A Comprehensive Review on Therapeutic Potential of *Glycyrrhiza glabra* L. in Treatment of Various Disorders

Korhalkar Anagha1*, Deshpande Manasi 2, Lele Priya 3, Modak Meera 4
1 Department of Gen. Pathology and Microbiology, Dental College and Hospital, Bharati Vidyapeeth Deemed University, Pune, Maharashtra, India.
2 Departments of Dravyaguna Vignan, College of Ayurveda, Bharati Vidyapeeth University, Pune, Maharashtra, India
3 Departments of Periodontology, Dental College and Hospital, Bharati Vidyapeeth Deemed University, Pune Maharashtra, India.
4 Departments of Microbiology, Medical College, Bharati Vidyapeeth Deemed University, Pune, Maharashtra, India.

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Corresponding Author*: anaghakorhalkar13@gmail.com.

ABSTRACT

*Glycyrrhiza glabra* (*Yashtimadhu*) has extensive pharmacological effects for human beings. It is used for treating upper respiratory ailments including Coughs, hoarseness, sore throat and bronchitis. The Liquorice (*Glycyrrhiza glabra*) extracts have been used to treat chronic hepatitis, and also have used for therapeutic benefits against viruses, including Human immunodeficiency virus (HIV), Cytomegalovirus (CMV), and Herpes simplex virus (HSV). Deglycyrrhizinated liquorice (DGL) preparations were useful in treating various types of ulcers, while topical liquorice preparations have been used to sooth and heal skin eruptions, such as Psoriasis and herpetic lesions. It has also been found to be an Anti-stress and anabolic agent and to possess good anti-bacterial, anti-fungal, anti-oxidant, anti-tussive, hepatoprotective, and anti-inflammatory activities. The present review also lists its use in Hyperpigmentation, immune cell activation; wound healing, treatment of atopic dermatitis, Familial Mediterranean Fever, induction of apoptosis, reduction of serum testosterone, etc. *Yashtimadhu* also acts as Anti-cancer agent, shows protective effect in radiation injury and is useful in management of functional dyspepsia. This review summarizes the therapeutic potential of the *Glycyrrhiza glabra* in the treatment of various disorders.

Key words: *Yashtimadhu*, Liquorice, *Glycyrrhiza glabra*, Pharmacological effects.

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INTRODUCTION

_Glycyrrhiza glabra_ belongs to Leguminosae family and has been used since ancient times as a medicinal herb. It has been referred in Indian traditional medicine some 5,000 years ago [Lodha R, Bagga, 2000]. In India, liquorice root carries the ancient Sanskrit name of ‘Yasthimadhu’ (sweet-stalk) and has been a mainstay of Ayurvedic and other traditional medicines. In ancient Ayurvedic system, more than 1250 preparations have been described containing _Yashtimadhu_ as one of its constituents. In traditional Ayurvedic medicine, herbs were used as special foods, serving to eliminate the excesses as well as strengthen the deficiencies, restore and rejuvenate. [Korhalkar Anagha et al, 2012]. _Glycyrrhiza glabra_ has been used as folk medicine, traditional and alternative medicine due to the wide spectrum of its pharmacological activities. The multifaceted therapeutic potential of _Glycyrrhiza glabra_ in the management of various disorders has been mentioned in various papers. The present review discusses various therapeutic effects in different disorders and possible mechanism of action of _Glycyrrhiza glabra_.

METHODS

Various scientific research and review articles published in English from 2000 to 2013 were identified through Pubmed and Google scholar websites using MeSH terms as _Glycyrrhiza glabra_, Liquorice, and _Yashtimadhu_, and by manual search of bibliographies. Two dissertation works based on the therapeutic potential of the drug were also included. More than 100 research articles including few review papers were found on it. These articles were grouped according to the various therapeutic effects of _Glycyrrhiza glabra_ and compiled in different sections in this review.

Clinical safety of Liquorice Flavonoid Oil (LFO) and Pharmacokinetics of Glabridin in healthy humans:

Licorice Flavanoid Oil [LFO] was assessed by Aoki F. et al in healthy humans for safety and pharmacokinetic analysis in the single-dose study with healthy male subjects. Result showed that glabridin was absorbed and reached the maximum concentration (Cmax) after approximately 4 hours. (Tmax), and then eliminated relatively slowly in a single phase with a T1/2 of approximately 10 hours at all doses. It was also found in this study that the Cmax and AUC (0-24 h)
increased almost linearly with dose. It was observed that glabridin reached steady state levels within 2 weeks with a single daily administration of 300 to 1200 mg/day LFO. All clinical events observed in this study were mild and considered to be unrelated to LFO [Aoki F et al, 2007].

