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Medical Importance of Ziziphora Pedicellata Pazij, Glycyrrhiza Glabra L., Plantago Major L. (Literature Review)

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Abstract

Natural medicinal plants have been widely used in medicine since ancient times. Bioactive substances extracted from them play an important role in the treatment and prevention of various diseases. This article analyzes the scientific literature on the chemical composition, pharmacological effects and medical use of Ziziphora pedicellata Pazij., Glycyrrhiza glabra L. and Plantago major L. plants.

Keywords: Extract, Ziziphora pedicellata pazij., Glycyrrhiza glabra L., plantago major L., folk medicine, phytotherapy, ulcer, peptic ulcer, medicinal plants.

Introduction

Medicinal substances derived from natural plants are an important part of pharmacology, and they are used as an alternative to modern drugs or as a component that increases their effectiveness. Plants such as Ziziphora pedicellata Pazij., Glycyrrhiza glabra L. and Plantago major L. are known in traditional medicine for their anti-inflammatory, antiseptic and regenerative properties. This article analyzes the pharmacological properties of these plants and their importance in medicine.

1. Ziziphora pedicellata Pazij. and its role in medicine

1.1. Chemical composition

According to the literature, Ziziphora pedicellata Pazij. contains the following bioactive substances:

- Essential oils (carvacrol, thymol, borneol) - have a strong antiseptic and antibacterial effect.
- Flavonoids - have antioxidant and anti-inflammatory effects.
- Polyphenols - protect the gastric mucosa.

1.2. Pharmacological properties

- Antibacterial effect - proven effectiveness against pathogenic bacteria such as Staphylococcus aureus and Escherichia coli.
- Spasmolytic effect - used to relieve intestinal and stomach spasms.
- Antioxidant properties - reduce oxidative stress in the body.

1.3. Medical use

- In the treatment of respiratory infections (bronchial asthma, tracheitis).
- In the treatment of gastrointestinal diseases.
- It is used in anti-inflammatory drugs.

Medicinal herbs are the "backbone" of traditional medicine. Medicinal herbs were commonly used by people in developing countries. According to the history of human culture and civilization in Egypt, Assyria, China, and Indie's valley, the elders and wise men used medicinal herbs to heal various ailments. Ancient literature, mythological legends, folklore, medical treatizes, epic ballads, and thousand-year-old manuscripts all include information on these medicinal plants [1,2,3]. Many believe "green medicine" is safer and more reliable than expensive synthetic drugs, which may have adverse side effects [4]. As a result of the indiscriminate use of commercial antimicrobial drugs, which are commonly used to treat infectious diseases, human pathogenic bacteria have developed diverse medication resistance [5]. In the last several years, screening essential oils of medicinal plants has been a popular and scientific interest worldwide. Essential oils are “natural preservatives” and can be used to control pathogens. Essential oils have been utilized as bactericidal, virucidal, fungicidal, antiparasitic, insecticidal, and antimicrobial agents. In addition, it is employed in the pharmaceutical, agricultural, and food industries [6]. Essential oils found in medicinal plants have antibacterial properties and can be used to combat pathogenic microbes [7], Z. clinopodioidesis belong to the Laminaceae family and is widely distributed in Iran, Turkey, and Iraq, specifically Kurdistan; its common Persian name is "Kakuti-e-kuhi", and it is also known as a "Field Mint' [8]. In traditional medicine, Z. clinopodioidesis used as an expectorant, stomach tonic, carminative, and antistress action of the central nervous system depression.

The main compounds of the essential oil are phenolic chemicals; higher concentrations of phenolic chemicals are thought to have stronger antibacterial actions against microorganisms, disrupt bacterial cell membranes and inhibit their proliferation, such as Carvacrol (65.22%), thymol (19.51%), p-cymene (4.86%) and ɣ-terpinene (4.63%). Geographical conditions, climate, seasonal oscillations, and the stage of plant development can all influence the chemical composition of plant essential oils and spices.

Several investigations have shown that thymol and Carvacrol have antifungal properties against fungal infections. Thymol is more effective than Carvacrol. Thymol's low toxicity and pleasant odour and taste indicate that it can be employed as a preservative to avoid bacterial deterioration. Some researchers believe that thymol's antibacterial action involves changes in membrane permeability and intracellular content escape. In addition, Carvacrol is effective at causing spores to germinate and mycelium to proliferate. Individually and in combination, carvacrol and p-cymene work as a unique technique for regulating Escherichia coli. Carvacrol or p- cymene reduced the numbers of E. coli O157:H7, p- cymene alone does not affect very well, but when combined with each, Carvacrol and thymol have a synergistic effect as an antimicrobial. The acidic nature of Carvacrol and thymol's hydroxyl group, as well as their role in hydrogen bond formation, is the most fundamental explanation for their high antibacterial actions.

