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Licorice in the Treatment of Acne Vulgaris and Postinflammatory Hyperpigmentation: A Review

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ABSTRACT

Clinical advantages of licorice (Glycyrrhiza spp.) have been investigated for several years. It has been traditionally used for a variety of disorders. Different constituents with various characteristics have been isolated from Glycyrrhiza spp. extracts. This review aimed to summarize the current knowledge on the pharmacological efficacy and safety of licorice extract constituents to treat the pathophysiology of acne vulgaris (AV) and the associated postinflammatory hyperpigmentation (PIH). Anti-androgenic, antimicrobial, anti-inflammatory, antioxidant, depigmenting, and skin-turnover-accelerating properties have been identified for licorice extract which could be effective against AV and PIH through multiple pharmacological mechanisms. The active compounds responsible for these pharmacological activities, molecular mechanisms, safety profile, as well as the *in vitro*, *in vivo*, animal, and clinical studies are discussed. Licorice extract possesses broad-spectrum activity and could be considered as an effective and safe option in the treatment of AV and its associated PIH. However, evidence-based clinical trials are required to prove its efficacy as well as safety. We hope this paper can provide new insights for further studies, particularly large controlled clinical trials.

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Introduction

Since ancient times, dried roots and rhizomes of licorice different species (Glycyrrhiza spp.) have been used as herbal remedies for local and systemic conditions. Licorice species are native to the Mediterranean and certain areas of Asia, now cultivated throughout the Europe. The genus Glycyrrhiza (family: Leguminosae) includes around 30 various species consisting G. glabra, G. uralensis, G. inflata, G. eurycarpa, G. aspera, and G. korshinskyi (1).

Based on the *in vitro*, *in vivo*, animal, and clinical studies, several useful pharmacological activities such as anticancer (2-8), antiviral (3, 9), immunomodulatory (6, 10), detoxifying (11), demulcent (12), gastroprotective (13-17), hepatoprotective (18, 19), cardioprotective (20, 21), anti-atherosclerotic (22-26), and several other effects have been reported for licorice.

Main factors in the pathogenesis of acne vulgaris (AV) are androgen-induced sebum rise, bacterial colonization, inflammatory responses of the immune system, and abnormal follicular keratinization. The management of AV does not only end to the point of lesions eradication but also consideration must be given to the treatment of postinflammatory hyperpigmentation (PIH). Herbal drugs and natural products might suggest added hopes in the development of novel medicines for the treatment of this condition.

Evident anti-inflammatory, antimicrobial, anti-androgenic, antioxidant, skin-lightening and -turnover-accelerating properties have been attributed to licorice in the literature. Therefore, the objective of this review

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is to explore the pharmacological efficacy and safety of licorice in the management of AV and PIH to provide data that may be useful for future anti-acne clinical researches on this herb and the development of complementary medicine.

Methods

The electronic databases Cochrane Library, MEDLINE/ PubMed, Web of Science, Scopus, and Google Scholar were searched to review all the relevant articles published in English up to March 2020. Single word or combinations of licorice, Glycyrrhiza, glycyrrhizin, glabridin, glabrene, isoliquiritigenin, licochalcone, anti-inflammatory, androgen, testosterone, antimicrobial, antibacterial, antioxidant, antioxidant, keratolytic, skin, tyrosinase, lightening, renewal, acne, postinflammatory, hyperpigmentatiom, hypopigmentation, and depigmentation were searched. The advanced search inputs were manipulated in order to obtain more pertinent results. Data of licorice extract constituents pharmacologically related to the pathophysiology of AV and PIH was obtained.

Results

Of 1189 search results, ultimately 43 full-texts of original papers and three English informative abstracts (non-English full-text) were included for this review. Figure 1 demonstrates the flow diagram of the search strategy.