**Wound healing:**
Finding of this review suggested that *Ficus bengalensis, Cynodon dactylon, Symplocos racemosa, Rubia cordifolia, Pterocarpus santalinus, Ficus racemosa, Glycyrrhiza glabra, Berberis aristata, Curcuma longa, Centella asiatica, Euphorbia nerifolia,* and *Aloe vera* were screened scientifically for the evaluation of their wound healing activity in different pharmacological models and patients, were found effective [Biswas T.K. et al, 2003].

In another study by Vijay Viswanathan et al [2011], effects of a polyherbal formulation cream on diabetic foot ulcers was studied. The Polyherbal formulation contained *Glycyrrhiza glabra, Musa paradisiaca, Curcuma longa, Pandanus odaratifissimus, Aloe vera,* and *Cocos nucifera* oil. This study found that there was a significant decrease in the size of the wound (length and width) in both the study groups ($P<0.001$) and the polyherbal formulation was effective as well as safe in healing diabetic foot ulcers like the standard Silver sulphadiazine cream [Vijay Viswanathan et al, (2011)]

**Effect of Glycyrrhiza glabra on hyperpigmentation:**
This study used fifty-two crude drugs which were selected based on the survey carried out among local healers and beauticians of different ethnic origin. They were screened for mushroom tyrosinase inhibitory activity. It was observed in this study that methanolic extracts of *Glycyrrhiza glabra* at concentration of 50 ug/mL, showed mushroom tyrosinase inhibitory activity of 78.9%, with 91.4% inhibitory activity of kojic acid taken as positive control [Adhikari A et al, 2008].

**CD69 expression and immune cell activation in humans:**
The ability of three herbs, *Echinacea purpurea, Astragalus membranaceus* and *Glycyrrhiza glabra,* to activate immune cells in human subjects was assessed in this pilot study. After seven days, the primary cell activation marker measured was CD69. It was measured using Flow cytometry. The results of this study showed that all three tinctures stimulated immune cells as quantified by CD69 expression on CD4 and CD8 T cells and activation took place within 24 hr of ingestion, and continued for at least 7 days [Julie Brush et al, 2006].
Oral Lichen Planus:
*Glycyrrhiza glabra* was screened scientifically in this open clinical trial. 17 hepatitis C-positive patients with oral lichen planus were given either routine dental care or 40 mL IV glycyrrhizin daily for one month. This study result showed that in glycyrrhizin treated group, among nine patients six patients noted improved clinical symptoms, such as decreased redness, fewer white papules, and less erosion of the mucosa [Da Nagao Y et al, 2005].

Glycyrrhizic acid in liquorice - Evaluation of health hazard:

Glycyrrhizic acid was critically reviewed in the literature on case reports, clinical studies and biochemical mechanisms to provide a safety assessment of its presence in liquorices sweets. It was observed in this review that regular intake of 100 mg glycyrrhizic acid/day was the lowest-observed-adverse-effect level and using a safety factor of 10, a daily intake of 10 mg glycyrrhizic acid would represent a safe dose for most healthy adults [F.C.Stermer et al, 2002].

Complementary and alternative therapies in the Chronic hepatitis C:

Review by Coon J.T, Ernst E., on complementary and alternative therapies on Hepatitis-C found twenty-seven eligible randomized clinical trials involving herbal products and supplements. The authors found that in 14 of the trials, patients received interferon-alpha in combination with the complementary therapy. Compared with the control group, there was significant improvement in virological and/or biochemical response in trials of vitamin E, thymic extract, zinc, traditional Chinese medicine, *Glycyrrhiza glabra* and oxymatrine. According to the authors conclusive remarks could not be drawn due to methodological limitations [Coon J.T., Ernst E., 2004].

