Efficacy of licorice extract in Acne vulgaris and Rosacea treatment

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Abstract

Licorice root has been used as a medicinal plant in Europe since prehistoric times, and the therapeutic use of the dried roots of different licorice varieties dates back to ancient Greece. According to in vitro and in vivo and clinical researches, several valuable medicinal properties such as anticancer, antiviral, strengthening the body's immune system, detoxification, sedative, treatment of digestive diseases, liver diseases treatment, treatment of heart diseases, atherosclerosis problems, and several other curative results have been confirmed. The purpose of the literature review is to investigate the effectiveness and safety of licorice derivatives in acne and rosacea, which may be useful for clinical trials on the dermatological effects of licorice and the development of complementary medicine in the future.

Keywords: Licorice, Acne, Rosacea, Anti-androgenic activities

Introduction

Licorice is one of the oldest medicinal plants that both its name and the plant have ancient origins. The records of its cultivation go back to the third century, that is, during the time of the Greeks and Romans era. Although at that time it was possible to extract from the plant's roots, its medicinal and commercial importance was understood. Licorice species are native to the Mediterranean and certain regions of Asia and are nowadays cultivated all over Asia and Europe. Glycyrrhiza species belongs to the Leguminosae family, which includes about 30 different species, including G. glabra, G. uralensis, G. inflata, G. eurycarpa, G. aspera and G. korshinskyi. Today, the development of technology practically led to the chemical analysis of its compounds, including the successful identification of the active ingredients like glycyrrhizin, chalcone, and glabridin, which made its medicinal importance known in more detail. Licorice contains more than 20 triterpenoids and approximately 300 flavonoids and is commonly used to treat some diseases.

Among its important active ingredients, it is a medicinal substance that is often used in clinical diseases. Chalcones are one of the main classes of flavonoids, which have various biological effects and are widely present in nature. Today, 42 chalcones have been identified in licorice, and play a key role in the licorice pharmacological effects. These compounds have many biological activities, including anticancer, anti-inflammatory, antiallergic, antibacterial, antioxidant, antiviral, antidiabetic, anti-depressant, hepatoprotective, etc. In the present century,

licorice extract has found many uses, it is used as a flavoring, sweetener and as an effective medicinal ingredient. Glycyrrhizin is one of the sweetest compounds known, 60 times sweeter than sugarcane sugar. In addition, since ancient times, the dried roots and rhizomes of many licorice species have been used as medicinal plants. Some useful medicinal properties include anti-cancer, anti-viral, strengthening the immune system, detoxifying, sedating, treating digestive diseases, liver diseases, treating heart disease, atherosclerosis, and many other medicinal effects based on in vitro, in vivo, and animals and human studies have been confirmed.

The first licorice was mentioned in the “The Code of Humnubari” around 2000 BC and the Assyrians made herbal pills from it. Ancient Egyptians used licorice to make sweet drinks.To quench thirst, soldiers used licorice extract on the battlefield. Records of the development of licorice's medicinal use date back to 500 BC. At that time this plant was called the grandfather of herbs. Hippocrates (460-370 BC), the father of medicine, discovered that licorice was an effective treatment for controlling ulcers and quenching thirst. Theophrastus (372-287 BC), a Greek botanist, in his book Historia Plantarum, called licorice sweet root and described its uses for coughs, asthma, and respiratory diseases. Pedanius Dioscorides (40-90 AD), a Roman physician and author of the Medicinal herbs Pharmacopoeia de Materia Medica, classified plants based on their nutritional and medicinal purposes. Pliny the Great (23-79 AD), author of Naturalis Historia, described the medicinal uses of licorice for clearing the voice, suppressing coughs, alleviating asthma and digestive problems. Avicenna (c. 980-c. 1037), was a great polymath, who wrote very famous medical textbooks of his time, The Canon of Medicine and The Book of Healing. In the Canon of Medicine book, Ibn Sina considered licorice to be a medicine for wounds and ulcers.

Carl Linnaeus (c. 1707–c. 1778) first recognized three species of licorice, G. glabra, G. echinata, and G. hirsuta. Bolognese jurist Pietro de Crescenzi (c. 1230–c. 1320), an important historical figure and author of Ruralia commode or Liber ruralium commodorum, first documented the cultivation of licorice.

