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Chronic Treatment of Diseases with Licorice - Mulethi (*Glycyrrhiza glabra* L.)

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Abstract **Review Article**

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotrans-mitter in the central nervous system, being GABAAreceptors a target for anaesthetics and neuroleptic, anxiolytic, and anticonvulsant com-pounds. *G. glabra* acts as a modulator of GABAA receptors, being able to induce sedative and anxiolytic effects. Glabridin potentiated GABA-induced responses by positive modulation of GABAA receptors, exhibiting sedative and hypnotic effects. 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 GABAA receptors. Glabridin could also contribute to the hypnotic effect, as it is able to cross the blood–brain barrier. Liquorice extract has potential therapeutic value for the treatment of depressive disorders. Liquo-rice extract produces significant antidepressant effects. The main skin benefits reported for *G. Glabra* are based on the antiox-idant and anti-inflammatory activities as well as on the ultraviolet (UV) protection. Mainly liquorice is used for skin eruptions, including dermatitis, eczema, pruritus, and cysts. G. glabra flavonoids present depigmenting capabilities and tyrosi-nase inhibition effects. The presence of anα-keto group in flavonoids is responsible for the skin protective effects of liquorice against damage from oxidative stress. Liquo-rice extract can scavenge DPPH free radicals with an inhibition of 80% and protect fibroblasts against oxidative stress. Nevertheless, when evaluated in the isolated form, glycyrrhizin showed a poor antioxidant activity, being not able to efficiently coun-teract the oxidative effect. Tyrosinase is essential for skin pigmentation due to its role in melanin biosynthesis. The use of tyrosinase inhibitors is important in the cosmetic and medicinal industries, due to their pre-ventive effect on pigmentation disorders such as melasma, age spots, and sites of actinic damage. Alternatively, tyrosi-nase inhibitors may be targets for developing medicines to treat hypopigmentation-related problems, such as albinism and piebaldism. In particular, glabridin, glabrene, isoliquiritigenin, licochalcone A, and liquiritin have been reported as G. glabracompounds able to inhibit the tyrosinase activity. Glabrene acts as a tyrosinase inhibitor, preventing the formation of melanin in melanocytes, probably acting as skin-lightening agent. Liquorice extract could be considered as an effective agent in the treatment of atopic dermatitis. Hydro-alcoholic extract of liquorice pro-motes hair growth, being safely used in herbal formulations for the treatment of various types of alopecia. Liquorice has been traditionally used as a sweetener due to its taste. Liquorice can reduce diabetes symptoms, such as polydipsia and frequent urination, but cannot reduce blood glucose. Glycyrrhizin has an antidiabetic effect in noninsulin-dependent diabetes mice model, reducing the postprandial blood glucose rise. Glycyrrhizin is a thrombin inhibitor. The intravenous administration of glycyrrhizin causes a dose-dependent reduction in thrombus size on a venous thrombosis model, combining stasis and hypercoagulability. The authors reported that doses between 180 and 360 mg/kg decreased the thrombus weight by 35% and 90%, respec-tively.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. 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.

Keywords: Chronic Treatment, Mulethi, Glycyrrhetic.

INTRODUCTION

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).

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotrans-mitter in the central nervous system, being GABAAreceptors a target for anaesthetics and neuroleptic, anxiolytic, and anticonvulsant com-pounds (Simmler *et al*., 2013). G. glabra acts as a modulator of GABAA receptors (Hoffmann *et al*., 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 GABAA 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 GABAA 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).

Liquorice extract may have potential therapeutic value for the treat-ment of depressive disorders. Recent studies have shown that liquo-rice extract produces significant antidepressant effects in mice during forced swim test (FST) and tail suspension test (Dhingra & Sharma, 2006).

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).

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). Kim and Park (2012) reported that isoflavones can influence sexual development and impair oestrous cycling and ovarian and hypothalamus and pituitary glands function (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 (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 *et al*., 2015). In concentrations between 2.5 and 25μg 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). In human premen-opausal 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 fertili-zation (Tung *et al*., 2014). This reveals that both phytoestrogens may be useful therapeutic agents for infertility treatments (Tung *et al*., 2015). Zamansoltani *et al*., (2009) reported that the alcoholic extract of G. glabra has antiandrogenic effects probably by increasing the testos-terone metabolism, down-regulating androgen receptors, or activating oestrogenic receptors.

The main skin benefits reported for G. Glabra are based on the antiox-idant and anti-inflammatory activities as well as on the ultraviolet (UV) protection (Halder & Richards, 2004). Saeedi *et al*., (2003) reported the use of liquorice mainly for skin erup-tions, including dermatitis, eczema, pruritus, and cysts. In particular, the G. glabra flavonoids present depigmenting capabilities and tyrosi-nase inhibition effects (Solano *et al*., 2006).

The presence of anα-keto group in flavonoids is responsible for this activity (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, liquo-rice 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 coun-teract 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 pre-ventive effect on pigmentation disorders such as melasma, age spots, and sites of actinic damage (Nerya *et al*., 2003). Alternatively, tyrosi-nase inhibitors may be targets for developing medicines to treat hypopigmentation-related problems, such as albinism and piebaldism (Kim & Uyama, 2005). In particular, glabridin, glabrene, isoliquiritigenin, licochalcone A, and liquiritin have been reported as G.

glabracompounds able to inhibit the tyrosinase activity (Ebanks *et al*., 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 causedby UV B radiation (Veratti *et al*., 2011). 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 pro-motes hair growth, being safely used in herbal formulations for the treatment of various types of alopecia (Saumendu *et al*., 2014).

Liquorice has been traditionally used as a sweetener due to its taste, (Tian *et al.*, 2013; Tong *et al*., 2015). According to Bahmani *et al*., (2014), liquorice can reduce diabe-tes 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%, respec-tively (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 *et al*., 2012). Mitra Mazumder *et al*., (2012) reported the increased production of lymphocytes and mac-rophages from human granulocytes after contact with G. glabra root extract.

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).

The pretreat-ment 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 *et al*., 2013). In particular, glycyrrhizic acid induced protection against myocardial ischaemia in rats, probably due to its antioxidant potential (Ojha *et al*., 2013). Similarly, Nakagawa et al. (2004) demonstrated that G. glabrais 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, osteo-genesis 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 dis-eases. 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 susceptibil-ity of low-density lipoprotein (LDL) to oxidation and the atheroscle-rotic lesion area (Fuhrman & Aviram, 2001; Grassi *et al.*, 2010).

The methanolic extract of G. glabrarhizomes, at a dose of 150 mg/kg, has antiarthritic activity in male rats by inhibition of leuko-cyte migration, autoantigen production, and exhibition of antiproteinase activity (Choudhary *et al*., 2015). Also, Mishra *et al*., (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 Kim *et al*., 2017). Finally, glabridin shows hypoglycaemic effects in an animal model with diabetes mellitus, significantly decreasing body weight (Wu *et al*., 2013). Ahn *et al*., (2013) stated that G. glabra effectively inhibits the adipogenesis of 3T3-L1 cells.

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 conse-quent 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*., (2010).associated the effects with the potential mineralocorticoid action of glycyrrhizin and its metabolite, glycyrrhetic acid, and quantified by liquid chromatography–tandem mass spec-trometry 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 liquo-rice ingested daily by patients with mineralocorticoid excess syn-dromes appears to vary over a wide range (1.5–250 g/day; Isbrucker & Burdock, 2006). An enterohepatic circulation of glycyrrhetic acid can occur, requiring sev-eral days for complete body elimination (Koga *et al*., 2013). Also, during premenstrual syndrome, the use of this plant may cause water retention and bloating.

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