Atopic dermatitis with Liquorice gel:

The effect of different gels as topical preparations was evaluated on Atopic dermatitis in this double-blind clinical trial in comparison with base gel by Saeedi M et al. They found that two percent liquorice topical gel was more effective in reducing the scores for erythema, oedema and itching. Other findings of this study were, Propylene glycol was the best co-solvent for the extract and Carbopol 940 as gelling agent showed the best results in final formulations. [Saeedi M. et al, 2003]
**Hepatoprotective activity:**

Thyagarajan provided the status report on the scientific approaches made with the herbal preparations used in Indian systems of medicine for the treatment of liver diseases in his review. Though there are more than 300 preparations for the treatment of Jaundice and chronic liver diseases in Indian systems of medicine using more than 87 Indian medicinal plants, only four terrestrial plants have been scientifically elucidated while adhering to the internationally acceptable scientific protocols. *Glycyrrhiza glabra* had been shown to be hepatoprotective and capable of inducing an indigenous interferon [Thyagarajan S.P, 2002].

**Cancer:**

An evidence based review on herbal medicine for cancer patients was carried out. Following result was found:

- Liquorice (*Glycyrrhiza glabra*), Garlic (*Allium sativum*), and Grape seed extract (*Vitis vinifera*) were all potential anti-cancer agents [Ray, Parikh and Bagchi 2005; Tanaka et al. 2006; Wang and Nixon 2001; Zhang et al, 2005].

- It indicated that liquorice and its derivatives may protect against carcinogen-induced DNA damage. Glycyrrhetinic acid was found to be an inhibitor of lipo-oxygenase and cyclo-oxygenase, and it inhibited protein kinase C, and down regulated the epidermal growth regulator factor [Wang and Nixon, 2001] [Janelle Wheat, Currie, Geoffrey, 2008].

**Tumor cell line:**

Rafi MM et al assessed liquorice root extract for effects on Bcl-2, as novel cytotoxic derivative. He showed that liquorice root contained beta-hydroxy-DHP. This molecule induced Bcl-2 phosphorylation in breast and prostate tumor cells, G2/M cell cycle arrest, apoptosis demonstrated by Annexin V and TUNEL assay, decreased cell viability demonstrated by a tetrazolium (MTT) assay, and altered microtubule structure [Rafi M.M et al, 2002].

**Anti-viral:**

Randomized controlled trials of glycyrrhizin were found to reduce hepatocellular damage in chronic hepatitis B and C. The risk of hepatocellular carcinoma was found to be reduced in hepatitis C virus-induced cirrhosis. *In vitro* studies revealed anti-viral activity against HIV-1, SARS related corona virus, respiratory syncytial virus, arbo viruses, vaccinia virus and vesicular stomatitis virus [Cristina Fiore et al, 2007].
**Familial Mediterranean fever:**

A double blind, randomized, placebo controlled pilot study was conducted on 24 patients with Familial Mediterranean Fever (FMF) by Amaryan G et al. 14 patients were treated with Immuno Guard, a standardized fixed combination of *Andrographis paniculata* Nees., *Eleutherococcus senticosus* Maxim., *Schizandra chinensis* Bail., and *Glycyrrhiza glabra* L. The medication was given three times of four tablets daily for one month. This study found that the duration, frequency, severity of attacks showed significant improvement in the test group as compared with the placebo. Both the clinical and laboratory results of this phase II (pilot) clinical study found that Immuno Guard was a safe and efficacious herbal drug for the management of patients with FMF [Amaryan G et al, 2003].

**Reduces serum testosterone in healthy women:**

Decio Armaninia et al suggested that Liquorice could be considered an adjuvant therapy of hirsutism and polycystic ovary syndrome and reduces serum testosterone probably due to the block of 17-hydroxysteroid dehydrogenase and 17–20 lyases. Study was carried out to investigate the effect of liquorice on androgen metabolism in nine healthy women [22–26 years old], in the luteal phase of the cycle. The results of the study indicated that, plasma renin activity and aldosterone were depressed during therapy, while blood pressure and cortisol remained unchanged [Decio Armaninia et al, 2004].

