GLABRIDIN FROM GLYCYRRHIZA- A VERSATILE NATURAL ANTIMICROBIAL

Lekshmy J[1*], Rakesh Nagaraju[2], Saraswathy G R[3]

Abstract:
Herbal mode of treatment has been in use since ancient times. Human evolutionary process has led to replacement of these herbal medications with allopathic preparations. The indiscriminate and wide spread use of antimicrobial drugs in recent years has led to acquired resistance in many microorganisms with side effects. Hence there is an off late resurgence back to herbal medications. The roots and rhizomes of Licorice has been identified to have been used worldwide as a herbal medicine and natural sweetner. Several species of Licorice have been identified which includes Glycyrrhiza glabra, G. uralensis, G.inflata. In traditional medicine Licorice has been used mainly in peptic ulcer treatment, in skin diseases, as demulcent, treatment in hepatitis C and some pulmonary diseases. Clinical and experimental studies have suggested the anti-inflammatory, anti-oxidant, anti-microbial, cardioprotective and hepatoprotective effects. Glabridin, an isoflavanoid present in Glycyrrhiza glabra contributes majorily to all its properties. This review provides a comprehensive description on the health effects of Licorice highlighting on the major constituent in it, Glabridin.

Key words: Licorice, Glabridin, Glycyrrhizin

[1]*Ph.D Scholar, M.S. Ramaiah University of Applied Sciences, Bangalore- 560054,
Email: dr.lekshmyj@gmail.com
[2]Ph.D Supervisor, Faculty of dental Sciences, M.S. Ramaiah University of Applied Sciences, Bangalore-560054
[3]PhD Co-Supervisor, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, Bangalore-560054

***Corresponding Author: -** Lekshmy J
*Ph.D Scholar, M.S. Ramaiah University of Applied Sciences, Bangalore- 560054,
Email: dr.lekshmyj@gmail.com

DOI: 10.53555/ecb/2023.12.Si13.217

Introduction:

Licorice refers to the roots and stolons of Glycyrrhiza species, belonging to family Leguminosae and is native to meditteranean and certain areas of Asia **[1]**. It is a perennial herb also called as Yastimadhuh (Sanskrit), Mulhatti (hindi), Yastimadhuka/Atimaddhura (Kannada). About 30 species of this genus exist of which Glycyrrhiza glabra and Glycyrrhiza uralensis are the most common [2]. Recent research suggests that licorice extracts and their active constituents possess a valuable potential for improving oral health. It has been widely used as herbal medicine dating back to 500BC. These plants contain a variety of secondary metabolites such as saponins, flavonoids, chalcones, isoflavanoids. Roots of this plant has several pharmacological properties such as antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, hepatoprotective and cardioprotective effects [3]. Glycyrrhizin, is a diglucuronide of glycyrrhetinic acid and is the active component to which all the positive properties of drug can be attributed and is also responsible for sweet taste of licorice [4]. Glycyrrhizin (GL), 18-β-glycyrrhetinic acid, Liquiritigenin, licochalcone A and Glabridin are the main active components which possess antiviral and antimicrobial activities [5]**.** Hardly any research has been conducted regarding the effect of licorice extracts in relation to oral mucosal lesions. Though many in vitro studies have been carried out, clinical trials in this field are scanty. Among the many compounds, only glycyrrhizin has been clinically developed as a drug. With additional research, there definitely will be a niche for Licorice and its components in dentistry. Development of effective and affordable licorice extracts can introduce dramatic improvements in treating many prevalent diseases.

Glabridin is an isoflavanoid present in licorice. Among the constituents of licorice, Glabridin has been found to have antioxidant, anti-inflammatory, anti-tumour, antifibrogenic, neuroprotective, anti-osteoporotic and anti-atherogenic properties. The principal objective of this review is to provide a comprehensive description on the health effects of Licorice highlighting on glabridin.