This study aimed to determine the antioxidant activity of essential oils of Z. clinopodioides as well as antibacterial activity against foodborne pathogens (Bacillus sp., Escherichia coli, Staphylococcus aureus and Pseudomonas sp.).

3.2. Calculation of the MIC and MBC Values

The MIC value of Z. clinopodioides essential oil for all test bacteria is displayed in table 2; figures 7 and 8. The essential oil inhibited B. subtilis growth in the fifth dilution (MIC=0.031 g/mL). And Escherichia coli (MIC=0.25 µg/mL) in the second dilution. Gram-positive bacteria were more sensitive during the MIC test than Gram-negative E. coli. In MBC, the essential oil killed 99.9% or more of E. coli in the first dilution (MBC=0.5 g/mL); while the essential oil did not kill Bacillus at any concentration, this indicates that the MIC was not equivalent to the MBC for E. coli and Bacillus sp. MBC was unable to obtain, indicating that the oil has a bactericidal effect.

Z. clinopodioides are widely employed in traditional medicine. Essential oils have long been used as flavouring ingredients in food and beverages, and they must act as natural agents for food preservation due to the presence of antimicrobial components. Furthermore, for removing pathogenic germs, researchers have been interested in biologically active chemicals extracted from plant species because of their resistance to antibiotics. The essential oil's antibacterial activity could be linked to the presence of some compounds such as pulegone content, piperitenone and 1-8 cineole. These components have been shown to have substantial antibacterial properties. Pulegone is also a prominent component of Ziziphora species (Z. hispanica, Z. brevicalyx and Z. tenuior), pulegone essential oil compound was (34.4%) in Z. clinopodioides Lam. Z.hispanica (78.6%), Ziziphorabrevicalyx ((75.0–88.0), and Z. tenuior (71.2–85.3) .

According to the results of this investigation, Z. clinopodioides essential oil has an excellent antibacterial impact on human pathogenic bacteria. Gram (+) bacteria are more vulnerable to essential oil than Gram (-) bacteria, according to numerous reports . This may be due to changes in the cell wall structure. Gram (-) bacteria's tolerance to essential oils has been attributed to a hydrophilic outer membrane that prevents hydrophobic essential oils from penetrating the target cell membrane.

The results of this study corroborate traditional usage of Z. clinopodioides, which appeared to be effective sources of antibacterial medicines, especially against Bacillus sp. and Escherichia coli. Based on these findings, it is feasible to conclude that essential oil extracted from Z. clinopodioidesleaves has potent and wide antibacterial action against various human pathogenic microorganisms. The presence of phytochemical compounds in the leaves of Z. clinopodioides makes it biologically active, and it may be responsible for disease control. Z. clinopodioidesleaves has led to finding that the DPPH is well exhibited. The results of this investigation indicate that Z. clinopodioides leaf essential oil extract has excellent antioxidant properties.

Authors' Contribution

Study concept and design: K. O. Q.
Acquisition of data: S. A. A. M. A.
Analysis and interpretation of data: H. H. A.
Drafting of the manuscript: D. F. A.
Critical revision of the manuscript for important intellectual content: K. O. Q. and S. A. A. M. A.
Statistical analysis: H. H. A.
Administrative, technical, and material support: D. F. A.

Conflict of Interest

The authors declare that they have no conflict of interest.

Anti-Inflammatory Properties of G. glabra

It is generally accepted that inflammatory mechanisms play a key role in the development of atherosclerosis [9,10,11,12,13,14]. Pathophysiologically, the inflammatory process at an early stage of atherogenesis includes the following stages: inflammatory activation of endothelial cells, recruitment of monocytes and other leukocytes to the intima of the vessel, the transition of monocytes to tissue macrophages, the uptake of multiple modified atherogenic LDL by macrophages with the formation of foam cells, their secretion of inflammatory cytokines, reactive oxygen species (ROS) and other mediators, which subsequently leads to the death of foam cells (for example, as a result of apoptosis) and the formation of atherosclerotic plaque [15]. Bioactive components of G. glabra may influence the above stages of inflammation associated with atherogenesis, thus exerting an anti-atherosclerotic effect [**16**].