**Alleviates Symptoms of Functional Dyspepsia:**

In this randomized, double-blind, placebo-controlled study by Raveendra K R et al the efficacy of GutGard; an extract of *Glycyrrhiza glabra*, in patients with functional dyspepsia was evaluated. The patients received either placebo or GutGard (75 mg twice daily) for 30 days. Efficacy was evaluated in terms of change in the severity of symptoms (as measured by 7-point Likert scale), the global assessment of efficacy, and the assessment of quality of life using the short-form Nepean Dyspepsia Index. In comparison with placebo, GutGard showed a significant decrease (P ≤ .05) in total symptom scores on day 15 and day 30, respectively. The study concluded that GutGard was safe and well-tolerated by all patients and it also showed significant efficacy in the management of functional dyspepsia [Raveendra K.R et al, 2012].
**Reduces side effects of Chemotherapy:**

This study evaluated 75 patients for seven weeks in four groups. The results suggested that the intensity of radiation and chemotherapy induced mucositis was reduced to a great extent by *Yashtimadhu ghrita*, which proved beneficial in two ways: (i) There were no interruptions in the treatment, and (ii) food intake was not severely affected leading to maintenance of nutritional status of the patients. The trial drug of group A *Yashtimadhu ghrita* orally and *Yashtimadhu powder* with honey locally had insignificant result \((P > 0.1)\) in skin reactions in both initial stage and in final week of the treatment when compared to the control group D (only on conventional modern medication) [Debabrata Das et al, 2011].

**Increases intelligence:**

In the study by A.K. Teltumbde et al, a single blind controlled clinical trial was conducted to re-assess and establish the Psychoneuropharmacological effect of *Yashtimadhu*. Two tests were performed - NVIT (Non Verbal Intelligence Test) and Memory tests (based on Guilford’s structure of intellect model). The findings of this study are, oral consumption of *Yashtimadhu* tablets BID improved the intelligence level among the students when compared to placebo group. It also improved the general intelligence rather than STM (short term memory). The authors also opined that, *Yashtimadhu* tablet form is an acceptable form of drug in adolescents which can be explored for in memory improvement and memory dysfunction cases [A.K. Teltumbde, 2013].

**Mental adjustment disorder of young adults:**

The effect of *Yashtimadhu Ghana Vati* and *Tagara Ghana Vati* along REBT (Rational Emotive Behavioural Therapy) counseling with *Satvavajaya chikitsa* was evaluated by Ganesh Kolhe et al. They found that that both the trial drugs were equally effective in management of anxiety, depression, difficulties in concentration and memory, fears, gastro-intestinal symptoms, genitourinary symptoms, muscular symptoms, sensory symptoms and tension. It also suggested that *Yashtimadhu* was found more effective in anxious mood behavior [Ganesh Kolhe, 2013].

**Yashtimadhu Taila in Parikartika:**

*Yashtimadhu Taila pichu* (Pichu - Swab or thick cotton pad (*kavalika*) soaked in the medicated ghee or oil and placed in the
desired position over the body for a prescribed time and *Jatyadi Taila pichu* had been screened scientifically in a comparative randomized clinical trial. 20 *Parikartika* (cutting and burning pain all around the anus) patients were given either *Yashtimadhu Taila* or *Jatyadi Taila*. This study result showed that in *Yashtimadhu Taila* treated group showed a higher degree of pain control [Kumar, Shinde Anant 2011].

**Quadruple therapy for Peptic ulcer:**

In this double-blind study, 40 patients with peptic ulcer were divided into two equal groups. The first group received Amoxicillin, metronidazole, and omeprazole and bismuth sub nitrate. In Group 2, the regimen was identical, but bismuth sub nitrate was replaced with liquorice. In liquorice group, healing of peptic ulcer, the eradicative effect against *H. pylori* and reduction in pain was more prominent [Marjan Rahnama et al, 2013].

**Shukrakshya (Oligospermia):**

Thirty patients of *Shukrakshaya* (Oligospermia) had been screened scientifically in this comparative randomized clinical trial. *Ashwagandha* (*Withania somnifera*) or *Yastimadhu choorna* was given for one month with 150 ml cow milk. Findings showed that *Yastimadhu choorna* was more effective in Erection, Desire, Ejaculation, Excitement and sperm count after follow up [Chowdhary Amit, 2013].

**CONCLUSION**

From the above review it is evident that *Glycyrhiza glabra* (*Yashtimadhu*) is very effective as preventive and curative agent for many disease conditions. It has been extensively used in Indian traditional systems and in other Asian countries since thousands of years. Even though *Yashtimadhu* has been extensively used in many clinical conditions as stated in this review, there are many more conditions described in Indian system of medicine which can be cured with *Yashtimadhu*. Since *Yashtimadhu* has been described as *Rasayana* in Ayurveda and as immunomodulator in modern system, it may prove important agent for emerging life style disorders. Work in this direction is required.
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