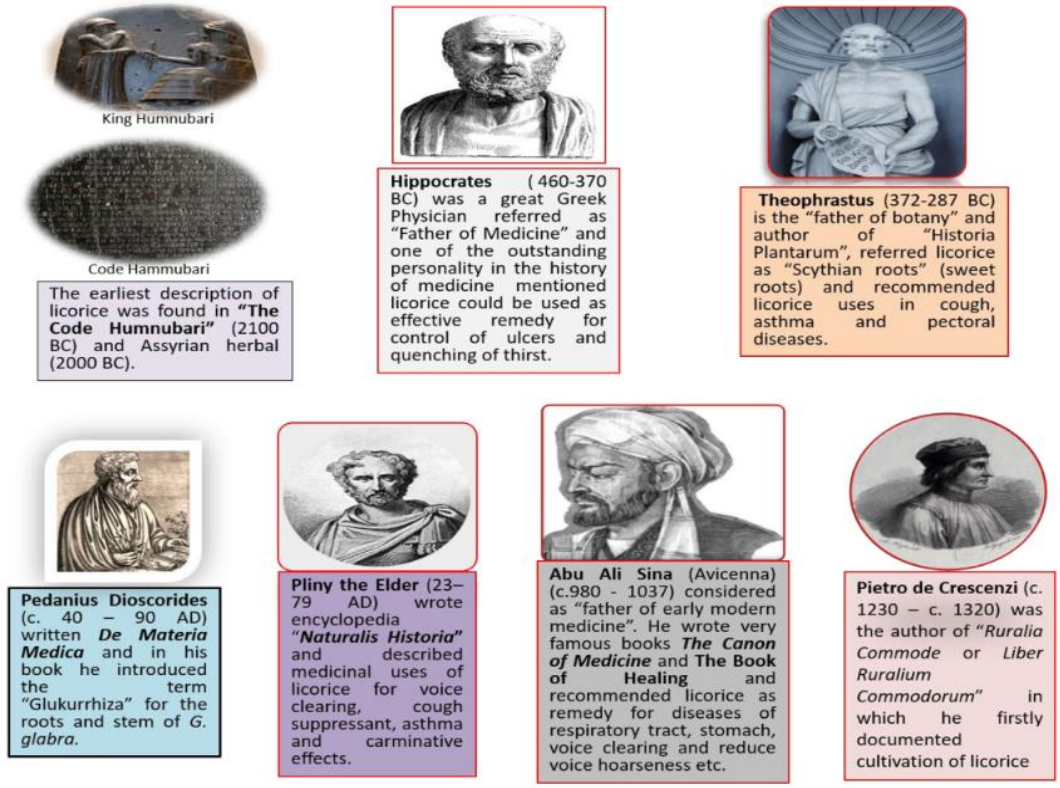

Figure 1. Historical Development of Licorice.

Theophrastus is the first source of information about the use of licorice for the treatment of skin lesions, This source states that the use of licorice can help with skin problems,and he also found the prescription of licorice in honey to be useful for treating wounds. In the current century, according to Ibn al-Bithaar, Dioscorides, its use is useful for the treatment of granulomas at the base of fingernails and toenails and foot ulcers. In his book of law, Ibn Sina considered licorice to be a medicine for wounds and ulcers.

The purpose of this review is to discuss the medical efficacy and safety of licorice in dermatology, which may help in the future clinical research and complementary medicine development of this plant in the field of dermatology. To date, 554 medicines containing licorice have been approved by the Chinese Food and Drug Administration.

Materials and methods

Data used in this study obtained from Springer, Hindawi, PubMed, ScienceDirect, Google Scholar, and other scientific sources. The data for this current study were collected, interpreted, and presented using keywords. This study paid more attention to the benefits of

licorice in dermatology and did not include irrelevant papers. This review article discusses the medical efficacy and safety of Glycyrrhiza species in dermatology, and also mentions related research papers and their results.

Pharmacognosy

Licorice is a widely distributed herbaceous perennial shrub that reaches up to 2.5 meters in height. The leaves are compound and have four to seven pairs of leaflets and one terminal leaflet. The flowers are irregular and in yellow, purple or purple colors and in a complex form at the end of the flowering stems that are placed in the hermaphrodite inflorescence.

The fruit is two to three centimeters long and date-colored. The sides of the fruit are narrow and more or less pointed. Inside the fruit there are three to five rectangular brown beans. The genus Glycyrrhiza are able to fix nitrogen through symbiosis with rhizobium on the root surface, and are suitable for sandy and clay soils, but prefer moist soils. The healing activity of G. glabra have been well documented since ancient Egypt. The most consumed part of licorice is the roots and its leaves are agricultural waste. However, in the recent years, the studies of phytochemical compounds of G. glabra leaves show that similar to the roots, although in lower amounts, certain compounds are present in the leaves.

