Dean&Francis

ISSN 2959-409X

The Medicinal Value and Clinical Use of Isoliquiritin

Shicheng Zhao

Abstract:

Isoliquiritin has garnered increasing interest in recent years due to its promising therapeutic properties. It is kind a flavonoid compound derived from the roots and rhizomes of plants from a traditional Chinese medicine licorice. This plant belongs to Leguminosae Glycyrrhiza genus and were listed in the *Pharmacopoeia of the People's Republic of China*. Traditionally, the dry root and the rhizomes of *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat., or *Glycyrrhiza glabra* L. has been used for the extraction of isoliquiritin. The active compound, isoliquiritin, is now emerging as a key player in modern clinical research, attributed to its diverse pharmacological activities and potential clinical applications. Recent studies have illuminated isoliquiritin's multifaceted roles in modulating cellular processes and its potential benefits in treating a range of conditions. Its antioxidant and anti-inflammatory properties are particularly noteworthy, as they contribute to mitigating oxidative stress and inflammation—two underlying factors in many chronic diseases. Additionally, isoliquiritin's effects on several signal pathways of cells have led to exploration in the context of relative disorders, including cancer and neurodegenerative diseases. The growing body of evidence supporting isoliquiritin's efficacy prompts a reevaluation of its clinical potential and therapeutic viability. This paper aims to explore the current state of research on isoliquiritin, focusing on its pharmacokinetics, mechanisms of action, and clinical applications. By analyzing currently available data and assessing ongoing clinical trials, this review seeks to provide a comprehensive overview about the role of isoliquiritin in modern medicine and to identify the future directions about its research and application.

Keywords: Isoliquiritin, Pharmacological properties, Therapeutic applications

1. Introduction:

Glycyrrhizae Radix et Rhizoma, as a traditional Chinese medicinal herb, has been widely used in traditional Chinese medicine practice for thousands of years. In traditional pharmacy, roots and rhizomes of licorice is used to harmonize various medicines, relieve cough, clear heat and detoxify, reduce swelling and relieve pain. Its classic application prescriptions include "Gan Mai Da Zao Tang" in "*Jin Kui Yao Lue*" and "Zhi Gan Cao Tang" in "*Shang Han Lun*", fully reflecting its importance in traditional Chinese medicine treatment (Ye et al., 2022; Huang et al., 2022). In recent years, with the development of modern science and technology, research on the components of licorice has gradually deepened, revealing its complex pharmacological mechanisms and wide clinical application potential.

Three species of Glycyrrhiza genus, *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat., and *Glycyrrhiza glabra* L., are listed in *the Pharmacopoeia of the People's Republic of China* (Chinese Pharmacopoeia Commission., 2020.). Plant that from belongs to these three species is not only valued for its unique medicinal value, but its main active ingredients have also attracted widespread attention in modern pharmacological research. The main active medical components of licorice concentrated its dry roots and rhizomes, which include glycyrrhetinic acid, licorice flavonoids, and various other compounds, which have demonstrated significant pharmacological activities in various clinical and experimental studies, such as anti-inflammatory, antiviral, anti allergic, and hepatoprotective effects (Ye et al., 2022).

Isoliquiritin is one kind of chalcone type flavonoid glycoside that can be extracted from the roots and rhizomes of *G. uralensis*, *G. inflata*, and *G. glabra*. It specific structure includes a beta-D-glucopyranosyloxy group and two hydroxy groups (figure 1). The expanding body of research into isoliquiritin has highlighted its role in modulating multiple biological pathways, contributing to its potential as a therapeutic agent for a range of diseases. Studies have demonstrated that isoliquiritin can effectively reduce oxidative stress and inflammation (Liu et al., 2019; Miao et al., 2024). Additionally, studies on drug targets and animal models have shown that isoliquiritin has therapeutic effects in diseases such as cancer (Alibakhshi et al., 2023), neurodegenerative diseases (Wan et al., 2022), microbial infections (Akash et al., 2023), and osteoporosis (Su et al., 2024).