The chemicals isolated from the roots of licorice exhibits several medical and dental health benefits. Experimental and clinical trials have been carried out to confirm these effects. Properties of the active constituents with details of experimental and clinical trials are described below

Antiinflammatory activity:

Inflammation is the initiation point for many chronic diseases including cardiovascular diseases, degenerative conditions and cancer. Among the various compounds isolated from licorice, majority of them exhibited anti-inflammatory effect. B-glycyrrhitinic acid has been reported to show anti-inflammatory properties in animal models [6]**.** In in-vivo studies along with glabridin, Licochalcone has been found to exhibit anti-inflammatory properties [7]

Demonstration of anti-inflammatory effect was first done by Yokoto et al. Glabridin at a concentration of 6.25 µgm/ml inhibits 31.9% of the COX activity stimulated by Arachidonic acid [8]. Glabridin exhibits anti-inflammatory effect in in-vivo studies. On a study investigating on the inhibitory effects of glabridin on inflammation by Yokota et al using B16 murine melanoma cells and guinea pig skins, anti-inflammatory effects of glabridin were demonstrated by inhibition of superoxide anion production and cyclooxygenase activities. Herold et al in their study with standardised hydroalcoholic extract of Glycyrrhiza glabra has demonstrated for the first time that extract of G. glabra efficiently inhibits eicosanoids and leukotrienes formation in cell free systems meaning the extract acts as a dual inhibitor of 5LO and COX-2 activities[9] . It has been demonstrated by C.V. Chandrasekaran et al that of the biologically active components of licorice glabridin exhibits significant inhibitory activity against PGE2 (Prostaglandin E2), TXB2 (Thromboxane B2) and (Leukotriene B4) LTB4 production. [10] .Glabridin has been found to attenuate dextran-sulphate sodium induced colonic inflammation in mice through glabridin mediated anti-inflammatory action on colorectal sites, which could be a useful therapeutic approach in Inflammatory bowel disease [11]

As per literature, the anti-inflammatory activities of glabridin has been reported to be due to inhibition of Lipopolysaccharide induced PGE-2, IL-1, NO, TNF-α and a down regulation of transcription factor NF-κβ and AP-1[12]

Antioxidative activity:

Licorice constituents exhibited superoxide scavenging activity. Licochalcone A, B,C, D, Hispaglabridin A,B, glabridin, isoprenyl chalcone and isoliquiritigenin have been demonstrated to inhibit lipid peroxidation [13]

The hydroxyl groups on the B rings of glabridin were confirmed to be the most important for its antioxidative properties [14]. Glabridin, has been considered as a potent antioxidant towards LDL oxidation in both invitro and invivo studies. Two mechanisms are supposed to act: firstly, by binding to low density lipoprotein (LDL) and protecting its oxidation. Secondly, it accumulating in cells such

as macrophages, causing a decrease in cellular oxidative stress by reducing NADPH oxidase activation and increasing cellular glutathione.
Jong et al in 2005 have quoted that glabridin suppressed the generation of reactive oxygen species in murine macrophages, RAW 264.7 cells. Haraguchi et al in 2000 have found that glabridin inhibited lipid peroxidation in rat liver microsomes and also protected the mitochondria from oxidative stress [15].
In 2005, De Mambro and Fonseca have carried out a clinical study to assess antioxidant and free radical scavenging activities in topical formulations of G.glabra extracts and the results suggested high antioxidant activity[16]. Clinical trials making use of this property is lacking and can be tried in potentially malignant diseases and other conditions of the oral cavity where antioxidant effect can be the treatment.

Antimicrobial activity:
In recent years, due to wide spread and indiscriminate use of antimicrobial and antifungal drugs, many organisms have acquired resistance with apparent side effects which has resulted in a resurgence towards herbal remedies. Licorice extracts showed significant antibacterial activities against two grampositive (Bacillus subtili and Staphylococcus aureus) and two gram-negative (Escherichia coli and Pseudomonas aeruginosa) bacteria which are common in causing dental infections. Antibacterial activity of Glycyrrhiza glabra against oral pathogens has been evaluated and it has been found that it is effective against the following six strains: Streptococcus mutans, Streptococcus sanguis, Actinomyces viscosus, Enterococcus fecalis, Staphylococcus aureus, Escherichia coli [17]. Based on the above inhibitory activities against bacteria, licorice may serve as an alternative therapy for treating dental caries, periodontal disease, digestive anabrosis and tuberculosis.
Glycyrrhizol A exhibits potent antibacterial effect against Streptococcus mutans [18] **.** Antiviral activity has been found be present in Glycyrrhizhic acid, glycocoumarin, licopyranocoumarin. Licochalcone A possess antiplasmodial activity along with antileshmanial activity [19]
Glabridin has an inhibitory effect on biofilm formation and it has shown to prevent yeasthyphael transition in Candida albicans. Licochalcone and glabridin have exhibited synergestic action with nystatin in inhibiting the growth of C.albicans [20] Antihelicobacter pylori properties have been displayed by licorice derived glabridin along with potent activity against amphotericin-B resistant strains of C.albicans [21] **.** All these suggest that glabridin can be developed as an effective antifungal agent in treating oral C.albicans infections. As per Vivek et al in 2008, glabridin had exhibited anti-bacterial properties against some strains among which it was more active against gram positive strains than negative [22].