Phytochemistry

To date, more than 400 phytochemicals have been identified in the Glycyrrhiza genus.These molecules can be classified as saponins, flavonoids, chromenes, coumarins, dihydroxyacetone, coumestans, benzofurans, and dihydrophenanthrene among these, flavonoids and triterpenoid saponins are abundant in licorice roots and rhizomes. Licorice root has 50% dry weight and 5% to 15% metabolites and water-soluble sugars (glucose, sucrose and mannitol), 25 to 30% starch, 10% to 16% glycyrrhizin, 1% to 2% amines. asparagine, betaine and choline) and sterols (stigmasterol and beta-sitosterol). Glycyrrhizin (glycyrrhizic acid, glycyrrhizic acid) licorice root extract accounts for 10-25% and is considered the main active ingredient. Glycyrrhizin is a saponin ingredient consisting of a triterpenoid aglycone, glycyrrhetic acid (glycyrrhetinic acid, Enoxolone) conjugated to the disaccharide glucuronic acid. Both glycyrrhizin and glycyrrhetic acid can exist in 18α and 18β stereoisomers.

Flavonoids, which are liquiritin, isoliquiritin, liquiritigenin, and rhamnoliquiritin, and five new flavonoids, including glucoliquiritin, Liquiritin apioside, prenyllicoflavone A, shinflavanone, shinpterocarpin, and 1-methoxyphaseolin isolated from the dried roots.

Although the roots are the most commonly used part, phytochemical studies have also been conducted on the leaves, which are considered agricultural chemical waste. The studies showed that certain compounds in the roots are also detected in the leaves of G. glabra to a lesser extent. In general, alkaloids and tannins were not detected. The flavonoid and saponin compounds of G. glabra, G. inflata and G. uralensis species have cosmetic effects that some studies focused on them and their biological activities (Figure 1).

Flavonoids

Around 300 flavonoid ingredients have been isolated from licorice species.Flavonoids,made up of two benzene rings (ring A and ring B) via a C ring creating a tricarbon chain, are divided into flavonols, flavones, flavanones, flavanols, dihydroflavones, chalcones, isoflavones, depending on the position of ring C, its degree of oxidation and the connection site of ring B. Different types of flavonoids are isolated from G. glabra, G. uralensis and G. inflata. Flavonoids have been studied as cosmetically active ingredients such as flavonone, flavonol, flavone, isoflavone, isoflavones, isoflavones and chalcones. The flavonoids that have been investigated are those that exhibit cosmetic activities such as flavonones, flavonols, flavones, isoflavones, isoflavones, Isoflavones, and chalcones.Liquiritin is one of the most important flavonoids that is a phytochemical indicator of medicinal licorice species. Liquiritigenin is another flavonoid extract from Glycyrrhiza uralensis that has various medicinal properties, including antioxidant, anti-inflammatory, antibacterial and anti-aging effects. Pinocembrin and liquiritin apioside also related to the class of flavanones. Other flavonols include kaempferol, protensein and the flavone chrysoriol.

phytochemicaly, glabrin is a common isoflavone compound in G. glabra and accounts for 11% of the total flavonoid content. With glabidine, hispaglabrin A, glyaspirin C, glyaspirin D and 3-hydroxy-40-O-methylglabrin. From a phytochemical perspective, glabrin is a common isoflavone compound G. Glabra and with glabidine, hispaglabrin A, glyaspirin C, glyaspirin D and 3-hydroxy-40-O-methylglabrin accounts for 11 of the total flavonoid content.

Licorice isoflavones such as glabrin, dehydroglyaspirin C, dehydroglyaspirin D, isoflavones such as glycyrrhizoflavone, hemiquaisoflavone B, alloliquiisoflavone B, isoangstone A, and formonontin, as well as isoflavanones such as dihydroidzein and glycyrrhizinone have been investigated for cosmetic properties (Figure 2).