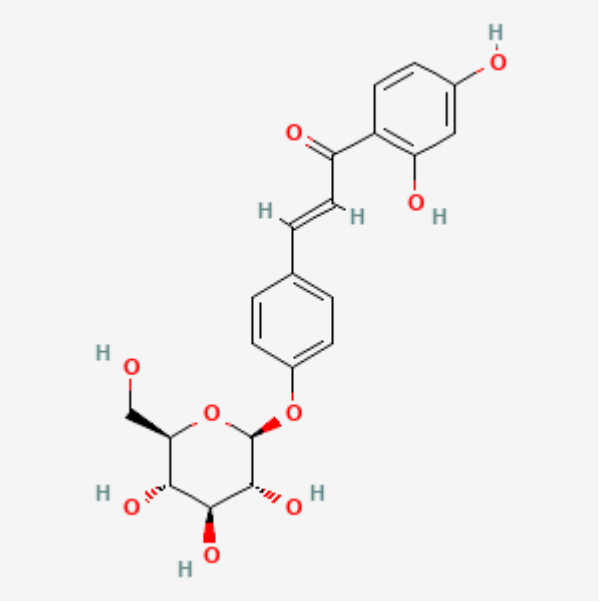

Figure 1: Structure of isoliquiritin (National Center for Biotechnology Information, 2024).

This review aims to provide a comprehensive overview of the modern pharmacological effects of isoliquiritin. By examining recent studies on its mechanism of action, therapeutic applications, and clinical efficacy, this paper seeks to elucidate the current understanding of isoliquiritin's role in contemporary medicine. Furthermore, it will explore the challenges and future directions for research, emphasizing the need for further investigation to fully realize the clinical potential of this versatile compound. Through this synthesis of current knowledge, we aim to offer insights into how isoliquiritin can be integrated into therapeutic strategies and highlight opportunities for future advancements in its clinical application.

2. Pharmacological Properties of Isoliquiritin

2.1 Absorption of Isoliquiritin

Licorice-related drugs are usually taken orally and can sometimes be used as topical medications to treat skin diseases. As kind of chalcone type flavonoid glycoside, isoliquiritin can pass through the epidermal cells by passive diffusion to reach its target. Papp of isoliquiritin in the bidirectional transport on Caco-2 shows significantly difference. The velocity of diffusion from basolateral to apical is $1.58\pm0.09\times10^{-6}$ cm/s, while that in the distinct direction is only $0.162\pm0.097\times10^{-6}$ cm/s (Dai, 2008). When using as a single component, isoliquiritin shows similar permeability (Papp) with other flavonoids in licorice. But when these ingredients are used together, Papp

ISSN 2959-409X

of isoliquiritin express an increased about 30% (figure 2) (Han et al., 2024).

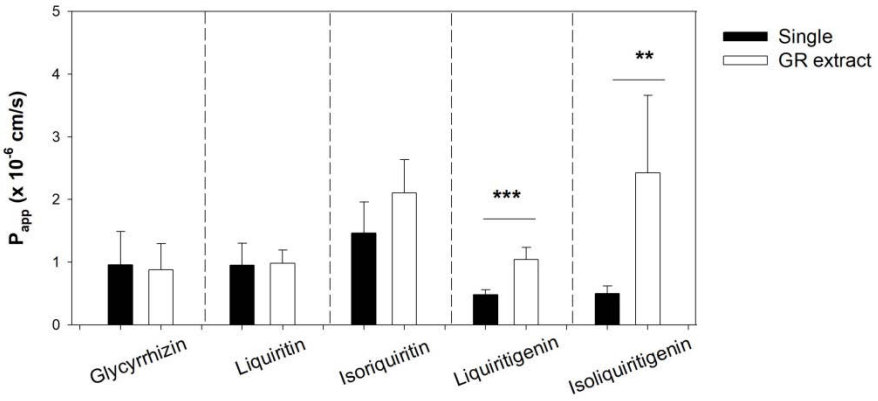

Figure 2: Papp of 5 licorice ingredients when them are used along or in GR extract; GR extract: glycyrrhizae radix extract (Han et al., 2024).