Anti-atherogenic activity:
Atherosclerosis is the condition in which there will be accumulation of cholesterol and oxidised lipid in the walls of the artery. Oxidised LDL is considered to be cytotoxic and atherogenic. Considered cellular sources of oxidants include mainly NADPH oxidase and P450 enzymes**.** Falk et al in his article on pathogenesis of atherosclerosis has stated that accumulation of oxidised LDL in macrophages and other phagocytes comprise the early atherogenesis stage [23]. Furhman et al has studied the effect of glabridin in atherosclerotic apolipoprotein E deficient mice and has demonstrated that the compound decreased the formation of macrophage foam cells and inhibited the development of atherosclerotic lesions[24].
Belinky et al and Vaya et al through their studies have also supported the above findings. The mechanism of this activity was studied in detail and it has been found that the intracellular accumulation of glabridin in macrophages caused inhibition of protein kinase C (PKC) activity which subsequently inhibited NADPH oxidase translocation to the plasma membrane and thereby affect macrophage superoxide production. As per Yehuda et al, glabridin has the potential to upregulate the antioxidant enzymes including superoxide dismutase, catalase and Paroxanase 2 under stress in human monocytes[25].
Hatrahimovich et al. through their study demonstrated that glab specifically interacted with paroxanase enzyme and subsequently prevented its inhibition by linoleic acid hydroperoxide[26]. To summarise, the anti-atherogenic effect of glabridin results from the capability of the compound in down regulating PKC, NADPH oxidase and up-regulating SOD, CAT, PON along with its ability to inhibit protein markers ICAM-1 and VCAM-1, thereby reducing vascular inflammation and favouring healing of atherosclerotic lesions.

Neuroprotective activity:
Neuroprotective effects of glabridin have been associated with its anti-inflammatory properties and its anti-oxidant effect. Aaron roth et al in their article on apoptosis in neurodegenerative diseases has mentioned that glabridin has a protective effect against neuronal damage that leads to apoptosis

[27]. Cui et al in their study has demonstrated that glabrin anticholinesterase activity along with it causing an increase in acetyl choline levels[28]. Ofir et al in their study to test the effect of isoflavans in serotonin reuptake , has concluded that glabridin inhibits serotonin re-uptake and so can be potentially beneficial in treating mild to moderate depression [29].

Anti-osteoporotic activity:

Osteoporosis has been linked with estrogen deficiency and Somjen et al in his comparative study of glab and genistein (an isoflavan which is a phytoestrogen) has observed that glabridin can act as a phytoestrogen at lower concentrations and also emphasizes the role of isoflavans in modulating bone-disorders in post menopausal women[30]. Glabridin was demonstrated to increase the function of osteoblasts which are the pivotal cells in bone matrix formation and calcification through a estrogen mediated action. Somjen et al have demonstrated in their study that glabridin and some other isoflavans induce the expression and increases the activity of 25 hydroxy-vitamin D(3)-1α hydroxylase [33]. Not only estrogen, but also Vit D3 is required in adequate concentrations for preventing osteo-porosis. Kim et al in their study has evaluated the effect of glabrdin on RANKL induced osteoclast differentiation in murine osteoclast progenitor RAW264.7 cells. They have observed that glabridin holds great promise in inhibiting osteoclastogenesis by inhibiting RANKL induced activation of signalling molecules. These findings have been suggested by authors to be useful in treatment options in bone destructive diseases.

Estrogenic activity:

Ability of glabridin to bind to estrogen receptors have been noted by several authors in literature. In a study by Tamir et al**,** the observations point that Glabridin induces Creatinine kinase in rat skeletal and vascular tissues and promotes weight gain in uterus [32]. Enough evidence present in literature to establish it as a phytoestrogen as it can act as an estrogen agonist in skeletal and vascular tissues. Somjen et al and Simons et al have concluded from their studies that glabridin exhibits both estrogen agonist and antagonistic activity to consider it as a Selective Estrogen Receptor Modulator (SERM) regarding its dual mode of action [33,34].

