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Glycyrrhiza glabra as Bioavailability Enhancer

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ABSTRACT

Despite the impressive in vitro findings of both synthetic and herbal medications, their in vivo activity is often insignificant due to poor bioavailability. According to the Biopharmaceutical Classification System (BCS), low solubility and/or permeation of drugs is a major concern that results in reduced absorption and poor bioavailability. To address these issues, various strategies have been employed, including the use of permeation enhancers, also known as bioenhancers. Bioenhancers are compounds, either synthetic or natural, that increase the bioavailability of drugs and nutrients such as vitamins, amino acids, and minerals into the systemic circulation and at the site of action, leading to improved therapeutic action. By improving bioavailability, enhancers can reduce drug dosage, shorten the treatment period, and overcome drug resistance. Although synthetic bioenhancers have been extensively studied, plant-based bioenhancers may be a superior alternative due to their natural origin. Literature reviews have shown that plant-based bioenhancers have been used in a wide range of antibiotics, antiviral, and anti-cancer therapeutics. These bioenhancers can be classified based on their sources and mechanisms of action. This review offers a systematic and comprehensive overview of various *Glycyrrhiza glabra* as bio-enhancers and their applications. There are over thirty kinds of the Glycyrrhiza genus that are widely distributed across the globe. It was the most recommended plant in Ancient Egyptian, Roman, Greek, East Chinese, and Western medicine during the Former Han era. Licorice root extracts have several advantageous impacts, including alleviating throat infections, tuberculosis, respiratory and liver disorders, as well as possessing antibacterial, anti-inflammatory, and immunodeficiency properties.

INTRODUCTION

For centuries, numerous civilizations have turned to nature, particularly to flora, as a means of medical and healthcare treatment. Presently, a significant portion of the global populace, especially in developing nations, relies on plants to address fundamental medical requirements. The utilization of plants for medicinal purposes is an age-old practice that can be traced back approximately 3000 years [2]. The natural world has consistently provided us with beneficial remedies, offering an array of healing plants that generate significant phytochemicals [1]. There has been a rise in global recognition of the utilization of herbal remedies in the diverse customary healthcare systems of emerging nations. Numerous studies approximated that nearly 80% of individuals in developing countries continue to depend on conventional medicine for their fundamental healthcare requirements [2].

Organic compounds play a vital role in discovering novel compounds that can be developed into drugs for various diseases. They are a valuable source of specialized structures that have been refined by evolution to interact with proteins and other molecules. About fifty percent of the drugs we use today are derived from natural sources. The outlook for botanicals as a source of therapeutic agents for research, prevention, and treatment of diseases is very positive. Natural products have given us some of the most crucial life-saving medications used in modern medicine. However, out of the estimated 250,000-400,000 plant species, only a mere 6% have been scrutinized for their biological activity, and 15% have been subjected to phytochemical analysis[2]. *Glycyrrhiza glabra* Linn, commonly known as Yashti-madhuh, is a herb extensively utilized in Ayurveda, both as a medicinal herb and a flavoring agent. It holds a significant place in ancient medical history. This herb is found mainly in the Mediterranean region and some parts of Asia. In Bengali, it is known as Madhuka, in Gujarati as Jaishbomodhu, in Hindi as Mulhatti, in Kannada as Yastimadhuka, in Malayalam as Iratimadhuram, in Marathi as Jeshtamadha, in Oriya as Jatimadhu, in Tamil as Atimaduram, and in Telugu as Yashtimadhukam or Atimadhuranu. In English, it is also referred to as Licorice, Liquorice, or Sweet wood[2]. The cultivation of licorice is carried out for commercial purposes in several countries such as Italy, Spain, Greece, France, Iran, Iraq, Turkey, Turkmenistan, Uzbekistan, Syria, Afghanistan, Azerbaijan, India, China, the United States, and England. Licorice is a highly prized plant in the global market due to its varied applications in the tobacco, cosmetic, food, and pharmaceutical industries. The phytochemical and pharmaceutical properties of licorice have been extensively studied and analyzed[1]. In the realm of Traditional Chinese Medicine (TCM), *Glycyrrhiza glabra* holds a significant place as an "indispensable herbal remedy." As per TCM beliefs, "licorice is present in nine out of ten formulations," and when used in conjunction with other herbal remedies, licorice proves to be one of the most potent herbal medicines for reducing toxicity and enhancing efficacy. Moreover, it is also regarded as a health supplement and natural sweetener, owing to its status as a "medicinal food homology" herbal medicine. Among the approximately 30 varieties of licorice, *Glycyrrhiza glabra* is one of the most commonly used species in the domains of feed and food[1,2].

