2012). Glabridin is a common component of herbal remedies used for the treatment of menopausal symptoms, resulting in favourable outcomes similar to those of 17β-oestradiol (Su Wei Poh et al., 2015). In concentrations between 2.5 and 25 µg per animal, glabridin induces similar effects to the administration of oestradiol in a concentration of 5 µg per animal. Glabridin was found to be three to four times more active than 2′-O-methylglabridin and 4′-O-methylglabridin (Tamir et al., 2000). Moreover, according to Tamir et al. (2001), glabrene has a considerable oestrogenic activity. Glabridin and glabrene are similar to 17β-oestradiol in the stimulation of the specific activity of creatine kinase, although at higher concentrations, differing in the extension rate of action as well as in the interaction with other drugs. In human premenopausal bone cells, the response to 17β-oestradiol and glabridin (at a higher concentration) was higher than in postmenopausal cells, whereas glabrene (at a higher concentration) was more effective in postmenopausal cells (Somjen et al., 2004).

Isoliquiritigenin has a strong oestrogen-like activity, suggesting that this compound may be cyclized to liquiritigenin, which is an active flavonoid under physiological conditions (Hajirahimkhan et al., 2013). In vivo, the stimulatory effects of glabrene are similar to those of oestradiol (Powers & Setzer, 2015). It is also interesting to observe that isoliquiritigenin and formononetin stimulate sperm during fertilization (Tung et al., 2014). This reveals that both phytoestrogens may be useful therapeutic agents for infertility treatments (Tung, Shoyama, Wada, & Tanaka, 2015). Zamansoltani, Nassiri-Asl, Sarookhani, Jahani-Hashemi, and Zangivand (2009) reported that the alcoholic extract of G. glabra has antiandrogenic effects probably by increasing the testosterone metabolism, down-regulating androgen receptors, or activating oestrogenic receptors.

4.13 | Skin effects

The main skin benefits reported for G. glabra are based on the antioxidant and anti-inflammatory activities as well as on the ultraviolet (UV) protection (Halder & Richards, 2004). Saeedi, Morteza-Semnani, and Ghoreishi (2003) reported the use of liquorice mainly for skin eruptions, including dermatitis, eczema, pruritus, and cysts. In particular, the G. glabra flavonoids present depigmenting capabilities and tyrosinase inhibition effects (Solano, Briganti, Picardo, & Ghanem, 2006). The presence of an α-keto group in flavonoids is responsible for this activity (Y. J. Kim & Uyama, 2005; Parvez et al., 2007). Castangia et al. (2015) have reported the skin protective effects of liquorice against damage from oxidative stress. According to the authors, liquorice extract can scavenge DPPH free radicals with an inhibition of 80% and protect fibroblasts against oxidative stress (Castangia et al., 2015). Nevertheless, when evaluated in the isolated form, glycyrrhizin showed a poor antioxidant activity, being not able to efficiently counteract the oxidative effect (Castangia et al., 2015).

Tyrosinase is essential for skin pigmentation due to its role in melanin biosynthesis (Solano et al., 2006). The use of tyrosinase inhibitors is important in the cosmetic and medicinal industries, due to their preventive effect on pigmentation disorders such as melasma, age spots, and sites of actinic damage (Nerya et al., 2003). Alternatively, tyrosinase inhibitors may be targets for developing medicines to treat hypopigmentation-related problems, such as albinism and piebaldism (Y. J. Kim & Uyama, 2005). In particular, glabridin, glabrene, isoliquiritigenin, licochalcone A, and liquiritin have been reported as G. glabra compounds able to inhibit the tyrosinase activity (Ebanks, Wickett, & Boissy, 2009; Nerya et al., 2003). Recently, Grippaudo and Di Russo (2016) described the effects of the topical application of glycyrrhetinic acid combined with fractional carbon dioxide laser for the benign treatment of hand hyperpigmentation during 4 weeks. Likewise, the treatment of human keratinocytes with 18β-glycyrrhetinic acid and glabridin was documented to directly and indirectly prevent DNA damage, avoiding the apoptosis activation caused by UV B radiation (Veratti et al., 2011). Indeed, Yokota et al. (1998) described that glabridin inhibits tyrosinase activity, melanogenesis, and skin inflammation. Besides, glabrene acts as a tyrosinase inhibitor, preventing the formation of melanin in melanocytes, probably acting as skin-lightening agent. Saeedi et al. (2003) exposed that liquorice extract could be considered as an effective agent in the treatment of atopic dermatitis. Finally, the hydro-alcoholic extract of liquorice promotes hair growth, being safely used in herbal formulations for the treatment of various types of alopecia (Saumendu, Raj, Suvakanta, Jashabir, & Biswajit, 2014).