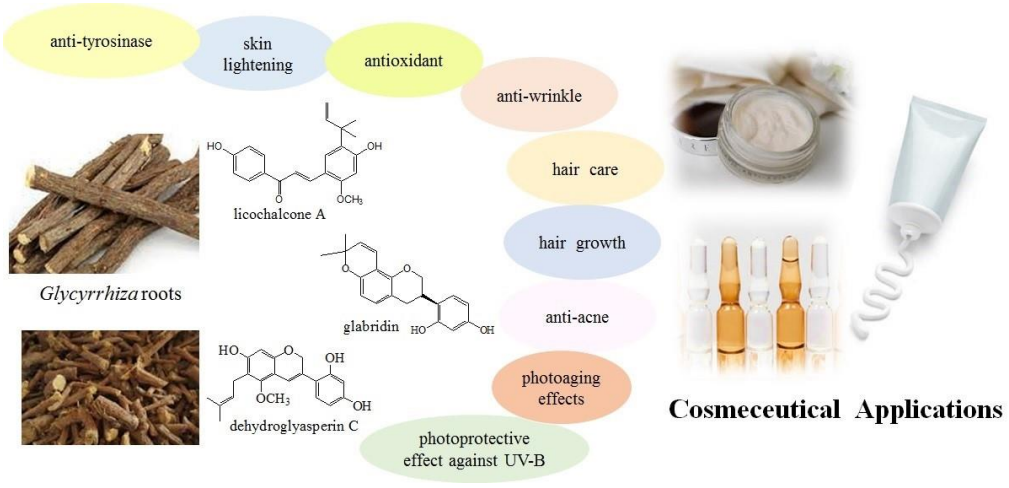

Figure2. Cosmetic applications of licorice isoflavones.

Chalcone has been reported frequently in licorice root. In this study the activities of isolico-ritigenin, isolicoritin, licochalcone A, licochalcone B, eicochalcone C, licochalcone D derivatives from Glycyrrhiza spp were discussed as effective ingredients for Cosmeceuticals formulation. Also, dibenzoylmethane, a structural analogue of curcumin (diferroylmethane), has been investigated for its cosmetic use. Among the flavonoids mentioned earlier, the main active ingredients of Glycyrrhiza licoricetin and isolicouritin are glycosides. Pharmacological properties of chalcones and their derivatives are mentioned in Figure 3.

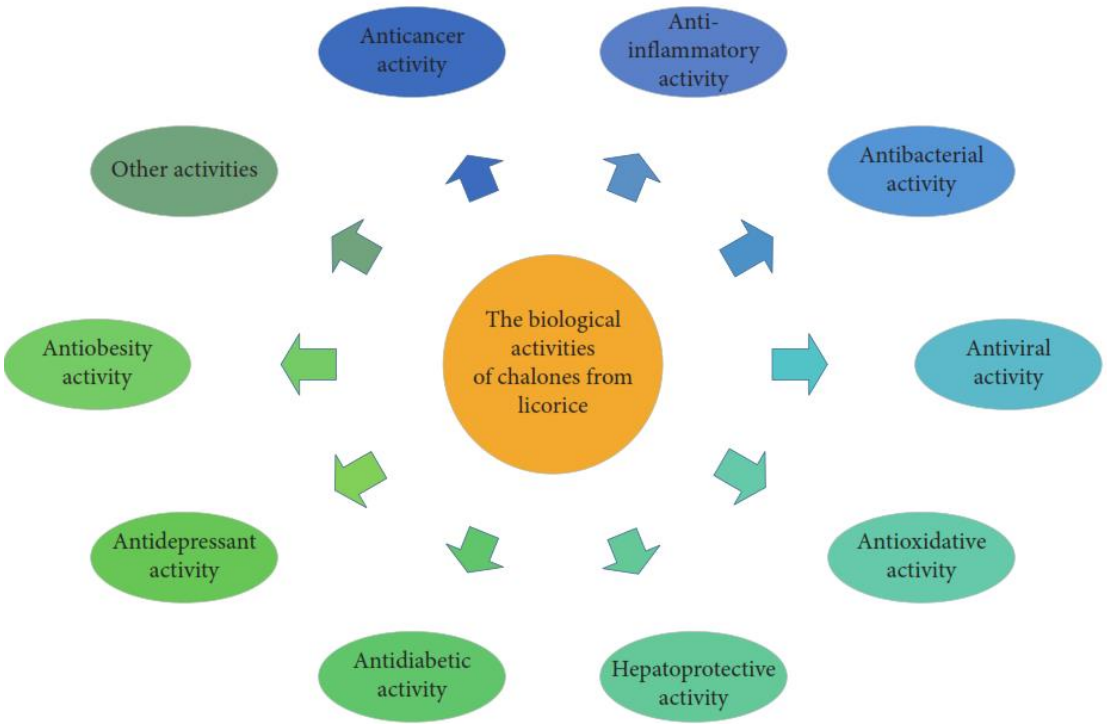

Figure 3.
Pharmacological properties of chalcones and their derivatives

Saponins

More than 70 saponins have been recognized in licorice roots and their structures have been demonstrated in a recent study. Glycyrrhizinic acid or its salt, glycyrrhizin, has been reported as the major secondary metabolite that exists in Glycyrrhiza species. The main and abundant active cosmeceutical ingredients in the root of the plant are glycyrrhizin and glycyrrhetic acid.Glycyrrhetic acid exists as two isomers: the 18α form and the 18β form. As a sweetener, glycyrrhizin has been reported to be 30 to 50 times sweeter than sucrose.Glycyrrhizal saponins, which are composed of aglycone and half sugar, can be classified into several categories, in which glucuronic acid, glucose, rhamnose are the main characteristic parts of the sugar part. Licorice saponin G2 (also known as 24-hydroxyglycyrrhizin) is shown below (Figure 4).