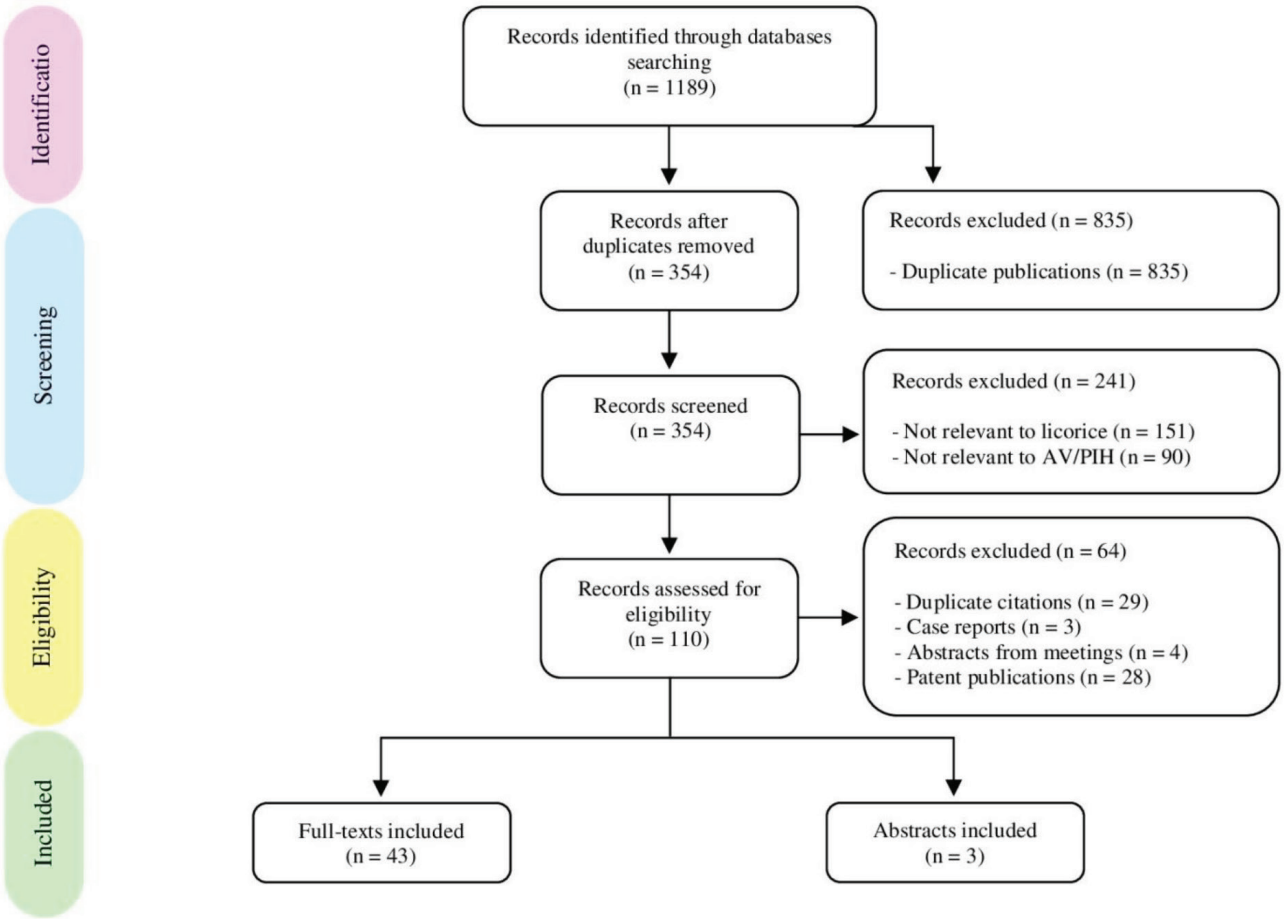

Figure 1. Flow diagram of the search strategy.

Licorice extract main constituents

Licorice potent effects are due to its various natural active compounds. To date, more than 20 triterpenoids and 300 flavonoids have been isolated from licorice (27). Some of the main constituents extracted from licorice are listed in Figure 2.

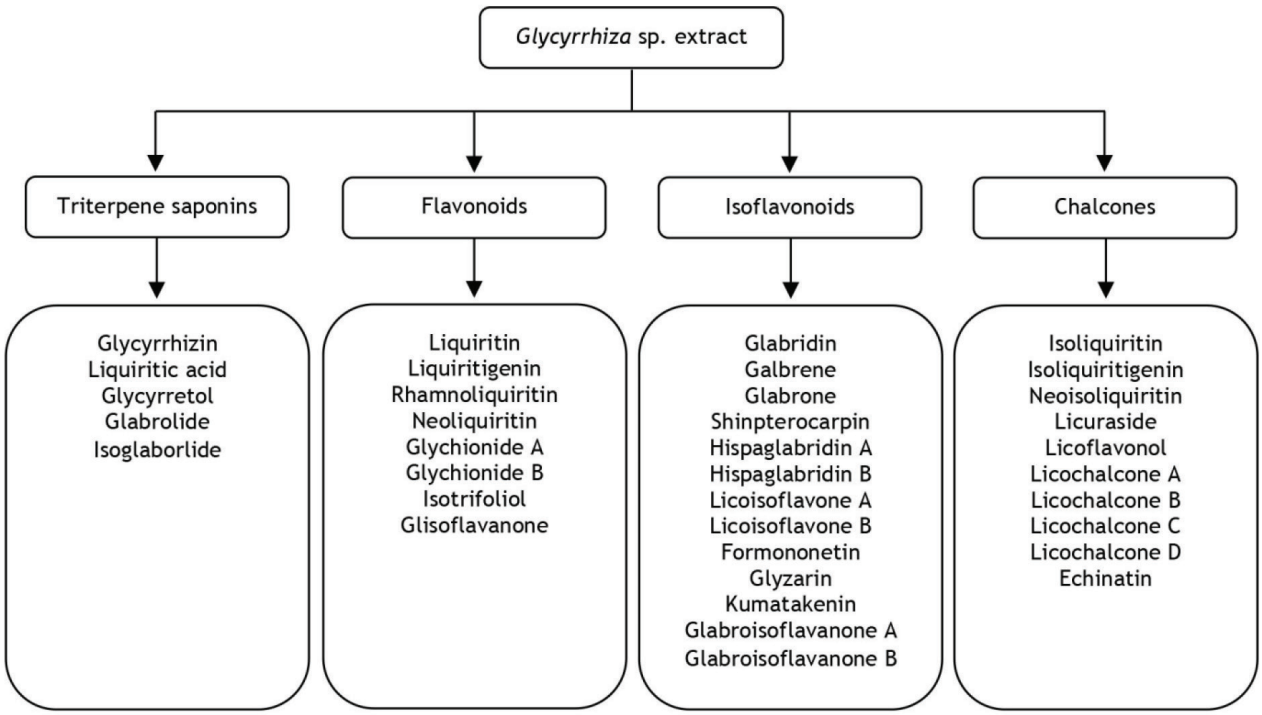

Figure 2. Main constituents of licorice extract.

Glycyrrhizin (or glycyrrhizic acid or glycyrrhizinic acid) is the chief pharmacologically active component of licorice extract, which is hydrolyzed to glycyrrhetinic acid *in vivo* (1). Related constituents of licorice extract to the pathophysiology of AV and PIH, based on their pharmacological activities are discussed in the following and summarized in Table 1. Types of studies of these constituents are listed in Table 2.

Table 1. Specific pharmacological activities of licorice extract constituents in relation to the pathophysiology of AV and PIH.

Pharmacological activity	Pathology	Identified constituents of licorice
Anti-androgenic	AV	Glycyrrhizin (28-30), licochalcone A (31), total extract (32-34)
Antimicrobial	AV	Licochalcone A (31), licochalcone E (35), total extract (36-42)
Anti-inflammatory	AV, PIH	Glycyrrhizin (43-50), licoflavanone (51), glabridin (52-55), isoliquiritigenin (53), licochalcone A (2,56,57), liquiritin (48), liquiritigenin (48), total extract (51)
Antioxidant	AV, PIH	Glycyrrhizin (43), glabridin (54,58-60), licochalcone A (4,31), licochalcones B and D (61), hispaglabridins A and B (58,60), total extract (51,62,63)
Skin lightening and turnover accelerating	PIH, AV	Glabridin (52,64,65), glabrene (66), isoliquiritigenin (66), licochalcone A (67), licuraside (67), isoliquiritin (67), liquiritin (68,69), glycyrrhisoflavone (70), glyasperin C (70), total extract (71)

Abbreviations: AV: acne vulgaris; PIH: postinflammatory hyperpigmentation.