Fig.1., *Glycyrrhiza Glabra* Plant

Fig.2., *Glycyrrhiza Glabra* Root

Phytochemistry: Roughly 400 compounds in total have been extracted from licorice, with nearly 300 flavonoid compounds among them. The primary potent elements are triterpenoid derivatives, namely glycyrrhizin and glycyrrhetinic acid. Humans can metabolize glycyrrhizin into glycyrrhetinic acid, resulting in identical pharmacological effects for both compounds[1]. The origins of *Glycyrrhiza glabra* Linn. hold glycyrrhizin, a saponin that is 60 times sweeter than cane sugar. The roots also comprise fractions that are rich in flavonoids such as liquirtin, isoliquertin, liquiritigenin, and rhamnoliquirilin. Furthermore, five new flavonoids, namely glucoliquiritin apioside, prenyllicoflavone A, shin flavanone, shinpterocarpin, and 1-methoxyphaseolin were isolated from the dried roots. Licopyranocoumarin, licoarylcoumarin, and glisoflavone were also obtained and their structures were determined. Additionally, a new coumarin-GU-12 was isolated. Four new phenolic constituents that are isoprenoid-substituted, namely semilicoisoflavone B, 1-methoxyficifolinol, isoangustone A, and licoriphenone were also isolated from the roots[2,3]. Glabridin is the prevalent isoflavone, representing 0.08 percent to 0.35 percent of the roots' dry weight. *Glycyrrhiza glabra* comprises one 18-glycyrrhetinic acid molecule and two glucuronic acid molecules (18-glycyrrhetinic acid-3-O—D-glucuronopyranosyl-(1 2)—D-glucuronide)[1]. A new prenylated isoflavan derivative, kanzonol R turned into additionally remoted 13. The presence of many volatile additives together with pentanol, hexanol, linalool oxide A and B, tetramethyl pyrazine, terpinen-4-ol, αterpineol, geraniol and others inside the roots is reported. Presence of propionic acid, benzoic acid, ethyl linoleate, methyl ethyl ketine, 2, 3-butanediol, furfuraldehyde, furfuryl formate, 1-methyl-2-formyl pyrrole, trimethylpyrazie, maltol and any different compounds is likewise remoted from the essential oil 13[2].

Morphology: *Glycyrrhiza glabra* Linn is a perennial shrub, accomplishing a peak upto 2.five m. The leaves are compound, imparipinnate, and alternate, having 4-7 pairs of oblong, elliptical or lanceolate leaflets. The plant life are narrow, commonly papilionaceous, borne in axillary spikes, and lavender to violet in color. The calyx is short, campanulate, with lanceolate guidelines and bearing glandular hairs. The fruit is a compressed legume or pod, upto 1.5 cm lengthy, erect, glabrous, particularly reticulately pitted, and commonly contains 3-5 brown, reniform seeds. The taproot is about 1.5 cm lengthy and subdivides into subsidiary roots, approximately 1.25 cm lengthy, from which the horizontal woody stolons arise. They might also additionally attain eight m and while dried and cut, collectively with the root, represent industrial licorice. It might also additionally be determined peeled or unpeeled. The portions of root break with a fibrous fracture, revealing the yellowish indoors with a feature scent and candy taste. Licorice enjoys fertile, sandy or clay soil close to a river or circulates wherein sufficient water is to be had for the plant to flourish inside the wild, or beneat hneath cultivation wherein it could be irrigated[2].