2.2 Distribution of Isoliquiritin

The maximum plasma concentration (C_{max}) of isoliquiritin is 18.47 ± 2.19 ng/mL. These values will be increased to 26.82 ± 8.50 ng/mL when isoliquiritin were used in the GR extract with other ingredients. 0.31 ± 0.13 hours is needed for the drug to reach the C_{max} (Han et al., 2024).

As isoliquiritin is insoluble in water, which means that it need other molecules as transporters to improve its distribution ability in human body (Selleckchem, 2024). The ability of passing through the blood brain barrier (BBB) is an important factor to evaluate a drug, especially those who show ability of treating neurological disorder and protecting nervous system. However, the poor lipid solubility of isoliquiritin renders it incapable of this ability (Shi et al., 2022; Dotiwala et al., 2024).

Hybrid membrane nanoparticles is one way to enhance the circulation ability of isoliquiritin in human body. The hybrid membrane (HM) was extracted under hypotention condition after fusing human glioma cells U251 with erythrocytes. And then isoliquiritin were encapsulated by HM to form HM-camouflaged isoliquiritin nanoparticles (ISL@HM NPs). HM allow the nanoparticles to have homologous targeting towards tumour cells. In the presence of ISL@HM NPs, cell viability of human foreskin fibroblasts (HFF) cells is more than 78%, while that of U251 cells declined to 38%. HM also improve the solubility of isoliquiritin. With concentration of isoliquiritin at 50 μg mL^{-1}, HM shows the best encapsulation rate of 55.63% (Shi et al., 2022).

2.3 Metabolism and Excretion of Isoliquiritin

The half-life of isoliquiritin is about 4.26 ± 3.94 hours as single component, and this value (4.68 ± 3.09 hours) does not change significantly when isoliquiritin is used in GR extract. The mean residence time (MRT) of single isoliquiritin 2.89 ± 0.73 hours, a litter shorter than that (3.07 ± 0.61 hours) in GR extract (Han et al., 2024).

Flavonoids compounds undergo will undergo phase I and phase II metabolism after absorption. Phase I metabolism occurred in liver, cytochromes like cytochrome 1A1, cytochrome 1A2, cytochrome 1B1, cytochrome 3A4, and cytochrome 2C9 are involved in the process. In Phase I metabolism, the flavonoids compounds are oxidised or *O*-demethylated. These minor metabolites undergo rapid glucuronidation, sulphation, or methylation in Phase II metabolism, by the effect of urine-5′-diphosphate glucuronosyltransferases (UGTs), sulphotransferases, and catechol-O-methyltransferases (COMTs) respectively. This make the flavonoids compounds become more polar and water soluble, which allow them to be excreted by kidney in the form of urine easier (Cassidy and Minihane, 2017). The detailed research on the metabolic process of isoliquiritin is insufficient, more research is needed on the role of intermediate products in metabolic processes.

3. Use of Isoliquiritin in the Treatment of Diseases

3.1 Use of Isoliquiritin in the Treatment of Cancer

3.1.1 Use of Isoliquiritin in the Treatment of Gastric Cancer

Four chemical compounds, including isoliquiritin, oleanolic acid, glycyrrhetinic acid and licochalcone A, that extracted from the root of *G. uralensis* shows its inhibitory ability in the growth of gastric cancer cell line SGC-7901. Flow cytometry with PI staining shows that the propor-

tion of cells undergo apoptosis was positively related to the concentration of the *G. uralensis* extract. Meanwhile, higher concentration of the Radix Glycyrrhizae extract also induce about 50% more (71.24±7.37% verses 47.43±6.54%) SGC-7901 cell cycle stay in the G0/G1 phase instead of the other two phases (Shi et al., 2014).