Compounds isolated from licorice have a pronounced anti-inflammatory effect. Studies show that licorice inhibits toll-like receptor 4 (TLR4) activation, mitogen-activated protein kinase (MAPK) signaling pathway, nuclear factor kappa B (NF-κB) expression, and activator protein (AP)-1 transcriptional activity, which subsequently leads to a decrease in the expression of pro-inflammatory cytokines and chemokines and other inflammatory mediators such as COX-2, inducible nitric oxide synthase (iNOS), TNF-α, IL-6, IL-1β, IL-12, and IL-23 and vascular endothelial growth factor (VEGF) [17]. It was shown that an intravenous injection of glycyrrhizin inhibited the expression of TLR-4 in BALB/c mice after intraperitoneal administration of LPS as well as a significantly decreased protein content, inflammatory cell counts, TNF-α, IL-1α, IL-6, myeloperoxidase activity, and expressions of COX-2iNOS, and NF-κB [18]. In cultured LPS-stimulated murine macrophages, licoflavanone, a natural compound isolated from G. glabra leaf extract, reduced the translocation of NF-κB into the nucleus, thus inhibiting inflammatory signal transduction at the NF-κB pathway level, so significantly decreasing the transcription of iNOS and COX2. In the same study, licoflavanone caused a reduction in MAPKs phosphorylation and activation [19]. The other study on murine macrophages also demonstrated the anti-cytokine effect of G. glabra phytoconstituents: isoliquiritigenin significantly decreased LPS-stimulated NO, IL-1β, and IL-6 production, and glabridin significantly inhibited NO and IL-1β [20]. Glabridin has been shown to inhibit the TNF-α-induced expression of ICAM-1, VCAM-1, and E-selectin genes in endothelial cells, which are among the early manifestations of inflammation in atherosclerosis [21]. In addition, it was found that licorice extract significantly increases the production of the anti-inflammatory cytokine IL-10 [22].

Licorice has a pronounced antioxidant activity, which is manifested in the reduction of oxidative stress. Oxidative stress is an imbalance between the production and removal of ROS and nitrogen species and free radicals, causing lipid peroxidation, protein oxidation, etc., which is important in the development of atherosclerosis [22]. It has been shown that glabridin reduces the release of superoxide from macrophages and inhibits the cell-mediated oxidation of LDL by inhibiting the activation of NADPH oxidase [23]. Glycyrrhizin also has an inhibitory effect on the formation of superoxide and hydroperoxide in macrophages, inhibits the production of prostaglandin E2 by activated macrophages, and suppresses the release of ROS by inflammatory cells [**24**]. Phenolic components of glabridin provide antioxidant activity due to the absorption of free radicals, the release of hydrogen, the chelation of metal ions, as well as a decrease in mitochondrial lipid peroxidation ability [25]. The revealed effects of reducing the activity of iNOS as well as NO allow us to consider licorice to be an effective antioxidant [26].

It is known that the expression of paraoxonase 2 (PON2) increases in monocytes during their differentiation into macrophages as a result of NADPH oxidase activation [27]. Therefore, the reduced expression of PON2 observed in hypercholesterolemia may be due to increased macrophage cholesterol rather than increased oxidative stress. Therefore, an increase in PON2 expression can be considered a selective cellular response that contributes to a decrease in oxidative load formation of foam cells [28]. It has also been shown that glabridin increases the expression of PON2 mRNA and protein, which, in turn, reduces oxidative stress and triglyceride accumulation in macrophages and endothelial cells [29].

All of the described above anti-inflammatory and antioxidant effects of licorice indicate a huge potential for its use in the treatment of atherosclerosis since it is considered to be a multifactorial chronic inflammatory disease.