The compounds from licorice also exhibit hepatoprotective effect, cardiovascular, immune-modulatory activites along with its action on kidneys. Nakamura et al in an in-vitro model has shown the hepato-protective effect of glycyrrhizin [35]. Gumpricht et al in 2009 has reported that glycyrrhetinic acid inhibits bile acid induced apoptosis and necrosis[36]. Some studies have suggested that glycyrrhetinic acid has a better hepato-protective effect when compared to glycyrrhizin. Antiplatelet aggregation effect of licorice compounds have been reported by Yu et al in 2005[37]. Thrombin inhibitor effect of glycyrrhizin has been demonstrated by Franceschetti et al and isoliquiritigenin has been found to have a vasorelaxant effect[38] . As from literature, glycyrrhizin, glycyrrhetinic acid, Licochalcone A and some analogues exhibited immunomodulatory effects. Utsunomiya et al in their research work has found out that glycyrrhizin improved the resistance of mice against herpes virus infection in a condition in which they were thermally injured. Moreover glycyrrhetinic acid improved the resistance of mice infected with LP-BM5 murine leukemia virus to Candida albicans infection. In the study by Abe et al, glycyrrhizin exhibited superior activity when compared to glycyrrhetinic acid in inducing interferon activity and augmenting natural killer cell activity[39]. Glabridin and glycyrrhizin have shown anti-nephritis effect in rat glomerular disease models.

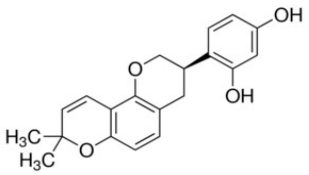
In addition to these major properties of glabridin, the isoflavan has few less reported bioactivities which includes antimelanogenic activity, anti-cancer activity, anti-tyrosinase and chemo-preventive effects. Chemopreventive effects of glabridin are mainly through its antiinflammatory properties and its ability to inhibit CoX-2 enxymes [40]. The ability to reduce cellular oxidative burst has also been reported to be of benefit in this bioactivity. Anticancer activities of glabridin can be explained by two different mechanisms: one is by inhibition of P-glycoprotein which acts as an anti-cancer drug efflux transporter in tumour cells. Secondly, glabridin inhibits integrin pathway, which plays a major role in tumour metastasis[12].

Conclusion:

Since historic times, ancient traditional medicines have been seen with an eye of speculation for their therapeutic properties. More clinical trials need to be conceded for standardization of these natural merchandises to identify their efficiencies. Further studies are definitely required to better evaluate the effect of these extracts. The development of effective and affordable licorice- related medicines could introduce dramatic improvements in treating the many prevalent diseases.

Among the many components of licorice, only glycyrrhizin has been clinically developed as a drug. Among the other components, glabridin has been found to have the required properties to be considered in treatment of potentially malignant

disorders of the oral mucosa. In-vitro and in-vivo trials are scanty in this field. Researchers need to identify the potential of this compound so that it can be benefitted in therapeutics.



Chemical structure of Glabridin

References:

1. Nor Amiyah binti Bismelah, Zethy Hanum Mohamed Kassim, Rohana Ahmad, Nor Hadiani Ismail (2016) Herbs in dentistry, Journal of Medicinal Plants Studies, 4(2), pp.18-23
2. Kenji Kondo, Mao Shiba , Rie Nakamura, Takashi Moroto, and Yukihiro Shoyama (2007) Constituent Properties of Licorices Derived from Glycyrrhiza uralensis, G. glabra, or G. inflata Identified by Genetic Information, Biol. Pharm. Bull, 30(7), pp.1271-1277.
3. Bahmani, M. et al. (2014) 'A review of the health effects and uses of drugs of plant licorice (Glycyrrhiza glabra L.) in Iran', Asian Pacific Journal of Tropical Disease, 4(S2), pp. S847–S849. doi: 10.1016/S2222-1808(14)60742-8.
4. Ramilowski, J. A. et al. (2013) 'Glycyrrhiza uralensis transcriptome landscape and study of phytochemicals', Plant and Cell Physiology, 54(5), pp. 697–710. doi: 10.1093/pcp/pct057. [5] Zadeh, J. B., Kor, Z. M. and Goftar, M. K. (2013) 'Licorice (Glycyrrhiza glabra Linn) As a Valuable Medicinal Plant', International journal of Advanced Biological and Biomedical Research, 1(10), pp. 1281–1288. Available at: http://www.ijabbr.com.
5. Amagaya S, Sugishita E, Ogihara Y, Ogawa S, Okada K, Aizawa T. (1984) `Comparative studies of the stereoisomers of glycyrrhetinic acid on anti-inflammatory activities', J Pharmacobiodyn, 7(12), pp. 923-8.
6. Friis-M??ller, A. et al. (2002) 'In vitro antimycobacterial and antilegionella activity of licochalcone A from Chinese licorice roots', Planta Medica, 68(5), pp. 416–419. doi: 10.1055/s-2002-32087.
7. Yokota, Tomohiro & Nishio, Hiroyuki & Kubota, Yasuo & Mizoguchi, Masako. (1999)`The inhibitory effect of glabridin from Licorice extracts on melanogenesis and inflammation', Pigment Cell Res, 11, 355-361.
8. Herold A, Cremer L, Calugaru A, Tamas V, Ionescu F, Manea S, Szeqli G. (2003)` Hydroalcoholic plant extracts with anti-inflammatory activity', Roum Arch Microbiol Immunol, 62(1-2), 117-129.
9. Chandrasekaran, C. V. et al. (2011) 'Dual inhibitory effect of Glycyrrhiza glabra (GutGard^{TM}) on COX and LOX products', Phytomedicine, 18(4), pp. 278–284. doi: 10.1016/j.phymed.2010.08.001.
10. Kwon, H. S., Oh, S. M. and Kim, J. K. (2008) 'Glabridin, a functional compound of liquorice, attenuates colonic inflammation in mice with dextran sulphate sodium-induced colitis', Clinical and Experimental Immunology, 151 (1), pp. 165–173. doi: 10.1111/j. 13652249. 2007.03539.x.
11. Simmler, C., Pauli, G. F. and Chen, S. N. (2013) 'Phytochemistry and biological properties of glabridin', Fitoterapia. Elsevier B.V., 90(July), pp. 160–184. doi: 10.1016/j.fitote.2013.07.003.
12. Vaya J, Belinky PA, Aviram M. (1997)` Antioxidant constituents from Licorice roots: isolation, structure elucidation, and antioxidative capacity towards LDL oxidation', Free Radic Biol Med, 23, pp. 302-313.
13. Belinky PA, Aviram M, Fuhrman B, Rosenblat M, Vaya J.(1998) `The antioxidative effects of the isoflavan glabridin on endogenous constituents of LDL during its oxidation', Atherosclerosis, 137, pp. 49-61.
14. Haraguchi H, Yoshida N, Ishikawa H, Tamura Y, Mizutani K, Kinoshita T. (2000)`
15. Protection of mitochondrial functions against oxidative stresses by isoflavans from Glycyrrhiza glabra', J Pharm Pharmacol, 52(2), pp. 219-223.
16. Di Mambro VM, Fonseca MJ. (2005)` Assays of physical stability and antioxidant activity of a topical formulation added with different plant extracts**',** J Pharm Biomed Anal, 37(2), pp.287-295.
17. Sedighinia, F. et al. (2012) 'Antibacterial activity of Glycyrrhiza glabra against oral pathogens: an in vitro study.', Avicenna journal of phytomedicine, 2(3), pp. 118–24. Available at:
18. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4075669&tool=pmcentrez&rendertype=abstract.
19. He, F. J., Nowson, C. A. and MacGregor, G. A. (2006) 'Fruit and vegetable consumption and stroke: meta-analysis of cohort studies.', Lancet (London, England), 367(9507), pp. 320–6. doi: 10.1016/S0140-6736 (06) 68069-0.
20. Cruz-Vega, D. et al. (2009) 'Review of pharmacological effects of Glycyrrhiza radix and its bioactive compounds', Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi

= China journal of Chinese materia medica, 22(April 2008), pp. 557–559. doi: 10.1002/ptr.
21. Wang, L. et al. (2015) 'The antiviral and antimicrobial activities of licorice, a widelyused Chinese herb', Acta Pharmaceutica Sinica B. Elsevier, 5(4), pp. 310–315. doi:
22. 10.1016/j.apsb.2015.05.005.
23. Fatima and Gupta, Luqman S, Negi AS, Kumar JK, Shanker K, Saikia D, Srivastava S. (2009), ` Antifungal activity of Glycyrrhiza glabra Linn extracts and its active constituent glabridin', Phytother Res., 23(8), pp.1190-1203.
24. Gupta, V. K. et al. (2008) 'Antimicrobial potential of Glycyrrhiza glabra roots', Journal of Ethnopharmacology, 116(2), pp. 377–380. doi: 10.1016/j.jep.2007.11.037.
25. Falk E. (1995)`Pathogenesis of Atherosc-lerosis', J Am Coll Cardiol, 76, pp.18-23.
26. Fuhrman B, Butch S, Vaya J, Belinky P, Coleman R, Havek T et al. (1997)`Licorice extract and its major polyphenol glabridin protect low density lipoprotein against lipid peroxidation: in vitro and in vivo studies in human and in atherosclerotic lipoprotein E deficient mice', Am J Clin Nutr ,66, pp.267-275.
27. Yehuda I, Madar Z, Szuchman-Sapir A, Tamir S. (2011)`Glabridin: A phytoestrogen from licorice roots upregulates manganese superoxide dismutase, catalase and parao-xonase 2 under glucose stress', Phytother Res, 25, pp.659-67.
28. Atrahimovich D, Vaya J, Tavori H, Khatib S. (2012)`Glabridin protects paraoxonase1 from linoleic acid hydroperoxide inhibition via specific interaction: a fluorescence quenching study', J Agric Food Chem, 60, 3679-85.
29. Roth KA, Shacka JJ. (2009)`Apoptosis in neurodegenerative disease', Encycl Neurosci, pp.531-7.
30. Cui YM, Ao MZ, Li W, Yu LJ. (2008)`Effect of Glabridin from Glycyrrhiza glabra on learning and memory in mice', Planta med, 74, pp. 377-80.
31. Ofir R, Tamir S, Khatib S, Vaya J. (2003)`Inhibition of serotonin re-uptake by licorice constituents', J Mol Neurosci, 20, pp.135-40.
32. Somjen D, Katzburg S, Vaya J, Kaye AM, Hendel D, Posner GH, et al.(2004)` Estrogenic activity of glabridin and glabrene from licorice roots on human osteoblasts and prepubertal rat skeletal tissues', J Steroid Biochem Mol Biol; 91, pp.241–6.
33. Kim H-S, Suh KS, Ko A, Sul D, Choi D, Lee SK, et al. The flavonoid glabridin attenuates 2-deoxy-D-ribose-induced oxidative damage and cellular dysfunction in MC3T3 E1 osteoblastic cells', Int J Mol Med 2013;31:243–51.
34. Tamir S, Eizenberg M, Somjen D, Stern N, Shelach R, Kaye A, et al. (2000)`Estrogenic and antiproliferative properties of glabridin from licorice in human breast cancer cells. Cancer Res ,60, pp.5704–9.
35. Somjen D, Katzburg S, Vaya J, Kaye AM, Hendel D, Posner GH, et al.(2004)` Estrogenic activity of glabridin and glabrene from licorice roots on human osteoblasts and prepubertal rat skeletal tissues', J Steroid Biochem Mol Biol, 91, pp.241–6.
36. Simons R, Vincken J-P, Mol LAM, The SAM, Bovee TFH, Luijendijk TJC et al. (2011)`Agonistic and antagonistic estrogens in licorice root (Glycyrrhiza glabra). Anal Bioanal Chem , 401, pp.305–13.
37. Nakamura T, Fujii T, Ichihara A. (1985) `Enzyme leakage due to change of membrane permeability of primary cultured rat hepatocytes treated with various hepatotoxins and its prevention by glycyrrhizin', Cell Biol Toxicol 1, pp.285–295.
38. Gumpricht E, Dahl R, Devereaux MW, Sokol RJ. (2005)` Licorice compounds glycyrrhizin and 18β-glycyrrhetinic acid are potent modulators of bile acid-induced cytotoxicity in rat hepatocytes', J Biol Chem 280, pp.10556–10563.
39. Yu SM, Kuo SC. (1995) `Vasorelaxant effect of isoliquiritigenin, a novel soluble guanylate cyclase activator, in rat aorta', Br J Pharmacol, 114, pp.1587–1594.
40. Francischetti IM, Monteiro RQ, Guimaraes JA. (1997)` Identification of glycyrrhizin as a thrombin inhibitor', Biochem Biophys Res Commun , 235, pp.259–263.
41. Abe N, Ebina T, Ishida N. (1982)` Interferon induction by glycyrrhizin and glycyrrhetinic acid in mice', Microbiol Immunol, 26, pp.535–559.
42. Choi E-M.(2005)`The licorice root derived isoflavan glabridin increases the function of osteoblastic MC3T3-E1 cells', Biochem Pharmacol , 70, pp.363–8.
43. Simmler C, Pauli G F, Chen S N (2013)` Phytochemistry and biological properties of glabridin', Fitoterapia, 90, pp.160-184