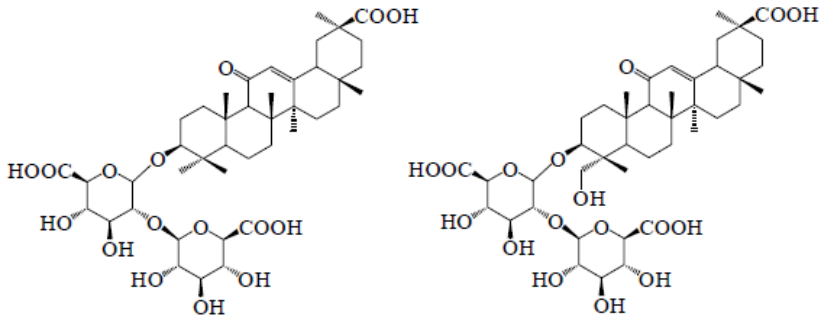

Figure 4. Licorice triterpenoids used in the cosmetic industry as active ingredients.

Polysaccharides

Among the biologically active components of glycyrrhiza plants, glycyrrhiza polysaccharides are more important.A recent report on their isolation, structural characterization, and biological activities. They are heteropolysaccharides mainly composed of arabinose, glucose, galactose, rhamnose, mannose, xylose, and galactronic acid in different ratios and types of glycosidic bonds. A preliminary research of the moisturizing capacity of polysaccharides showed that their water-holding capacity was greater than that of glycerol solutions, suggesting their potential for use as a moisturizing products in cosmetics.

Acne Vulgaris

Acne vulgaris, an acute multifactorial inflammatory disease, affects the pilosebaceous unit in the skin. This disease is usually seen in an area with high-density pilosebaceous units (face, neck, upper chest, shoulders, and back) and the presence of seborrhea, non-inflammatory lesions (open comedones or blackheads, and closed comedones or whiteheads), Inflammatory lesions (papules and pustules), and different degrees of scarring. The pathogenesis of acne includes the interaction between four main factors, including hypersborrhoea (excess production of sebum) by some androgens and changes in the fatty acid composition of sebum, hyperkeratinization in the follicle that leads to the formation of keratin plug (micro-comedone), colonization of the pilosebaceous unit. Acne is caused by Cutibacterium acnes (Propionibacterium acnes). Colony of Cutibacterium acnes (air-tolerant anaerobic bacteria) and the release of inflammatory mediators in response to the presence of Cutibacterium acnes, it was shown that Staphylococcus epidermidis (a facultative anaerobic bacterium) also plays a beneficial role by limiting the colonization of Cutibacterium acnes and inflammation. Licorice extract has anti-androgenic, anti-microbial, anti-inflammatory, antioxidant, brightening, and blood circulation-enhancing properties that

can be effective with multiple anti-acne and anti-inflammatory post-blemish medicinal mechanisms.The components of licorice extract responsible for these medicinal activities have been studied in various studies in terms of molecular mechanisms and safety profile, as well as in vitro, in vivo, animal, and clinical studies. Licorice extract has a wide range of activity and can be considered an effective and safe option in anti-acne and anti-blemish treatment after inflammation. Glycyrrhizic acid is the key active ingredient of licorice extract, which is hydrolyzed to glycyrrhetinic acid in vivo.

Today, bacterial resistance is increasing due to improper use of antibacterial drugs.Therefore, it is very important to find new, safe and effective antibacterial drugs. Some herbal extract in licorice have antibacterial activity. Certain bacteria such as Coutibacterium acnes, Staphylococcus aureus, Staphylococcus epidermidis, and Streptococcus pyogenes play an important role in the pathogenesis of acne vulgaris by stimulating inflammatory processes. Licochalcone A, Licochalcone E and licorice root extract have antimicrobial properties against bacterial strain for acne. In vitro tests have indicated remarkable antibaterial function of licorice extract against Cutibacterium acnes, Staphylococcus aureus, Staphylococcus epidermidis, and Streptococcus pyogenes. The active methanolic extract of G. glabra indicated promising antibacterial effects against Staphylococcus aureus, Staphylococcus epidermidis, and Cutibacterium acnes, as demonstrated by in vitro screening. Another laboratory study showed antibacterial activity of G. glabra for two strains of Cutibacterium acnes with a minimum inhibitory concentration of 200 µg/ml for strain ATCC 6919 and a minimum inhibitory concentration of 100 µg/ml for strain ATCC 11827S. In addition, the minimum bacterial inhibitory concentration of licorice extract is 0.25 and 2.5 mg/ml against methicillin-sensitive Staphylococcus aureus and methicillin-resistant Staphylococcus aureus, respectively.