Effect of Licorice in Different Diseases:

1. **Anticancer effects of Licorice**: One of the primary constituents present in the roots of Glycyrrhiza is isoliquiritigenin (ISL). This particular compound has demonstrated a direct inhibitory effect on different types of cancers, including cervical, hepatoma, colon, breast, prostate, and others. ISL has the potential to hinder the multistage carcinogenesis process by enhancing cell cycle, apoptosis, autophagy, and anti-angiogenesis, thereby promoting progression, formation, and migration. Moreover, licorice has been found to possess anticancer, anti-inflammatory, antioxidant, and antibacterial properties, which have been associated with various health benefits in pharmacological studies[1]. The growth factor receptor-2 for vascular endothelial and the vascular endothelial growth factor can potentially be restrained for the treatment of breast cancer with naturally occurring isoliquiritigenin. ISL augmented HIF-1 proteasome degradation, thereby reducing VEGF expression in breast cancer cells and interacting with VEGFR-2 to curtail its kinase activity. ISL administered for breast cancer treatment exhibited a decline in breast cancer progression and neoangiogenesis[1,2,3].

2. **Licorice in Respiratory Tract Infection**: Isoliquiritigenin, a flavonoid obtained from the licorice root, is a natural compound that possesses antioxidant and anti-inflammatory characteristics. Scientists conducted a study on mice with cigarette smoke-induced COPD to investigate the impact of isoliquiritigenin. The study findings revealed that isoliquiritigenin decreased the infiltration of inflammatory cells and cytokines, and also regulated the NF-κβ and Nrf2 signaling pathways. Moreover, isoliquiritigenin provided protection against COPD induced by cigarette smoke. A mice model with inflammation was utilized to investigate the impact of glabridin on ovalbumin-induced airway hyperresponsiveness. The results revealed that glabridin could potentially serve as a treatment for asthma. Glabridin's anti-inflammatory properties are attributed to its ability to decrease serum IgE levels, total protein levels, and WBC count, while also enhancing respiratory function[1,2].

3. **Licorice effect on the Cardiovascular System:** Three hundred active constituents are found in licorice, utilized for thousands of years. The primary functioning constituent of licorice is glycyrrhizin. Glycyrrhizin is a precursor of licorice converted to 3β-monoglucuronyl-18β glycyrrhetinic acid (3MGA) and 18β-glycyrrhetinic acids in the intestines. 3MGA and GA inhibit the enzyme 11β-hydrogenase type II (11β-HSD2) that converts cortisol to cortisone. Elevated cortisol levels arise from a modest mineralocorticoid abundance in the kidney and increase systemic vascular resistance by stimulating mineralocorticoid receptors. Prolonged inhibition of 11 beta-HSD2 due to excessive licorice consumption results in hypernatremia, hypokalemia, and high fluid content, leading to significant life-threatening consequences, particularly in individuals with cardiovascular disease. Meta-analyses with 26 and 18 investigations have reported that licorice consumption and blood pressure significantly elevate systolic and diastolic. This study has demonstrated that licorice consumption impacts the human body and illustrates the distinction between licorice's health benefits and its potential for adverse effects[1,6].

4. **Licorice effect on Hepatoprotective System**: Licorice flavonoid oil, glycyrrhizin, GA, and specific licorice preparations exhibit strong liver-protective effects. Japan and China have developed glycyrrhizin as a medication for protecting the liver. GA has been found to possess hepatoprotective properties. Within the human body, GA is converted into glycyrrhetinic acid, meaning that both substances have the same pharmacological effects [148]. GA has demonstrated anti-inflammatory and antiapoptotic effects by inhibiting TNF-α and caspase-3, which explains its hepatoprotective properties. GA also promotes liver regeneration by increasing the expression of proliferating cell nuclear antigens. Glycyrrhizin may be an effective medication for safeguarding the liver against damage caused by endotoxins, especially following a major hepatectomy[1,6,9].