Table 2. Studies of licorice extract constituents in relation to the pathophysiology of AV and PIH.

	Anti-androgenic	Antimicrobial	Anti-inflammatory	Antioxidant	Skin lightening and turnover accelerating
Glabrene					*In vitro* (66)
Glabridin			*In vitro* (52-55) *Ex vivo* (52) Animal (54)	*In vitro* (54,58,60) Animal (54,59)	*In vitro* (52,64) *Ex vivo* (52) Human (65)
Glyasperin C					*In vitro* (70)
Glycyrrhisoflavone					*In vitro* (70)
Glycyrrhizin	*In vitro* (30) *Ex vivo* (28) Human (29)		*In vitro* (43,45,47,48) *Ex vivo* (45,48) Animal (44,46,49,50) Human (45)	*In vitro* (43)	
Hispaglabridin A				*In vitro* (58,60)	
Hispaglabridin B				*In vitro* (58,60)	
Isoliquiritigenin			*In vitro* (53)		*In vitro* (66)
Isoliquiritin					*In vitro* (67)
Licochalcone A	*In vitro* (31)	*In vitro* (31)	*In vitro* (2,56,57) Human (57)	*In vitro* (4,31)	*In vitro* (67)
Licochalcone B				*In vitro* (61)	
Licochalcone D				*In vitro* (61)	
Licochalcone E		*In vitro* (35)			
Licoflavanone			*In vitro* (51)		
Licuraside					*In vitro* (67)
Liquiritigenin			*In vitro* (48) *Ex vivo* (48)		
Liquiritin			*In vitro* (48) *Ex vivo* (48)		Human (68,69)
Total extract	Animal (33) Human (32,34)	*In vitro* (36-42)	*In vitro* (51)	*In vitro* (51,62,63)	*In vitro* (71)

Anti-androgenic activities

Increased production of androgens in the cutaneous sebaceous glands (SGs) leads to augmented sebum secretion and development of AV. Six major enzyme systems are involved in cutaneous androgen metabolism, namely steroid sulfatase, 3β-hydroxysteroid dehydrogenase (HSD), 17β-HSD, steroid 5α-reductase, 3α-HSD, and aromatase (72, 73).

Licorice is known as an anti-androgenic herb through different pharmacological mechanisms. Glycyrrhizin (28-30), licochalcone A (31), and total extract of licorice (32-34) have been identified with anti-androgenic activities.

Licorice has reduced the production of testosterone by blocking 3β-HSD, 17β-HSD, and 17-20 lyase in humans (32, 34). Administration of high amounts of pure licorice extract to male volunteers could significantly reduce total serum testosterone, however, the values of testosterone never dropped below the normal range (34). Moreover, licorice showed anti-androgenic properties in male rats due to increasing testosterone metabolism, down-regulating androgen receptors, or activating estrogen receptors (33).

Licochalcone A inhibited 5α-reductase and antagonized androgen receptors *in vitro* (31). Glycyrrhizin and glycyrrhetinic acid significantly decreased the testosterone production by inhibiting 17β-HSD *in vitro* (30) and stimulating the aromatase activity *ex vivo* (28). Additionally,

in a Chinese clinical trial glycyrrhizin reduced the serum level of testosterone in women, and was safe and effective in the treatment of post-adolescent AV (29).

Antimicrobial activities

Certain bacteria such as Propionibacterium acnes, Staphylococcus aureus, Staphylococcus epidermidis, and Streptococcus pyogenes have important roles in the pathogenesis of AV by stimulating inflammatory processes (74, 75). Licochalcone A (31), licochalcone E (35), and the total extract of licorice (36-42) have been identified as bioactive compounds against acne-causing bacteria. *In vitro* studies have shown significant antimicrobial activities of licorice extract against P. acnes (41, 42), S. aureus (35, 36, 42), S. epidermidis (42), and S. pyogenes (37, 38).

In vitro screening clearly indicated that active methanolic extract of G. glabra had promising antimicrobial activity against P. acnes (MIC: 1.25 mg/ml), S. aureus (MIC: 2.5 mg/ml), and S. epidermidis (MIC: 2.5 mg/ml) (42). Another *in vitro* investigation, showed G. glabra antibacterial activities for two strains of P. acnes, with MICs of 200 µg/ml for ATCC 6919 and 100 µg/ml for ATCC 11827 (41). Moreover, the MIC of licorice extract has been found to be 0.25 and 2.5 mg/ml against methicillin susceptible S. aureus and methicillin resistant S. aureus, respectively (36).

Anti-inflammatory activities

P. acnes induce the pro-inflammatory mediators such as the tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, leukotriene (LT)-B4, prostaglandin (PG)-E2, and nuclear factor-κB (NF-κB) through Toll-like receptors. Reactive oxygen species (ROS) are also responsible for AV inflammatory processes (76). Mechanistically, P. acnes induce the inducible nitric oxide synthase/nitric oxide (iNOS/NO) and cyclooxygenase-2/PG-E2 (COX-2/PG-E2) expressions via a ROS-dependent NF-κB cascade (77).

Glycyrrhizin (43-50), licoflavanone (51), glabridin (52-55), isoliquiritigenin (53), licochalocone A (2, 56, 57), liquiritin (48), and liquiritigenin (48) have been identified as the main licorice constituents with anti-inflammatory properties.

Glycyrrhetinic acid dose-dependently inhibited the activation of classical complement pathway *in vitro* (47). Furthermore, Glycyrrhetinic acid inhibited glucocorticoids metabolism and intensified their effects by inhibiting 11β-HSD in mice and *in vitro* (44, 45).

Glycyrrhizic acid, liquiritin, and liquiritigenin have strongly inhibited the iNOS and COX-2 expressions without cellular toxicity (48, 49). Glabridin (100 nM) inhibited gene expression of the iNOS, production of NO, and formation of nitrotyrosine (marker of the potent oxidant ONOO−) *in vitro* and mice (55).