4.14 | Other activities

Liquorice has been traditionally used as a sweetener due to its taste, (Tian, Liu, Zhen, & Tong, 2013; Tong, Xie, Rong, Zhou, & Meng, 2015). According to Bahmani et al. (2014), liquorice can reduce diabetes symptoms, such as polydipsia and frequent urination, but cannot reduce blood glucose. Takii et al. (2001) suggested that glycyrrhizin has an antidiabetic effect in noninsulin-dependent diabetes mice model, reducing the postprandial blood glucose rise.

Glycyrrhizin is a thrombin inhibitor. An in vivo assay performed in rats demonstrated that the intravenous administration of glycyrrhizin causes a dose-dependent reduction in thrombus size on a venous thrombosis model, combining stasis and hypercoagulability (Mendes-Silva et al., 2003). The authors reported that doses between 180 and 360 mg/kg decreased the thrombus weight by 35% and 90%, respectively (Mendes-Silva et al., 2003).

The immunomodulatory activity of an aqueous root extract of G. glabra was demonstrated in vitro to be linked to the presence of the phenolic compound glycyrrhizin (Mitra Mazumder, Pattnayak, Parvani, Sasmal, & Rathinavelusamy, 2012). Mitra Mazumder et al. (2012) reported the increased production of lymphocytes and macrophages from human granulocytes after contact with G. glabra root extract.

Different liquorice compounds, such as licochalcone A, 18β-glycyrrhetinic acid, and glabridin, have antimalarial activity. Licochalcone A is the most promising one, inhibiting in vitro the growth of chloroquine-susceptible and chloroquine-resistant *Plasmodium*

falciparum strains (Chen et al., 1994). Glabridin also showed in vitro activity against this parasite, probably by an induction of oxidative stress, mainly through the generation of reactive oxygen and nitrogen species that lead to apoptosis (Cheema et al., 2014).

It is well known that myocardial ischaemia is one of the principal diseases in the Western world. This disease occurs through occlusion or blockage of coronary arteries, resulting in myocardial cell death. However, the reperfusion produces the salvage of ischaemic tissue but also contributes to the myocardial cellular injury. The pretreatment with *G. glabra* significantly attenuates the ischaemic reperfusion, through an improvement of the heart antioxidant status, a positive modulation of the perturbed haemodynamic, and a recovery of left ventricular contractile function, along with histological salvage (Di Paola et al., 2009; Ojha, Golechha, Kumari, Bhatia, & Arya, 2013). In particular, glycyrrhizic acid induced protection against myocardial ischaemia in rats, probably due to its antioxidant potential (Ojha et al., 2013). Similarly, Nakagawa, Kishida, Arai, Nishiyama, and Mae (2004) demonstrated that *G. glabra* is safe for cardiomyocytes in a long-term administration.

The extract of *G. glabra* has been used in the treatment of low bone mass, osteoporosis, fractures, bone defects, osteomalacia, osteogenesis imperfecta, bone disease, and periodontal diseases (Kumar et al., 2015). Rajesh (2004) described the inhibitory effect on bone reabsorption of *G. glabra*, whereas Choi (2011) reported that glabridin is responsible for this activity. Mitochondrial dysfunction, especially respiratory chain disruption, is responsible for aging-related bone diseases. Hence, the target of glabridin is the reduction of mitochondrial dysfunction induced during aging and the prevention of osteoblast damage in osteoporotic patients (Choi, 2011).

Study on mice demonstrated that *G. glabra*, particularly glabridin, when integrated in a dietary supplement, could reduce the susceptibility of low-density lipoprotein (LDL) to oxidation and the atherosclerotic lesion area (Fuhrman & Aviram, 2001; Grassi, Desideri, & Ferri, 2010). These results could be related to the absorption and binding of glabridin to the LDL and a subsequent protection of the LDL from oxidation (Fuhrman et al., 1997).

The methanolic extract of *G. glabra* rhizomes, at a dose of 150 mg/kg, has antiarthritic activity in male rats by inhibition of leukocyte migration, autoantigen production, and exhibition of antiproteinase activity (Choudhary, Kumar, Malhotra, & Singh, 2015). Also, Mishra, Bstia, Mishra, Chowdary, and Patra (2001) reported that a combined formulation of *G. glabra* and *Boswellia serrata* (1:1) had a significant synergistic action on arthritis.