3.1.2 Use of Isoliquiritin in the Treatment of Breast Cancer

After treated human breast cancer cell lines MDA-MB-231 (CL-0150) and MCF-7 (CL-0149) with isoliquiritin, Fe^{2+} level shows an obviously enhancement, which indicate that it can induce ferroptosis. Ferroptosis is a new form of cell death that caused by iron-induced lipid peroxidation (Zhang et al., 2022). These results were verified by isoliquiritin administrated with ferroptosis activator, Erastin, or the ferroptosis inhibitor, Fer-1. When isoliquiritin was administrated, the level of Fe^{2+}, malondialdehyde (MDA), and reactive oxygen species (ROS) all shows obviously increase. This mechanism is related to the inhibition of NF-κB signaling pathway in MDA-MB-231 cells, which result in the regulation of oxidative stress, glycolysis, and inflammation (Wang et al., 2023).

Doxorubicin (Dox) is kind of traditional chemotherapy of breast cancer, it is the first choice for this disease. Dox is able to insert into the base pair of DNA. This can break down the DNA and inhibit the synthesis of both DNA and RNA. When Dox combined with iron, they can further limit the synthesis of DNA by free radical-mediated oxidative damaging (Johnson-Arbor and Dubey, 2024). There are chemoresistance exist in the use of Dox in breast cancer treatment. This can be reduced by the use of isoliquiritin, which obviously increase the apoptosis rate of both MDA-MB-231/Dox and MCF-7/Dox cells (Wang et al., 2023).

3.1.3 Use of Isoliquiritin in the Treatment of Colorectal Cancer

In the investigation of colorectal cancer, isoliquiritin extracted from *G. glabra* shows its anticancer ability by targeting the anticancer protein MAPK8. The analysis of molecular docking study results by PyMol and Discovery-Studio software shows that isoliquiritin can form a stable complex with the protein, 14 binding sites were discovered in the complex (Alibakhshi et al., 2023). MAPK8 also named JNK1, is part of the MAPK pathway. MAPK8 is responsible for the activation of flavonoid apigenin (API) and JunD gene, and the inhibition of nuclear factor of activated T-cells 2/4 (NFAT-2/4). This will lead to the apoptosis of cells (figure 3). MAPK8 also activates the p53 signaling pathway, which also induces apoptosis.

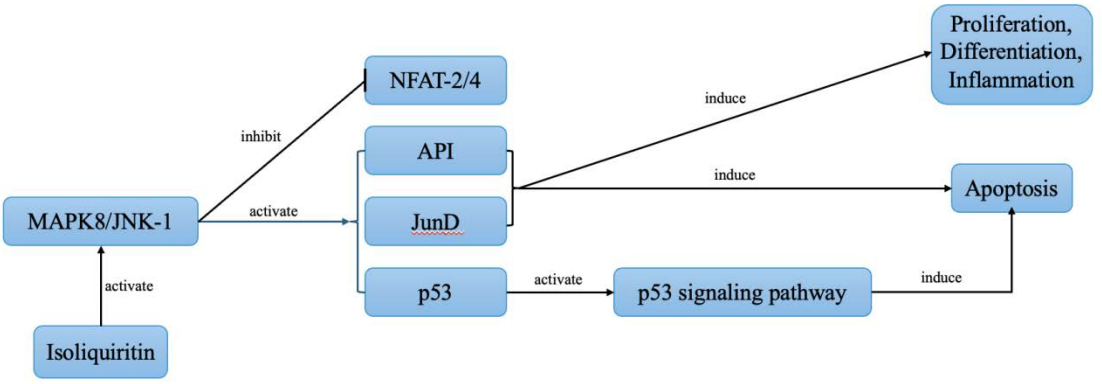

Figure 3: Part of the MAPK signaling pathway and the effect of isoliquiritin on this pathway and its downstream signaling pathways.