Isoliquiritigenin and glabridin were recognized as dual inhibitors of COX and lipooxygenase (LOX) by reducing the synthesis of PG-E2, TX-B2, and LT-B4 *in vitro* (52, 53). Licochalcone A effectively inhibited UV-induced COX-2 expression and P-E2 generation through the inhibition of activator protein 1 transcriptional activity (2, 56).

In a randomized vehicle-controlled clinical trial accompanied by *in vitro* experiments, topical licochalcone A significantly reduced the erythema in both the shave- and UV-induced irritation tests and potently inhibited the PG-E2, LT-B4, IL-6, and TNF-α formation (57).

Licoflavanone and glycyrrhizinic acid significantly decrease pro-inflammatory cytokines and COX-2/iNOS expression by inhibiting NF-κB pathway (51). Then, licorice root extract could be a good source to suppress inflammation through multiple pathways.

Antioxidant activities

Antioxidants scavenge the ROS and free radicals, so reduce the inflammation and peroxidation of the sebum. Naturally the production rate of ROS is slow and they are removed by endogenous antioxidants, principally superoxide dismutase (SOD), catalase, and glutathione. The blood levels of these antioxidants have been significantly low in AV patients compared to normal individuals (78). Consequently, high levels of ROS in epidermis damage the membranes of cells by lipid peroxidation and malondialdehyde production (79).

Licorice extract has demonstrated potent antioxidant and free-radical-scavenging effects in topical preparations (51, 62, 63). Glycyrrhizin (43), glabridin (54, 58-60), hispaglabridins A and B (58), licochalcone A (4, 31), and licochalcones B and D (61) have been reported with antioxidant activities.

Glabridin, hispaglabridin A and B, licochalcone A, B, C, D and echinatin have strongly inhibited mitochondrial and microsomal lipid peroxidation *in vitro* (58, 61). Glycyrrhizin and licochalcones B and D showed potent antioxidant and superoxide-scavenging activities by significantly inhibiting ROS generation (43, 61). Glabridin has been reported for increasing glutathione content (59), while licochalcone A exhibited SOD-like properties (31).

Skin-lightening and -turnover-accelerating activities

Immune changes and inflammatory responses precede hyperkeratinization and AV formation. PIH is the consequence of either overproduction or unbalanced distribution of melanin after cutaneous inflammations (80). Various investigations have established the melanocyte-stimulating effects of LT-C4, LT-D4, PG-E2, PG-D2, TX-2, IL-1, IL-6, TNF-α, and ROS. Dermic inflammation can damage the basal keratinocytes and release large amounts of melanin ending in PIH.

The other mechanism that increases the synthesis of melanin is depletion of the antioxidants, e.g. glutathione. Antimelanogenic effects of antioxidants could be explained by interfering with lipid peroxidation in melanocytes membranes, stimulating intracellular glutathione synthesis, and scavenging ROS and free radicals (81, 82). Therefore, the novel anti-acne products are strongly recommended to contain agents with antioxidant properties.

Tyrosinase is the rate-limiting enzyme involved in the melanogenesis pathway of PIH (Figure 3). A number of tyrosinase inhibitors from both natural and synthetic sources have been identified.

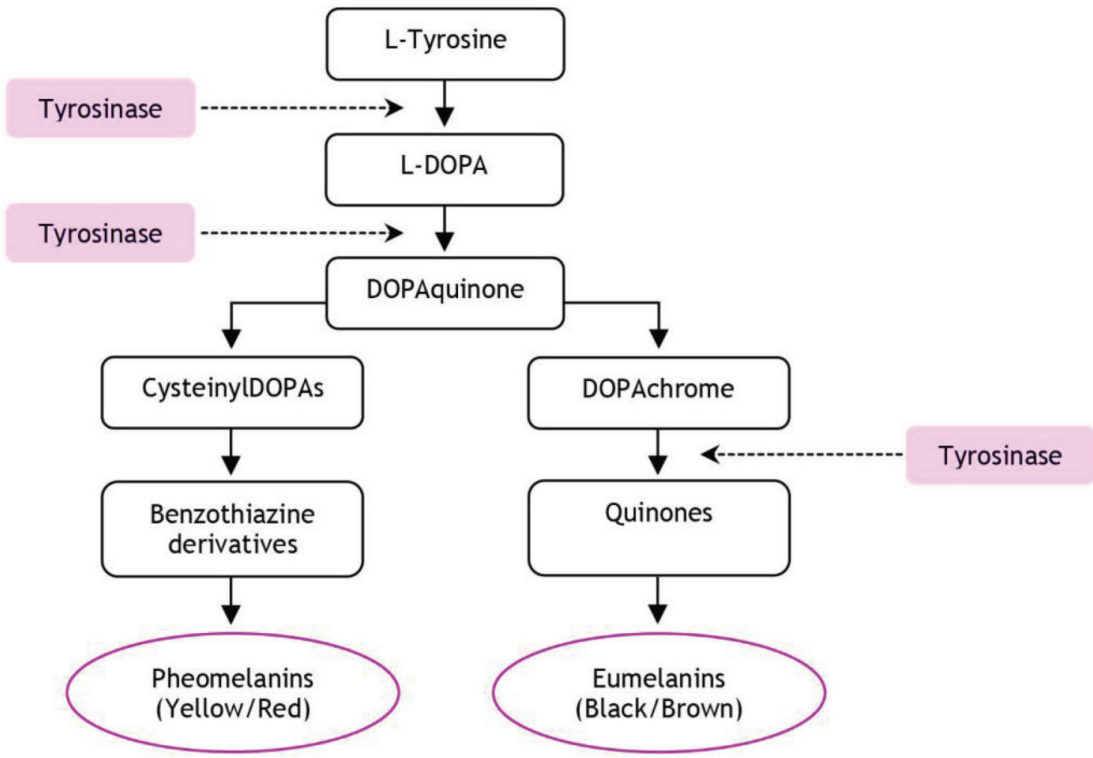

Figure 3. Pathway of melanin synthesis. The first two steps are catalyzed by tyrosinase, in which L-tyrosin converts to L-DOPA and then L-DOPA changes to a quinone which spontaneously polymerizes to form melanin pigments.