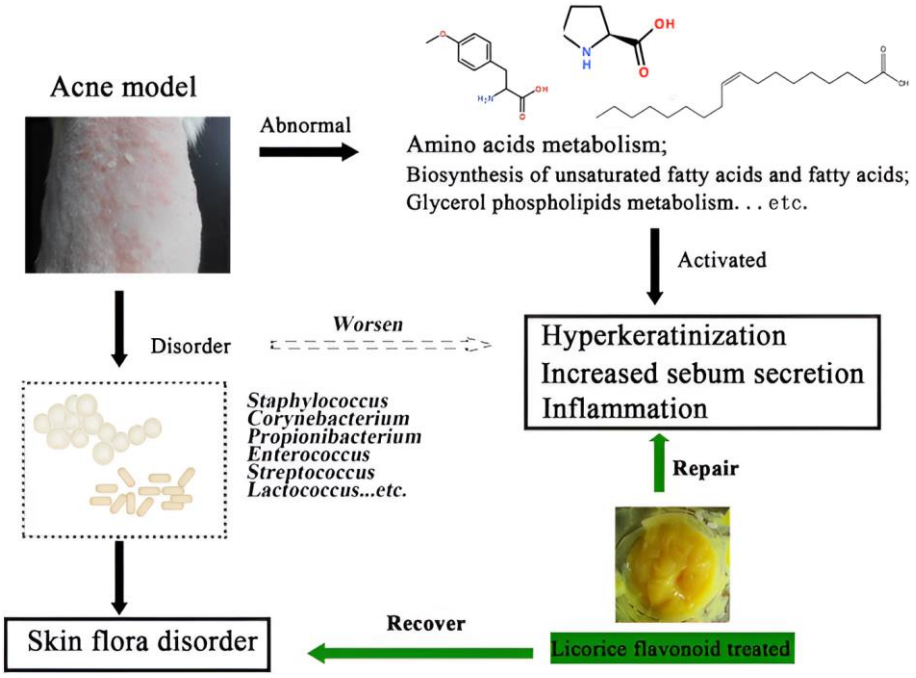

Figure 5- The mechanism of licorice flavonoids in healing acne vulgaris.

Regarding its antibacterial effect, laboratory studies have shown the inhibitory activity of aqueous and ethanol extracts of licorice on Staphylococcus aureus and Streptococcus pyogenes cultures, the first one indicated the strongest inhibition with a diameter of inhibition zone of 10-15 mm. Gupta et al. showed antibacterial activity against Gram-positive and Gram-negative bacteria. The results of the evaluation of the effectiveness of cosmetic products including glycolic acid, salicylic acid, gluconolactone and licochalcone A as an adjunctive treatment for adapalene in mild to moderate acne in a 28-day double-blind study on 25 people from each patient asked for two products including (1) a cosmetic product and health in combination with 0.1% adapalene and (2) 0.1% adapalene. The number of acne lesions, severity of acne, overall doctor and patient assessment of acne severity, visual analog brightness scale, skin biophysics, safety assessment and VISIA camera system were evaluated. The mean results did not show a difference in the reduction of inflammatory lesions on the seventh day, but there is no obstacle to using a cosmetic drug along with standard cure. However, this cosmetic product also reduces the complications of acne.

According to prior studies, isoliquiritigenin had a demonstrable inhibitory activity on methicillin-resistant Staphylococcus aureus. Licochalcone A, as one of the essential antibacterial ingedients which shows bactericidal activity against Staphylococcus aureus. Many studies show that G. glabra may be a potent remedy against acne. G. glabra indicated significant antibacterial activity against Cutibacterium acnes by inducing minimal resistance versus to the significant development of resistance in bacteria treated by erythromycin.

Multifactorial effects such as mechanisms are antimicrobial activity, moisturizing effect of licorice, anti-androgenic function, inhibiting PI3K-Akt signaling pathways, mitochondrial activity and regulating skin microbes has been suggested as a mechanisms related to the anti-acne effect.