5. **Antimicrobial Effect:** Additionally, the aqueous extract of licorice leaves also showed antimicrobial activity against Klebsiella pneumoniae and Escherichia coli. These findings suggest that licorice extracts could be used as a natural antimicrobial agent in the treatment of various bacterial infections[1]. Karahan F et al. explored the antioxidant and antibacterial properties of methanolic root extracts of *Glycyrrhiza glabra* var. glandulifera. Samples of the plants were gathered from the eastern Mediterranean region of Turkey. MIC and disc-diffusion methods were utilized to assess the antibacterial efficacy. The antibacterial tests revealed that

methanolic root extracts were less effective against the Gram-negative bacteria compared to the Gram-positive bacteria. Moreover, root methanolic extracts exhibited greater effectiveness against Candida species compared to other bacteria. Findings from the study demonstrated that environmental factors impact the composition of chemical constituents and biological properties of the common licorice in each habitat. Additionally, the study's results supported the traditional use of licorice and suggested its potential in treating other infections[1,5,6]. The antibacterial properties of *Glycyrrhiza glabra* were assessed against Bacillus cereus, Escherichia coli, Pseudomonas aeruginous, and Staphylococcus aureus. This was investigated using the agar well diffusion and dilution test methods. The findings of this research indicate that the greatest efficacy was observed against S. aureus, while the least impact was observed against P. aeruginosa. Therefore, the outcomes of this study confirm that the extract of G. glabra has the potential to be used as a treatment for bacterial infections. The results of the study demonstrate that G. glabra could serve as an alternative medication for bacterial agents[1].

The Concept of Using Bioenhancers: A Revolutionary Trend

Drawing from the principles of ayurvedic medicine, the utilization of bio-enhancers presents a viable strategy for mitigating treatment expenses by augmenting drug bioavailability. Presently, there is a worldwide emphasis on techniques that aim to diminish drug dosages and, consequently, treatment expenditures, making medication accessible to a broader spectrum of individuals, including those who face financial constraints [14].

Bioenhancer:

Bioavailability refers to the speed and degree at which a medically effective substance enters the systemic circulation and is accessible at the intended site of action. Intravenous medications achieve the highest level of bioavailability, whereas oral administration results in a lower percentage due to incomplete drug absorption and initial metabolism [14]. A bioenhancing substance is a compound that can increase the absorption and effectiveness of a specific medication when used together [8,14].

Mechanism of Action of Herbal Bioenhancer:

The mechanisms of action vary depending on the type of herbal bioenhancer chosen. Nutritional bio-enhancers work on the gastrointestinal tract (GIT) to improve absorption, while antimicrobial bioenhancers affect the metabolism pathway. These herbal bio-enhancers are utilized to increase the pharmacological effect of the core ingredient. Piperine and other herbal bioenhancers can be categorized based on their specific mechanisms of action. Ayurveda introduced Piperine as the first herbal potentiator or bioenhancer in the form of Trikatu churna[8].

Inhibition of Drug Metabolism Pathway:

The drug acts on enzymes responsible for the metabolism and breakdown of drugs in the liver. Specifically, it primarily inhibits the P-glycoprotein class and CYP3A4 (Cytochrome P-450). Other enzymes of the Cytochrome P-450 class that may be inhibited or induced include CYP1A1, CYP1B1, CYP1B2, CYP2E1, and CYP3A4. P-glycoprotein is a major cell efflux pump, particularly important in the case of antimalarial or antineoplastic drugs. This pump removes the ingested drug from cells, thereby reducing its efficacy. By inhibiting P-glycoprotein, the drug can remain in cells for longer periods and have a more significant therapeutic effect[8,14].

Inhibition of Glucuronic acid:

It hinders the degree of glucuronidation in the intestine. Primarily, it diminishes the inherent content of UDP-glucuronic acid and also curbs the transferase activity. Piperine has exhibited potent inhibition of UDP-glucuronyl-transferase in numerous rat-based research experiments[14].

The extent of Absorption:

The drug molecule's absorption in the gastrointestinal region is enhanced as it causes vasodilation of tissues, resulting in increased perfusion in the area[14].

Stimulation of Gamma Glutamyl Transpeptidase:

GGT is a crucial transporter of amino acids found in the gastrointestinal region. Its activation promotes the assimilation of amino acids, leading to an increase in the assimilation of pharmaceuticals that are associated with amino acids[14].