Licorice extract contains several active antimelanogenic components, providing a choice for skin-lightening products (71). Glabridin (52,64,65), glabrene (66), isoliquiritigenin (66), licochalcone A (67), licuraside (67), isoliquiritin (67), liquiritin (68,69), glycyrrhisoflavone (70), and glyasperin C (70) from licorice have exerted depigmenting properties.

Topical glabridin 0.5% prevented UVB-induced erythema and pigmentation in the skin of guinea pigs (52). Furthermore, glabridin 0.1% applied three times daily for four weeks was claimed to significantly lighten the skin (65).

Concentrations of 0.1% and 0.4% of licorice extract applied once daily have been satisfactorily resulted in skin lightening in about 14% and 20% of patients, respectively (65). Glabrene, isoliquiritigenin, licochalcone A, licuraside, isoliquiritin, glycyrrhisoflavone, glyasperin C, and extract of G. glabra have demonstrated strong inhibitory effects on diphenolase activities of tyrosinase *in vitro* (66, 67, 70, 71).

Topical liquiritin 1 g/day for 4 weeks was therapeutically effective in the treatment of melasma-associated hyperpigmentation (68). In another clinical trial, topical liquiritin 4% for 8 weeks was significantly more effective than 2%, and topical liquiritin 2% was significantly more effective than hydroquinone 4% (69).

Two mechanisms were suggested for liquiritin depigmenting properties: melanin dispersibility by pyran ring of its flavonoidal nucleus, and accelerating epidermal regeneration. In fact, liquiritin has no effects on tyrosinase and is classified as a skin turnover accelerator (68). Therefore, this property can be effective against both AV keratinization and PIH melanogenesis.

Safety profile

Licorice needs to be used with caution during pregnancy. It has selective cytotoxic effects on cancerous cells. Generally, neurologic, cardiovascular, endocrine, and hematologic adverse effects have been reported with systemic consumption of licorice.

In a 28-day course of treatment with up to 10 g/kg of an oral

anti-acne formula containing licorice, no toxic effect was detected in male and female rats (83). At a level of 800 mg/kg/day in female rats and 400 mg/kg/day in male rats, no adverse effect was observed with oral licorice flavonoid oil in a 90-day toxicity study (84).

The most important adverse effects of licorice are hypertension and hypokalemic-induced secondary disorders. The risk of adverse effects increases with hypokalemia, prolonged gastrointestinal transient time, 11β-HSD type 2 enzyme deficiency, hypertension, anorexia nervosa, old age, and female sex. Excessive daily licorice supplementation may cause hypokalemia due to licorice-induced hyperaldosteronism and may lead to hypertension, although reversible by discontinuation (85). Licorice flavonoid oil has been safe when orally administered once daily up to 1200 mg/day in humans (86).

Glabridin can inhibit at least three human cytochrome P (CYP450) isoenzymes (3A4, 2B6, 2C9) and interact with the medicines which are the substrates of these enzymes (87). CYP3A4 and CYP2D6 isoenzymes were weakly inhibited by glycyrrhizin, indicating mild herb-drug interactions (88). In addition, the inhibition of CYPs by herbal constituents may decrease the formation of toxic metabolites and thus inhibit carcinogenesis, as CYPs play important roles in the procarcinogens activation. Further research should be conducted to ensure the safety (89).

Conclusions

Glycyrrhiza spp. extracts possess broad-spectrum activities and could be considered as effective and safe options in the treatment of AV and its associated PIH. Four mechanisms of the AV pathogenesis can pharmacologically be inhibited by various active constituents of licorice extract. In addition, the pathway of melanogenesis can be suppressed at the same time to manage PIH. Hence, anti-androgenic, antimicrobial, anti-inflammatory, antioxidant, antimelanogenic, and exfoliative effects of licorice can antagonize the mechanisms involved in the pathogenesis of both AV and PIH simultaneously.

Total extracts of Glycyrrhiza spp. sound probably more effective than isolated constituents against AV and PIH, due to containing all the active elements with various pharmacological activities. In Chinese medicine, licorice is used for the treatment of acne and pimples; however, no clinical trials so far have evaluated the efficacy and safety of licorice on AV and its PIH alongside. Due to the huge demands for the treatment of these common dermatoses, it is fully justified to make practical recommendations for future investigations and clinical trials on mixtures and purified compounds from licorice