3.1.4 Use of Isoliquiritin in the Treatment of Lung Cancer

The combination of isoliquiritin with liquiritin and isoliquirigenin show their ability in the treatment of A549 non-small cell lung cancer. They achieve this effect by inducing apoptotic cell death through regulate the expression of multiple proteins and factors that related to cell survival in the cancer cells. The use of isoliquiritin, liquiritin, and isoliquiritigenin extract from *G. uralensis* significantly lower the cell viability of A549 cell in the lung cancer cell line. The leakage of lactate dehydrogenase (LDH) is often used as symbolize of necrosis of the cell. All *G. uralensis* extract with different solvent shows their effect on LDH leakage, and the ethyl acetate extract reaches the maximum value of about 55% (Zhou and Ho, 2014).

The activation of Bcl-2 family proteins is one of the anti-tumour mechanisms of isoliquiritin. The members of Bcl-2 family can be either inhibitors or inducers of the apoptosis process. Proteins like Bax promote the cell

ISSN 2959-409X

death through multiple process like the release of cytochrome c and caspase cascade reaction, while the other group of proteins like Bcl-2 binds with them to inhibit their effect (Hardwick and Soane, 2013). After treated with *G. uralensis* extract, the ratio between Bax and Bcl-2 shows significantly increase, which prove that the ingredients of *G. uralensis* can promote cell death through Bax/Bcl-2 pathway (Zhou and Ho, 2014).

The serine/threonine protein kinase Akt (protein kinase B/PKB) can inhibit apoptosis to induce cancer. The phosphorylation forms of PKB are able to mediate the cell survival and death by the process that included in the PI3K/AKT signaling pathway, and its interaction with JNK signaling pathways (Wang et al., 2012). PI3K regulate the phosphorylation of phosphatidylinositol-4,5-diphosphate ($PI(4,5)P_2$) to generate phosphatidylinositol-3,4,5-triphosphate ($PI(3,4,5)P_3$/PIP3). PIP3 is an second messenger on the plasma membrane that responsible for the activation of AKT. AKT is able to activate cAMP-response element binding protein (CREB), inhibitor of nuclear factor-κB (IκB) kinase (IKK), mouse double minute 2 homolog (MDM2), and inhibit BAD protein, caspases 9 (Casp9), retinoid X receptor alpha (RXRα), nuclear receptor 4A1 (NUR77). These factors are related to cell survival (figure 2). It has shown that the expression level of AKT falls to about 10-20% of the original value after the cancer cell treated with isoliquiritin. Meanwhile, isoliquiritin also up-regulate the expression of p21 and p53, and lowering that of MDM2. The expression of p53 start another signal pathway that initiate the apoptosis (Zhou and Ho, 2014).

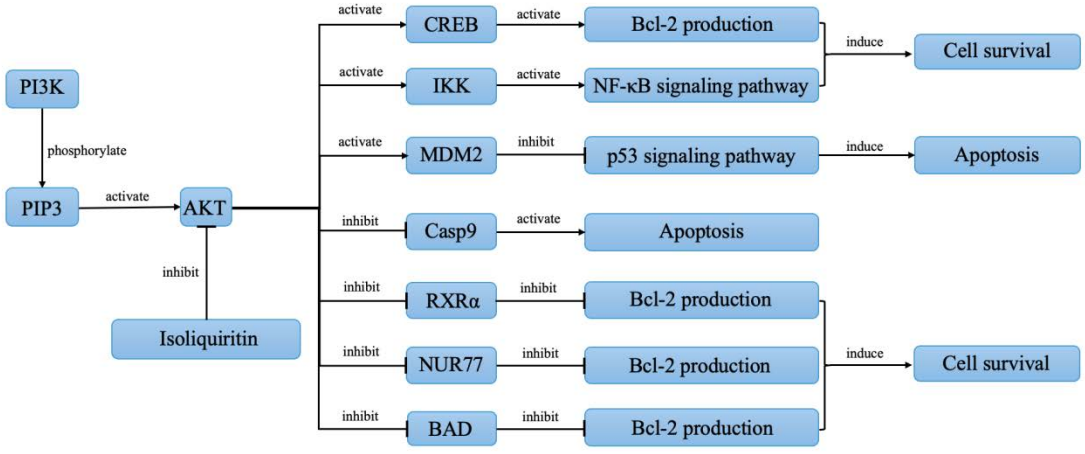

Figure 2: Part of the PIP3/AKT signaling pathway and the effect of isoliquiritin on this pathway and its downstream signaling pathways.