Shin et al. (2007) studied the antiallergic effects, namely, the antiscratching behaviour and the IgE production inhibitory activity, of glycyrrhizin, 18β-glycyrrhetinic acid, isoliquiritin, and liquiritigenin in dermatitis and asthma (Shin et al., 2007). In particular, 18β-glycyrrhetinic acid attenuated the airway inflammation in an asthmatic mouse model, being classified as a novel therapeutic component for the treatment of allergic asthma (S. H. Kim, Hong, Lee, & Lee, 2017).

Finally, glabridin shows hypoglycaemic effects in an animal model with diabetes mellitus, significantly decreasing body weight (Wu, Jin, & Jin, 2013). J. Ahn, Lee, Jang, Kim, and Ha (2013) stated that *G. glabra* effectively inhibits the adipogenesis of 3T3-L1 cells.

5 | SIDE EFFECTS AND TOXICITY

Different adverse side effects were reported for high doses of *G. glabra* such as hypertension, hypokalaemia, or fluid retention (Omar et al., 2012). The exposure to high levels of glycyrrhizin can produce hypermineralocorticoid-like effects. Glycyrrhetic acid and liquorice saponins can inhibit 11-β-hydroxysteroid dehydrogenase enzyme, leading to a cortisol-induced mineralocorticoid effect and a consequent tendency to the elevation of sodium and reduction of potassium levels (Isbrucker & Burdock, 2006). For example, in 2010, a 34-year-old woman was suspected to have suffered a lethal acute intoxication from eating liquorice over a period of several months (Albermann et al., 2010). Albermann et al. associated the effects with the potential mineralocorticoid action of glycyrrhizin and its metabolite, glycyrrhetic acid, and quantified by liquid chromatography–tandem mass spectrometry these compounds in the blood. Nevertheless, only traces of glycyrrhetic acid had been found in the blood and stomach content of the deceased woman, which means that the possibility of acute lethal glycyrrhetic acid intoxication could be eliminated (Albermann et al., 2010).

Based on in vivo assays and clinical evidence, the amount of liquorice ingested daily by patients with mineralocorticoid excess syndromes appears to vary over a wide range (1.5–250 g/day; Isbrucker & Burdock, 2006). In addition to hypertension, patients may experience hypokalaemia and sodium retention, resulting in oedema. Studies on rodents and humans demonstrated that glycyrrhizin is poorly absorbed by the gastrointestinal tract but extensively metabolized by the intestinal microflora to glycyrrhetic acid and monoglucuronyl glycyrrhetic acid, which are both readily absorbed. Thus, an enterohepatic circulation of glycyrrhetic acid can occur, requiring several days for complete body elimination (Koga, Kawamura, Iwase, & Yoshikawa, 2013). Also, during premenstrual syndrome, the use of this plant may cause water retention and bloating.

6 | CONCLUDING REMARKS

This review has presented a comprehensive view about the phytochemistry composition and pharmacology activities of *G. glabra*. This plant has been broadly used as a traditional medicine and food industry ingredient, particularly as a flavour and sweetening agent. The roots are used in the prevention and treatment of several complications, especially microbial/viral infection, cancer, and skin inflammation. Among the bioactive compounds, flavonoids are the most important, being responsible for most of the biological activities. Different phytochemicals, including glycyrrhizin, 18β-glycyrrhetinic acid, glabrin A and B, or isoflavones, have been identified and associated with the biological activities reported, namely, antioxidant, antiviral, antimicrobial, anticancer, or anti-inflammatory activities as well as hepatoprotection. These activities generally agree with traditional knowledge and folk medicine. Indeed, the side effects and toxicity associated with liquorice are few and are mainly linked with hypertension and fluid retention. Regarding this particular thematic, to date, few studies have been conducted, aside from some isolated ones. Thus, side effects remain an area of potential future study. This review

not only details and explains the traditional use of this plant but also highlights its potential uses for other industries, such as cosmetic or pharmaceutical ones. More clinical trials should be performed to provide scientific basis for new uses.

In conclusion, although evidence has grown in the past decade, there is still a need to conduct further robust double-blind randomized controlled trial about *G. glabra*. There is also an immense scope to explore different combinations of liquorice preparations in a wide range of disorders.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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