References

1. Nassiri Asl M, Hosseinzadeh H. Review of pharmacological effects of Glycyrrhiza sp. and its bioactive compounds. Phytother Res 2008;22(6):709-24.
2. Song NR, Kim JE, Park JS, et al. Licochalcone A, a polyphenol present in licorice, suppresses UV-induced COX-2 expression by targeting PI3K, MEK1, and B-Raf. Int J Mol Sci 2015;16(3):4453-70.
3. Fukuchi K, Okudaira N, Adachi K, et al. Antiviral and antitumor activity of licorice root extracts. *In Vivo* 2016;30(6):777-85.
4. Chen X, Liu Z, Meng R, Shi C, Guo N. Antioxidative and anticancer properties of licochalcone A from licorice. J Ethnopharmacol 2017;198:331-7.
5. Tang ZH, Li T, Tong YG, et al. A systematic review of the anticancer properties of compounds isolated from licorice (gancao). Planta Med 2015;81(18):1670-87.
6. Ayeka PA, Bian Y, Githaiga PM, Zhao Y. The immunomodulatory activities of licorice polysaccharides (Glycyrrhiza uralensis Fisch.) in CT 26 tumor-bearing mice. BMC Complement Altern Med 2017;17(1):536.
7. Wang ZF, Liu J, Yang YA, Zhu HL. A review: the anti-inflammatory, anticancer, antibacterial properties of four kinds of licorice flavonoids isolated from licorice. Curr Med Chem 2020;27(12):1997-2011.
8. Rossi T, Benassi L, Magnoni C, Ruberto AI, Coppi A, Baggio G. Effects of glycyrrhizin on UVB-irradiated melanoma cells. *In Vivo* 2005;19(1):319-22.
9. Wang L, Yang R, Yuan B, Liu Y, Liu C. The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. Acta Pharmaceutica Sinica B 2015;5(4):310-5.
10. Guo A, He D, Xu HB, Geng CA, Zhao J. Promotion of regulatory T cell induction by immunomodulatory herbal medicine licorice and its two constituents. Sci Rep 2015;5:14046.
11. Gong H, Zhang BK, Yan M, et al. A protective mechanism of licorice (Glycyrrhiza uralensis): isoliquiritigenin stimulates detoxification system via Nrf2 activation. J Ethnopharmacol 2015;162:134-9.
12. Ghalayani P, Emami H, Pakravan F, Nasr Isfahani M. Comparison of triamcinolone acetonide mucoadhesive film with licorice mucoadhesive film on radiotherapy-induced oral mucositis: A randomized double-blinded clinical trial. Asia Pac J Clin Oncol 2017;13(2):e48-e56.
13. Sadra A, Kweon HS, Huh SO, Cho J. Gastroprotective and gastric motility benefits of AD-lico/Healthy Gut Glycyrrhiza inflata extract. Anim Cells Syst (Seoul) 2017;21(4):255-62.
14. Hajiaghamohammadi AA, Zargar A, Oveisi S, Samimi R, Reisian S. To evaluate of the effect of adding licorice to the standard treatment regimen of Helicobacter pylori. Braz J Infect Dis 2016;20(6):534-8.
15. Fukai T, Marumo A, Kaitou K, Kanda T, Terada S, Nomura T. Anti-Helicobacter pylori flavonoids from licorice extract. Life Sci 2002;71(12):1449-63.
16. Krausse R, Bielenberg J, Blaschek W, Ullmann U. *In vitro* anti-Helicobacter pylori activity of Extractum liquiritiae, glycyrrhizin and its metabolites. J

Antimicrob Chemother 2004;54(1):243-6.

17. Momeni A, Rahimian G, Kiasi A, Amiri M, Kheiri S. Effect of licorice versus bismuth on eradication of Helicobacter pylori in patients with peptic ulcer disease. Pharmacognosy Res 2014;6(4):341-4.

18. Ji S, Li Z, Song W, et al. Bioactive constituents of Glycyrrhiza uralensis (licorice): discovery of the effective components of a traditional herbal medicine. J Nat Prod 2016;79(2):281-92.

19. Tanemoto R, Okuyama T, Matsuo H, Okumura T, Ikeya Y, Nishizawa M. The constituents of licorice (Glycyrrhiza uralensis) differentially suppress nitric oxide production in interleukin-1β-treated hepatocytes. Biochem Biophys Rep 2015;2:153-9.

20. Xu C, Liang C, Sun W, Chen J, Chen X. Glycyrrhizic acid ameliorates myocardial ischemic injury by the regulation of inflammation and oxidative state. Drug Des Devel Ther 2018;12:1311-9.

21. Zhang X, Zhu P, Zhang X, et al. Natural antioxidant-isoliquiritigenin ameliorates contractile dysfunction of hypoxic cardiomyocytes via AMPK signaling pathway. Mediators Inflamm 2013;2013:390890.

22. Somjen D, Knoll E, Vaya J, Stern N, Tamir S. Estrogen-like activity of licorice root constituents: glabridin and glabrene, in vascular tissues *in vitro* and *in vivo*. J Steroid Biochem Mol Biol 2004;91(3):147-55.

23. Fuhrman B, Buch S, Vaya J, et al. Licorice extract and its major polyphenol glabridin protect low-density lipoprotein against lipid peroxidation: *in vitro* and *ex vivo* studies in humans and in atherosclerotic apolipoprotein E-deficient mice. Am J Clin Nutr 1997;66(2):267-75.

24. Belinky PA, Aviram M, Fuhrman B, Rosenblat M, Vaya J. The antioxidative effects of the isoflavan glabridin on endogenous constituents of LDL during its oxidation. Atherosclerosis 1998;137(1):49-61.

25. Vaya J, Belinky PA, Aviram M. Antioxidant constituents from licorice roots: isolation, structure elucidation and antioxidative capacity toward LDL oxidation. Free Radic Biol Med 1997;23(2):302-13.

26. Rosenblat M, Belinky P, Vaya J, et al. Macrophage enrichment with the isoflavan glabridin inhibits NADPH oxidase-induced cell-mediated oxidation of low density lipoprotein a possible role for protein kinase C. J Biol Chem 1999;274(20):13790-9.

27. Yang R, Wang LQ, Yuan BC, Liu Y. The pharmacological activities of licorice. Planta Med 2015;81(18):1654-69.

28. Takeuchi T, Nishii O, Okamura T, Yaginuma T. Effect of paeoniflorin, glycyrrhizin and glycyrrhetic acid on ovarian androgen production. Am J Chin Med 1991;19(01):73-8.

29. Shi P, Mo R, Liu Q, et al. Clinical efficacy and safety of compound glycyrrhizin in the treatment of post-adolescent acne in women. Southern China Journal of Dermato-Venereology 2008;15(3):133-136.

30. Sakamoto K, Wakabayashi K. Inhibitory effect of glycyrrhetinic acid on testosterone production in rat gonads. Endocrinol Jpn 1988;35(2):333-42.

31. Kambara T, Zhou Y, Kawashima Y, et al. A new dermatological availability of the flavonoid fraction from licorice roots-effect on acne. Journal of Society of Cosmetic Chemists of Japan 2003;37(3):179-86.

32. Armanini D, Mattarello MJ, Fiore C, et al. Licorice reduces serum testosterone in healthy women. Steroids 2004;69(11-12):763-6.

33. Zamansoltani F, Nassiri-Asl M, Sarookhani M, Jahani-Hashemi H, Zangivand AA. Antiandrogenic activities of Glycyrrhiza glabra in male rats. Int J Androl 2009;32(4):417-22.