In mice, Lakshmi et al., (2019) investigated the pharmacological effects of Licorice and concluded that in disease models, the volume and thickness of sebaceous glands were significantly increased compared to control animals and decreased when Licorice extract was used. Several articles report herbal formulations with anti-acne glycyrrhizin synergistic with anti-acne herbal formulations. The most recent of them was proposed by Keshri and Khare in 2020, although other synergistic formulas were proposed earlier. Activation of NLRP3 (nucleotide-binding domain, leucine-rich Containing family, inflammasome containing pyrin-3) inflammasome by Cutibacterium acnes is a critical for inducing inflammation and exacerbating of acne lesions. The anti-acne activity of licochalcone A resulted in effective suppression of the NLRP3.

Under in vitro conditions, Cutibacterium acne has no bacterial resistance to licorice extract. It appears that Glycyrrhiza, in the treatment of acne has the potential to become a promising treatment. It seems that when topical cosmetic medications are correctly prescribed, they can improve acne treatment outcomes.

In a clinical study on 91 adult patients with mild acne, Federica Dal Oglio et al. (2019) evaluated the effectiveness and tolerability of a novel daily formula regimen in the remedy of mild facial acne.

In this study, patients were use a solution containing licochalcone A, salicylic acid and L-carnitine in the morning and a cream containing 10% complex of licochalcone A and hydroxy at night for 8 weeks. Clinical effectiveness with the Global Acne Grading System (GAGS) score and the number of comedone lesions, papules, and with the evaluation of the VISIA-CR tool (Canfield's Visia CR skin analysis imaging system: takes high-quality, standardized images of the face for clinical research) was evaluated in weeks 4 and 8.

In the fourth week, a statistically significant decrease was observed compared to the base of the global acne grading system. In addition, the average total number of comedones and papules decreased by 41% and 45%, respectively, compared to the baseline level and a significant decrease in the average sebum by 47%. At the 8th week, a statistically significant reduction compared to the Global Acne Grading System baseline, total number of comedones and papules (64% and 71%, respectively), along with a 52% reduction in excess sebum was also recorded. The results of this research show that the daily regimen based on licochalcone A solution, salicylic acid and L-carnitine or cream containing licochalcone A complex and 10% hydroxy is an effective aesthetic approach for mild acne treatment. A combination of 0.1% adapalene gel and moisturizer containing licochalcone A, L-carnitine and 1,2-decanediol also showed a synergistic effect in reducing inflammatory lesions without interfering with the effect of each of the active ingredients. Several chalcone derivatives showed anti-acne activity mainly as antibacterial and anti-inflammatory agents. Licochalcone A has been studied as a potent anti-inflammatory agent and has been combined with other active ingredients in several anti-acne formulations. A skin care formulation containing licochalcone A, L-carnitine, and 1,2-decanediol was evaluated in a 9-week, double-blind, randomized, placebo-controlled study to evaluate the independent efficacy of the formulation in volunteers with mild to moderately severe facial acne (10- 25 inflammatory lesions) were evaluated in 60

patients for 8 weeks, the results of this study showed that this formula can reduce pustular lesions, common lesions, total lesions and sebum level.

Antiandrogenic activities of licorice

An increase in androgen production in the sebaceous glands of the skin leads to an increase in sebum secretion and acne. Six major enzyme systems are involved in cutaneous androgen metabolism, namely steroid sulfatase, 3β-hydroxysteroid dehydrogenase, β-HSD17, steroid 5α-reductase, α-HSD 3, and aromatase. Licorice is known as an anti-androgen herb through various pharmacological mechanisms. Glycyrrhizin, licochalcone A and licorice root extract have anti-androgen activities. By blocking β-HSD3, β-HSD 17 in humans, licorice reduces testosterone production. Administration of high doses of pure licorice extract to male volunteers can significantly decrease serum testosterone levels, however, testosterone levels never fall below the normal range. In addition, licorice showed anti-androgenic properties in male rats due to increased testosterone metabolism, downregulation of androgen receptors, or activation of estrogen receptors. Licochalcone A inhibited 5 alpha-reductase and antagonized androgen receptors in vitro. Glycyrrhizin and glycyrrhetinic acid significantly reduced testosterone production by inhibiting β-HSD 17 in vitro and stimulating aromatase activity in vitro. Furthermore, in a Chinese clinical trial, glycyrrhizin reduced serum testosterone levels in women and was safe and effective in the treatment of postadolescent acne.