3. Anti-Atherogenic Properties of G. glabra

Atherosclerosis is accompanied by an excessive accumulation of LDL in the arterial wall. As a result of multiple modifications, LDL is converted into oxLDL, which triggers innate and adaptive immune responses, leading to the progression of inflammation and the development of atherosclerotic complications [30]. It has been shown that licorice significantly reduces the level of cholesterol, triglycerides, and LDL in blood plasma while increasing HDL levels [31], and it also directly affects the atherogenic modifications of LDL, reducing their oxidation [32]. In addition, it was found that licorice compounds can inhibit the activity of acyl-CoA cholesterol acyltransferase (ACAT), the main enzyme involved in the intracellular esterification of free cholesterol by fatty acyl-CoA with the formation of cholesterol ester. The inhibition of ACAT can lead to cholesterol-lowering and anti-atherosclerotic activity by blocking intestinal absorption of dietary cholesterol, inhibiting the hepatic secretion of very-low-density lipoproteins, and preventing the formation of foam cells in vessel walls [33]. The decrease in cholesterol levels may also be associated with the effect of licorice on the activity of enzymes involved in the biosynthesis and catabolism of cholesterol in the liver. It was found that licorice compounds reduced the activity of hydroxymethylglutaryl-CoA synthase and increased the activity of cholesterol-7α-hydroxylase—enzymes regulating these processes [34]. An interesting fact is the synergistic effect of licorice with other plant compounds. For example, The Ger-Gen-Chyn-Lian-Tang, which is a traditional mixture of extracts from four herbs of Chinese medicine, including licorice, is able to reduce cholesterol levels in the atherogenic $ApoE^{-/-}$ mouse model, throughout visibility, due to the activation of adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor α (PPARα), increased the expression of peroxisome proliferator-activated receptor γ (PPARγ), which also provides an anti-atherosclerotic effect [35]. Another study showed that glabridin activates AMPK and subsequently induces the translocation of the insulin-dependent glucose transporter protein GLUT4 in mouse skeletal muscle, thereby preventing hyperglycemia, which is important in diabetes and atherosclerosis [36]. It is known that PPARs can modulate the atherosclerotic process by interacting their direct effects on reducing inflammation and increasing insulin sensitivity with the indirect effects of PPAR activation on glucose and lipid metabolism [37]. Studies have shown that glabridin acts as a PPARγ activator,

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thereby lowering blood glucose and lipid levels [38]. In addition, some derivatives of glycyrrhetinic acid showed antitumor activity in models using MCF-7, HepG2 cell lines no worse than the classic PPARγ agonist Rosiglitazone, and also showed themselves as low-toxic compounds [39]. Studies have also shown that licorice is a natural inhibitor of 11-beta-hydroxysteroid dehydrogenase type 1, an elevated level of which correlates with the development of obesity, type 2 diabetes mellitus, and insulin resistance [40], which are known to lead to the development of vascular complications, in particular atherosclerosis [41]. Other data also demonstrate the positive effects of licorice (in particular, licorice flavonoid oil containing glabridin on high-fat diet-induced obesity in C57BL/6J mice, manifested in the reduction of hyperinsulinemia, abdominal adipose tissue, visceral fat, as well as body weight. These effects are associated with the suppression of the synthesis of fatty acids and the activation of their catabolism in the liver [42].

Vascular smooth muscle cells (VSMC) have an increased ability to change phenotype, proliferation, and migration, and by penetrating into the intima of the vessel and changing the phenotype, they play an important role in the initiation and progression of atherosclerosis [43]. It was found that the licorice flavonoid Isoliquiritigenin significantly reduces the expression of transient receptor potential canonical 5, the main subtype of store-operated channels, localized in VSMCs, thereby inhibiting the proliferation of VSMCs [44]. In addition, the endothelium-independent vasodilatory effect of this compound has been shown [45]. The vasodilating effects of licorice can be realized through endothelium-dependent and endothelium-independent actions. These effects are associated not only with the influence of licorice on the release of NO, but also with a partial blocking of the Inositol trisphosphate receptor (IP3R), which prevents the intracellular release of calcium ions into the cytosol [46]. It was found that the components of licorice can have an estrogen-like effect, modulating vascular damage and atherogenesis. The inhibition of VSMC proliferation is very important for the prevention of atherosclerosis. Studies have shown the estradiol E2-like activity of glabridin, which inhibits VSMC proliferation and stimulates DNA synthesis in endothelial cells when incubated with VSMC and ECV-304 endothelial cells. In addition, in animal studies, glabridin, similar to E2, stimulated creatine kinase (CK), which is a marker of estrogen response in the aorta and left ventricle of the heart [47].

Plants have been used for their medicinal properties for thousands of years. Since ancient times, various scientists and healers have used various types of herbs to treat diseases, and many books and treatises have been written describing the effects of different plants on various diseases. Plantago major is one of these herbs, the value of which has been praised since ancient times. Plantago major (Plantago major ssp. Major L.) is a perennial plant belonging to the Plantaginaceae family. Plantago major has been used to treat various diseases, including infectious diseases. Plantago major is reported to have antimicrobial, antidiabetic, antispasmodic, antiviral, anti-inflammatory, and wound-healing properties. The emergence of drug-resistant pathogens in recent decades has prompted scientists to evaluate the effects of medicinal plants on pathogens. The study of plants traditionally used as medicines should still be considered a useful and logical research strategy in the search for new antimicrobial and other anti-infective agents. Traditional chemicals have many side effects compared to their herbal counterparts. Plant extracts are an attractive alternative because they are a rich source of biodegradable secondary metabolites such as phenols, flavonoids and saponins, alkaloids, etc., which have antimicrobial, anti-inflammatory, wound healing and antiviral properties and reduce the likelihood of disease. The main objective of this review is to introduce the broad therapeutic potential of Plantago major extracts and their potential applications as herbal medicines.