34. Armanini D, Bonanni G, Palermo M. Reduction of serum testosterone in men by licorice. N Engl J Med 1999;341(15):1158.

35. Zhou T, Deng X, Qiu J. Antimicrobial activity of licochalcone E against Staphylococcus aureus and its impact on the production of staphylococcal alpha-toxin. J Microbiol Biotechnol 2012;22(6):800-5.

36. Rohinishree YS, Negi PS. Effect of licorice extract on cell viability, biofilm formation and exotoxin production by Staphylococcus aureus. J Food Sci Technol 2016;53(2):1092-100.

37. Wijesundara NM, Rupasinghe HPV. Bactericidal and anti-biofilm activity of ethanol extracts derived from selected medicinal plants against Streptococcus pyogenes. Molecules 24;24(6):1165.

38. Siriwattanasatorn M, Panthong S, Itharat A. Antimicrobial activities of medicinal plants mostly used for acute pharyngitis treatment. J Med Assoc Thai 2016;99 Suppl 4:S144-52.

39. Irani M, Sarmadi M, Bernard F, Ebrahimi Pour GH, Shaker Bazarnov H. Leaves antimicrobial activity of Glycyrrhiza glabra L. Iran J Pharm Res 2010;9(4):425-8.

40. Astafeva OV, Sukhenko LT. Comparative analysis of antibacterial properties and chemical composition of Glycyrrhiza glabra L. from Astrakhan region (Russia) and Calabria region (Italy). Bull Exp Biol Med 2014;156(6):829-32.

41. Nam C, Kim S, Sim Y, Chang I. Anti-acne effects of Oriental herb extracts: a novel screening method to select anti-acne agents. Skin Pharmacol Appl Skin Physiol 2003;16(2):84-90.

42. Nand P, Drabu S, Gupta R. Phytochemical and antimicrobial screening of medicinal plants for the treatment of acne. Indian J Nat Prod Resour 2012;3(1):28-32.

43. Akamatsu H, Komura J, Asada Y, Niwa Y. Mechanism of anti-inflammatory action of glycyrrhizin: effect on neutrophil functions including reactive oxygen species generation. Planta Med 1991;57(2):119-21.

44. Amagaya S, Sugishita E, Ogihara Y, Ogawa S, Okada K, Aizawa T. Comparative studies of the stereoisomers of glycyrrhetinic acid on anti-inflammatory activities. J Pharmacobiodyn 1984;7(12):923-8.

45. Teelucksingh S, Mackie A, Burt D, Edwards C, Mclntyre M, Brett L.

Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid. Lancet 1990;335(8697):1060-3.

46. Inoue H, Mori T, Shibata S, Koshihara Y. Modulation by glycyrrhetinic acid derivatives of TPA□induced mouse ear oedema. Br J Pharmacol 1989;96(1):204-10.

47. Kroes B, Beukelman C, Van Den Berg A, Wolbink G, Van Dijk H, Labadie R. Inhibition of human complement by β□glycyrrhetinic acid. Immunology 1997;90(1):115-20.

48. Yu JY, Ha JY, Kim KM, Jung YS, Jung JC, Oh S. Anti-inflammatory activities of licorice extract and its active compounds, glycyrrhizic acid, liquiritin and liquiritigenin, in BV2 cells and mice liver. Molecules 2015;20(7):13041-54.

49. Kim GH, Paik S-S, Park YS, Kim HG, Kim I-B. Amelioration of mouse retinal degeneration after blue LED exposure by glycyrrhizic acid-mediated inhibition of inflammation. Front Cell Neurosci 2019;13:319.

50. Liu W, Huang S, Li Y, et al. Glycyrrhizic acid from licorice down-regulates inflammatory responses via blocking MAPK and PI3K/Akt-dependent NF-kappaB signalling pathways in TPA-induced skin inflammation. Medchemcomm 2018;9(9):1502-10.

51. Frattaruolo L, Carullo G, Brindisi M, et al. Antioxidant and anti-inflammatory activities of flavanones from Glycyrrhiza glabra L.(licorice) leaf phytocomplexes: identification of licoflavanone as a modulator of NF-kB/MAPK pathway. Antioxidants 2019;8(6):186.

52. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. Pigment Cell Res 1998;11(6):355-61.

53. Chandrasekaran CV, Deepak HB, Thiyagarajan P, et al. Dual inhibitory effect of Glycyrrhiza glabra (GutGard) on COX and LOX products. Phytomedicine 2011;18(4):278-84.

54. Kang JS, Yoon YD, Cho IJ, et al. Glabridin, an isoflavan from licorice root, inhibits inducible nitric-oxide synthase expression and improves survival of mice in experimental model of septic shock. J Pharmacol Exp Ther 2005;312(3):1187-94.

55. Yehuda I, Madar Z, Leikin-Frenkel A, Tamir S. Glabridin, an isoflavan from licorice root, downregulates iNOS expression and activity under high-glucose stress and inflammation. Mol Nutr Food Res 2015;59(6):1041-52.

56. Furuhashi I, Iwata S, Sato T, Inoue H, Shibata S. Inhibition by licochalcone A, a novel flavonoid isolated from liquorice root, of IL□1β□induced PGE2 production in human skin fibroblasts. J Pharm Pharmacol 2005;57(12):1661-6.

57. Kolbe L, Immeyer J, Batzer J, et al. Anti-inflammatory efficacy of licochalcone A: correlation of clinical potency and *in vitro* effects. Arch Dermatol Res 2006;298(1):23-30.

58. Haraguchi H, Yoshida N, Ishikawa H, Tamura Y, Mizutani K, Kinoshita T. Protection of mitochondrial functions against oxidative stresses by isoflavans from Glycyrrhiza glabra. J Pharm Pharmacol 2000;52(2):219-23.

59. Rosenblat M, Coleman R, Aviram M. Increased macrophage glutathione content reduces cell-mediated oxidation of LDL and atherosclerosis in apolipoprotein E-deficient mice. Atherosclerosis 2002;163(1):17-28.

60. Belinky PA, Aviram M, Mahmood S, Vaya J. Structural aspects of the inhibitory effect of glabridin on LDL oxidation. Free Radic Biol Med 1998;24(9):1419-29.