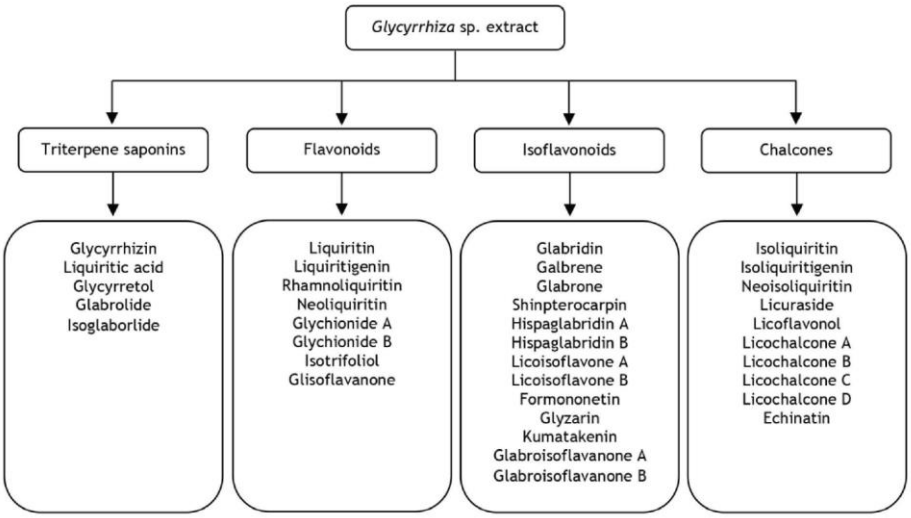

Figure 6. The main components of licorice extract

Acne rosacea

Rosacea is a multifactorial chronic inflammatory skin disorder characterized by persistent or periodic redness and several types of phymatosis changes in the central facial skin (cheeks, chin, nose, and central forehead). Based on the appearance of some of the main phenotypes, rosacea is divided into erythematotelangiectatic rosacea, papulopustular rosacea, glandular/hyperplastic rosacea, ocular rosacea, and other specific forms such as rosacea conglobata, rosacea fulminans, and gram-aceacean neoester. Rosacea (Lupoid), Morbihan's disease and rosacea in children. The pathogenesis of rosacea is still not fully understood, but there are several factors that include (1) genetics, Haber syndrome with rosacea as one of the clinical features can be hereditary. (2) Environment Certain environmental factors can trigger rosacea, including extreme air temperature, sudden temperature changes, food (caffeine, alcohol, hot and spicy food), sunlight (ultraviolet and infrared rays), etc. (3) overproduction of antimicrobial peptides (AMPs) by the innate immune system such as LL-37. (4) inflammation caused by oxidative stress produced by adaptive immune cells. (5) overexpression of toll-like receptors (TLRs). (6) inflammations caused by demodex folliculorum. and (7) neuroinflammation and vascular hyperactivity.

Hesperidin methylchalcone, licochalcone A and tetracarboxymethylnaringenin chalcone show significant activity in improving skin with rosacea. Clinical studies showed that topical formulations containing hesperidin methylchalcone can improve the condition of infected skin by reducing the proportion of dilated vessels, total vessel surface area and IL8 production. These formulas showed a complementary effect between each of the active ingredients in relieving inflammation and reducing redness. Another study reported that hesperidin methylchalcone has anti-inflammatory and analgesic activities, which are dual targets in the treatment of rosacea by inhibiting the potential receptor for vanilloid receptor type 1 (TRPV1), oxidative stress, TNF-α, production of interleukin (IL) 1β, IL -6 and IL-10), and NF-kB activity. Licochalcone A is a natural product of glycyrrhizin that shows strong activity in the treatment, especially in mild and moderate symptoms. In vivo studies have shown that skin care formulations containing licochalcone A provide various activities such as UVA/UVB protection, moisturizing, and redness concealing abilities that improve the appearance of skin with rosacea. These formulas showed high compatibility with sensitive skin and can be combined with other treatments such as metronidazole treatment. The moisturizing formula containing licochalcone A also increases skin hydration and reduces water loss through the skin. The most recent chalcone derivative used as an anti-rosacea is the stabilized form of naringenin chalcone, tetracarboxymethyl naringenin chalcone (TNC). TNC was obtained from naringenin chalcone by total esterification reaction of methyl chloroacetate. An in vitro study showed that tetracarboxymethylnaringenin chalcone significantly reduced LL-37, calcitriol, and several LL-37-induced inflammatory mediators in keratinocytes. Clinical testing also showed that the formulation containing tetracarboxymethylnaringenin chalcone as an active ingredient reduced the redness of rosacea-affected skin compared to untreated skin areas.

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