NO inhibitory assay, fibroblast proliferation assay, and high glucose migration assay were used to study the in vivo wound healing and in vitro wound healing effects of Planatgo major leaf extracts, the main biologically active compounds of which are ursolic acid (U) and hyperoxic acid (U), in diabetic rats. These studies showed that UA could promote the wound healing process with PMLE, UA, and OA, without causing significant skin irritation when applied topically. PMLE and UA have anti-inflammatory properties, as they significantly reduced NO generation in RAW264.7 cells after LPS application at all doses. In addition, NO generation was reduced by OA (2.5–10 μg/ml). Fibroblast proliferation is one of the important steps in tissue regeneration. NIH/3T3 fibroblast cells were used to study the concentration range of PMLE, UA and OA in the proliferation phase. PMLE at 31–500 μg/mL stimulated fibroblast proliferation, while UA and OA had the opposite effect at 7.81–125 μg/mL [48]. We also evaluated the clinical efficacy of hydroalcoholic extract of Plantago major in the treatment of diabetic foot ulcers (DNS) and pressure ulcers (PS) by applying a 10% gel with Plantago major extract. Topical application of Plantago major extract gel to wounds for two weeks, in addition to wound dressing and standard wound care, showed a greater reduction in wound size compared to control after the first week (64.90 ± 29.75% vs. 33.11 ± 26.55%; $p < 0.001$ ± 26.55%; $p < 0.001$ and 8 ± 4, 2 weeks) 52.87 ± 32.41%; $p < 0.001$). Furthermore, the proportion of patients in the drug group (n = 32, 64%) who had complete wound healing was higher than in the control group (n = 9, 20.45%; OR: 3.129, 95% CI: 1.685-5.80; $p < 0.001$). This effect is due to the polyphenolic compounds and antioxidant properties of the extract. A polyphenol compound called plantamajoside in Plantago major extract is responsible for the anti-inflammatory and healing properties of the extract. In addition, proteins isolated from the plantago extract have been reported to affect the proliferation of fibroblasts, which leads to accelerated wound healing. Nitric oxide (NO) production is increased by Plantago major extract, and this effect may contribute to wound healing. Hispidulin and baicalein, two major flavonoids from Plantago major, have anti-inflammatory and antifungal effects. In addition, they inhibit the release of histamine and prostaglandins, preventing their tissue-damaging effects. Furthermore, the astringent effect of flavonoids may play a key role in accelerating wound healing [49].

The effect of a 50% aqueous solution of Plantago major on the healing of burn wounds was compared with 20% silver sulfadiazine and ozerin in rats. There was no significant difference between the groups of rats given these drugs on days 7 and 14, but the difference was significant on day 21. The best results were observed in the group treated with 50% of Plantago major [50,51,52,53,54,55,56] .

In a study by Zubair et al. (2016) the wound-healing properties of Plantago major extracts (water and ethanol) were evaluated using an ex vivo wound healing model in pigs. Both types of extracts promoted wound healing in pig skin, but the ethanol-based extracts were slightly more effective. A concentration of 1.0 mg/ml (based on dry weight) gave the best results for both types of extracts. The fact that the ethanol-based polyphenol-rich extracts stimulated wound healing activity more than the water-based extracts with comparable amounts of dry Plantago major leaves suggests that the polyphenol content has a significant effect. The significant positive effects of water-based extracts at doses of 1.0 and 0.1 mg/ml are attributed to some water-soluble chemicals in these extracts that have wound-healing properties. Several substances may act alone or in concert, or they may be involved in stimulating or controlling other substances during wound healing. Plantamajoside, acteoside, aucubin, and ursolic acid are among the chemicals present in the leaves of Plantago major that have wound-healing properties.

Glycyrrhiza glabra L. (Licorice) and its medicinal value

This section discusses the chemical composition, pharmacological properties and medicinal uses of licorice.

3. Plantago major L. (Wormwood) and its medicinal value

This section discusses the chemical composition, pharmacological effects and medicinal uses of wormwood.

Conclusion

Ziziphora pedicellata Pazij., Glycyrrhiza glabra L. and Plantago major L. are medicinal plants widely used in medicine. Their bioactive composition is of great importance in the creation of natural medicines. Preparations prepared from these plants are effective in the treatment of gastrointestinal diseases, respiratory tract infections and inflammatory processes.

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