61. Haraguchia H, Ishikawaa H, Mizutanib K, Tamurab Y, Kinoshitac T. Antioxidative and superoxide scavenging activities of retrochalcones in Glycyrrhiza inflata. Bioorg Med Chem 1998;6(3):339-47.

62. Di Mambro VM, Fonseca MJ. Assays of physical stability and antioxidant activity of a topical formulation added with different plant extracts. J Pharm Biomed Anal 2005;37(2):287-95.

63. Pratibha N, Sushma D, Gupta Rajinder K. Screening for antioxidant and antibacterial potential of common medicinal plants in the treatment of acne. International Journal of Drug Development & Research 2012;4(1):65-71.

64. Ma J, Feng S, Li F, Huang L, Zheng Z. Effects of glabridin on B16 cell metabolism. Journal of Shanghai Medica (University) 2003;4:015.

65. Piamphongsant T. Treatment of melasma: a review with personal experience. Int J Dermatol 1998;37(12):897-903.

66. Nerya O, Vaya J, Musa R, Izrael S, Ben-Arie R, Tamir S. Glabrene and isoliquiritigenin as tyrosinase inhibitors from licorice roots. J Agric Food Chem 2003;51(5):1201-7.

67. Fu B, Li H, Wang X, Lee FS, Cui S. Isolation and identification of flavonoids in licorice and a study of their inhibitory effects on tyrosinase. J Agric Food Chem 2005;53(19):7408-14.

68. Amer M, Metwalli M. Topical liquiritin improves melasma. Int J Dermatol 2000;39(4):299-301.

69. Zubair S, Mujtaba G. Comparison of efficacy of topical 2% liquiritin, topical 4% liquiritin and topical 4% hydroquinone in the management of melasma. Journal of Pakistan Association of Dermatologists 2009;19:158-163.

70. Kim HJ, Seo SH, Lee B-g, Lee YS. Identification of tyrosinase inhibitors from Glycyrrhiza uralensis. Planta Med 2005;71(08):785-7.

71. Adhikari A, Devkota HP, Takano A, et al. Screening of Nepalese crude drugs traditionally used to treat hyperpigmentation: *in vitro* tyrosinase inhibition. Int J Cosmet Sci 2008;30(5):353-60.

72. Chen W, Thiboutot D, Zouboulis CC. Cutaneous androgen metabolism: basic research and clinical perspectives. J Invest Dermatol 2002;119(5):992-1007.

73. Zouboulis C, Schagen S, Alestas T. The sebocyte culture: a model to study the pathophysiology of the sebaceous gland in sebostasis, seborrhoea and acne. Arch Dermatol Res 2008;300(8):397-413.

74. Kumar B, Pathak R, Mary PB, Jha D, Sardana K, Gautam HK. New insights into acne pathogenesis: Exploring the role of acne-associated microbial populations. Dermatologica Sinica 2016;34(2):67-73.

75. Dhillon K, Varshney KR. Study of microbiological spectrum in acne vulgaris: an *in vitro* study. Scholars Journal of Applied Medical Sciences 2013;1(6):724-7.

76. Dréno B. What is new in the pathophysiology of acne, an overview. J Eur Acad Dermatol Venereol; 2017 Sep;31 Suppl 5:8-12.

77. Lin Y, Tang G, Jiao Y, et al. Propionibacterium acnes induces intervertebral disc degeneration by promoting iNOS/NO and COX-2/PGE2 activation via the ROS-dependent NF-kappaB pathway. Oxid Med Cell Longev 2018;2018:3692752.

78. Sarici G, Cinar S, Armutcu F, Altınyazar C, Koca R, Tekin N. Oxidative stress in acne vulgaris. J Eur Acad Dermatol Venereol 2010;24(7):763-7.

79. Ghosh VK, Nagore DH, Kadbhane KP, Patil MJ. Different approaches of alternative medicines in acne vulgaris treatment. Oriental Pharmacy and Experimental Medicine 2011;11(1):1-9.

80. Davis EC, Callender VD. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. J Clin Aesthet Dermatol 2010;3(7):20-31.

81. Yamamura T, Onishi J, Nishiyama T. Antimelanogenic activity of hydrocoumarins in cultured normal human melanocytes by stimulating intracellular glutathione synthesis. Arch Dermatol Res 2002;294(8):349-54.

82. Del Marmol V, Solano F, Sels A, et al. Glutathione depletion increases tyrosinase activity in human melanoma cells. J Invest Dermatol 1993;101(6):871-4.

83. Li S, Zou Y, Jiao K, Qiao X, Jiao R, Wang J. Repeated-dose (28 days) oral toxicity study in rats of an antiacne formula (BC-AF) derived from plants. Drug Chem Toxicol 2011;34(1):77-84.

84. Nakagawa K, Kitano M, Kishida H, et al. 90-Day repeated-dose toxicity study of licorice flavonoid oil (LFO) in rats. Food Chem Toxicol 2008;46(7):2349-57.

85. Kao TC, Wu CH, Yen GC. Bioactivity and potential health benefits of licorice. J Agric Food Chem 2014;62(3):542-53.

86. Aoki F, Nakagawa K, Kitano M, et al. Clinical safety of licorice flavonoid oil (LFO) and pharmacokinetics of glabridin in healthy humans. J Am Coll Nutr 2007;26(3):209-18.

87. Kent UM, Aviram M, Rosenblat M, Hollenberg PF. The licorice root derived isoflavan glabridin inhibits the activities of human cytochrome P450S 3A4, 2B6, and 2C9. Drug Metab Dispos 2002;30(6):709-15.

88. Pandit S, Ponnusankar S, Bandyopadhyay A, Ota S, Mukherjee PK. Exploring the possible metabolism mediated interaction of Glycyrrhiza glabra extract with CYP3A4 and CYP2D6. Phytother Res 2011;25(10):1429-34.

89. Zhou SF, Xue CC, Yu XQ, Wang G. Metabolic activation of herbal and dietary constituents and its clinical and toxicological implications: an update. Curr Drug Metab 2007;8(6):526-53.