Hurdles with Bioenhancers: Although bio-enhancers in drug delivery have been successful, not all approaches have achieved the same level of success. New bio-enhancers currently being developed present challenges that must be overcome. One of these challenges is to enhance the properties of drug formulations, such as prolonging their circulation in the bloodstream, increasing their functional surface area, protecting the incorporated drug from degradation, facilitating their crossing of biological barriers, and enabling site-specific targeting. Another challenge in the research and development of herbal bio-enhancers is the production on a large scale. There is always a need to scale up laboratory or pilot technologies for eventual commercialization. The challenges of scaling up include dealing with low concentrations of nanomaterials, preventing agglomeration, and managing the chemistry process. It is easier to modify nanomaterials at the laboratory scale to improve their performance compared to doing so at a large scale. Advancements in herbal bio-enhancers also bring new challenges for regulatory control. There is an increasing need to establish regulations that take into account the physicochemical and pharmacokinetic properties of nano-drug products, which differ from those of conventional drug products[11].

Advantages of bioenhancement:

The bioavailability is directly correlated with the plasma concentration that is accessible, thus ultimately linked. This not only makes the costly medications more accessible, but also alleviates the financial burden on patients. Additionally, it lessens the risk of adverse reactions by decreasing the necessary dosage[8].

***Glycyrrhiza Glabra* as Bioenhancer:**

Glycyrrhiza, a category of plants commonly known as licorice, has been utilized in Asian nations since ancient times as a traditional medicine intended to treat allergies, viral infections, and inflammation. Recently, glycyrrhizin was extracted from Glycyrrhiza plant species and has been employed as a sweetener and flavoring agent in prepared foods. *Glycyrrhiza glabra*, G. inflata, and G. uralensis are the three species of the plant that is mostly utilized in dietary supplements. Although the three species are frequently used interchangeably, they exhibit slightly different phytochemical constituents. Studies identified six flavonoids extracted from Glycyrrhiza plants that exhibited the ability to inhibit CYP450-mediated metabolism[12]. Licochalcone A hindered CYP450 in a time-dependent manner and hence the possibility exists that certain components of dietary supplements such as licorice may improve the pharmacokinetic properties of extensively metabolized drugs. The variation in enzyme hindrance by different phytochemical components requires determination of the exact chemical compound in a given dietary supplement that causes the drug bioavailability enhancement effect. A study conducted on the transporter hindrance potential of 18β-glycyrrhetinic acid, showed significant reduction (56%) of p-aminohippurate (PAH) transport via the hOAT1 transporter. This indicates the ability to decrease renal secretion and stimulate re-absorption into the blood. The same study also showed a significant stimulation of estrone sulfate (ES) uptake via hOAT4 transporters. As the hOAT4 transporter is mainly responsible for reuptake into the blood from the urine, stimulation thereof may be used as a beneficial interaction to maintain therapeutic levels of really excreted drugs[8,12]. Liquorice is composed of dehydrated, stripped or unstripped, root and runner of *Glycyrrhiza glabra* and shows properties of preventing liver damage, reducing fertility, reducing inflammation, promoting the expulsion of phlegm, and preventing oxidation. It includes glycyrrhizin which increases the effectiveness of rifampicin by 6.5 times at a concentration of 1 µg/ml. It also increases the effectiveness of taxol by 5 times at a concentration of 1 µg/ml[11].

It is widely recognized as Liquorice which includes Glycyrrhizin. It enhances the suppression of cell proliferation with the fundamental antineoplastics medication. Research has demonstrated its impact on taxol amplification; this blend is utilized against bosom malignant growth. Suppression of cell development by taxol with glycyrrhizin was more noteworthy than taxol alone. Studies additionally report its beneficial outcomes on the transportation of antibiotics like rifampin, tetracycline, ampicillin, and nutrients B1 and B12 across the intestinal membrane. It falls under the isoflavones classification and is a widely recognized natural estrogen. Genistein is said to have the capability to hinder the efflux function of P-gp, BCRP, and MRP-22. When combined with genistein, the absorption of paclitaxel in the intestines is significantly enhanced, but only at a low dosage of 10 mg/kg[8]. Active ingredient of licorice responsible for its bioenhancing activity is Glycyrrhizin - a non-alkaloid compound that boosts the bioavailability of antibiotics and other medications including anti-infective and anticancer drugs. The molecule facilitates the absorption/uptake of antibiotics and other molecules across the cell membrane in plant and animal cells as well as Gram-positive and Gram-negative bacteria. It has no antimicrobial or cytotoxic activity of its own, and is a safe candidate to decrease the drug dosage towards overcoming the issue of drug resistance and the other adverse effects in anti-infective and anticancer therapies. The bioenhancing concentration of glycyrrhizin ranges from 0.05 to 50% of the weight of the antibacterial compounds, 0.10 to 10% of the weight of the nutraceutical compounds and 0.25 to 20% of the weight of the antifungal agents. It increases the inhibitory effect on cell division of the anticancer drug `Taxol` (paclitxel®) by 5 times against the proliferation and multiplication of breast cancer cell line MCF-7. Glycyrrhizin is also known to boost (2-6 times) the transportation of antibiotics such as rifampicin, tetracycline, nalidixic acid, ampicillin and vitamins B1 and B12 through the intestinal membrane[14]. Genistein (5,7-Dihydroxy-3-(4-hydroxyphenyl) chrome-4- one) is a member of the isoflavone group of flavonoids. It is additionally well known as a plant-based estrogen. Since genistein was found to have the ability to block P-gp, BCRP and MRP2 efflux function, the absorption of paclitaxel, a substance that is transported out of the body by P-gp, BCRP and MRP2, was significantly increased when co-administered with genistein. The blocking of these transporters by genistein also contributed to the enhancement of the overall exposure of paclitaxel in the body. The presence of genistein (10 mg/kg) led to an increase in AUC (54.7%) and a decrease in the total plasma clearance (35.2%) after the oral administration of paclitaxel at a dose of 30 mg/kg in rats[13].

Future Perspective:

The idea of bioenhancing is considered extremely groundbreaking in the contemporary period. Despite the immense advantages of bio-enhancers for humanity, the task of discovering novel botanical bio-enhancers is still in its early stages. There are still numerous herbal bio-enhancers that need to be examined in various crucial domains. There is an extensive array of untapped plants that require investigation for their effectiveness in enhancing biological processes[15]. Certain aspects of bioenhancement still require further clarification and a strong emphasis on understanding their active components, mechanisms of action, clinical results, assessments of potential toxicities, and compatibility with other medications. This will enable us to discover new principles that possess potent bioenhancing capabilities while minimizing harmful side effects[8].

Conclusion: Bioenhancers encompass a groundbreaking, fresh idea as this creation is rooted in the age-old and traditional framework of Indian medicine. It is anticipated that the synergistic effect of bioenhancers will result in a decrease in the expense of treatment, toxicity, negative consequences, and will positively impact the economy of the country. Bioenhancers are discovered to be effortlessly grown, obtained, cost-effective, non-habit-forming, secure, efficacious, and possess a broad spectrum of uses[15]. Formulations containing organic bio-enhancers with improved bioavailability and effectiveness of active components unveil new opportunities in the pharmaceutical and healthcare industry. Decreased dosage and expenses, coupled with safety and effectiveness, are the distinctive selling points of these formulations. Currently, extensive research is being conducted on diverse categories of bioactives to enhance their bioenhancing potential, thereby enabling the introduction of superior pharmaceutical formulations in the market[14]. Biopotentiation through the use of naturally derived substances has greatly improved the availability of many drugs that are poorly absorbed when taken orally. Natural herbs such as Piper longum or nigrum, Zingiber officinale, Aloe barbedensis, Sinomenium acutum, *Glycyrrhiza glabra*, Moringa oleifera, Cuminum cyminum, Carum carvi, Allium sativum, Capsicum annum, Stevia rebaudiana, Ipomoea species, as well as juices from citrus and grapefruits, are included in this category[8].

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