3.1.5 Use of Isoliquiritin as an Adjunct to Cisplatin for Cancer Chemotherapy

In cells under different contexts, isoliquiritin exhibits different role in apoptosis (Zhou et al, 2017). Cisplatin is kind of drug that widely used in chemotherapy for the treatment of solid tumors and hematologic malignancies. Cisplatin can form covalent bond with the purine base guanine and adenine with the DNA double strands, which is able to damage the DNA structure and induce apoptosis. Mechanism of cisplatin makes it more useful to those cells that undergo rapid division. So, it has a certain targeting ability towards cancer cells (Gold and Raja, 2024). However, the off target effect of cisplatin makes it bring cytotoxicity to multiple types of cell among various tissue. Isoliquiritin had been verified to have the ability to ameliorate cisplatin-induced injury, it reduced about half of the cells to apoptosis due to the presence of cisplatin. Isoliquiritin achieve this effect bu adjusting the level of related proteins. It significantly reduced the increasing level in Bax, cytochrome c, cleaved caspase-3, and cleaved caspase-3/casepase-3 in Mouse Proximal Tubular Cells (mPTCs) after platinum stimulation or corticosterone-treated PC12 cells, and 20 μmol L^{-1} is the concentration of isoliquiritin that exhibit the best protective effect (Zhou et al., 2017; Pei et al., 2022).

3.1.6 Use of Isoliquiritin in the Inhibition of Angiogenesis

Angiogenesis ability is one important characteristic of tumour cells. This allows them to form new vessels to bring more oxygen and nutrients to the tumour for the growth and division of the cells. Angiogenesis is also important for the cancer metastasis, as cancer cells can translocation to other region in human body through the new vessels formed (Nishida et al., 2006). Among all ingredients in the water extracts of licorice roots, isoliquiritin ranks second only to isoliquiritigenin in terms of its anti-tube formation

ability (Kobayashi et al, 1995).

3.2 Use of Isoliquiritin in the Treatment of Neurodegenerative Diseases

3.2.1 Use of Isoliquiritin in the Treatment of Depression

Serotonin (5-HT), norepinephrine (NE), and dopamine (DA) are three types of neurotransmitters, their absence was thought to be highly related to the cause of depression (Hasler, 2010). The results of Forced Swimming Test (FST) and Tail Suspension Test (TST) on mice indicated that the use of isoliquiritin significantly lower the immobility time of animals. Drug concentration at 20 mg/kg shows the greatest activity, which shorten the immobility time in FST and TST to about 48% and 38.8% respectively. According to the result of monoamine neurotransmitter concentrations analysis in the mouse hippocampus, hypothalamus, and cortex, amount of 5-HT and NE shows obviously increased by 1.31 (169.11 ng/g verses 129.4 ng/g) to 3.33 (341.4 ng/g verses 102.6 ng/g) times. This indicate that the production of 5-HT and NE will be the target of isoliquiritin (Wang et al., 2008).

Neuron damage due to NLRP3-mediated pyroptosis is another important pathological mechanism of depression. This mechanism is mediated by caspase-1. Inactive caspase-1 recruit NLRP3, and NLRP3 cleavage the procaspase-1 into active caspase-1. Caspase-1 responsible for the maturation of IL-18 and IL-1β that lead to inflammation, and the maturation of Gasdermin D (GSDMD) that can cause pyroptosis and the release of pro-inflammation cytokines. One kind of microRNAs, miRNA-27a can lower the expression of NLRP3 and the activity of NF-κB signaling pathway by inhibit the gene that encode spleen tyrosine kinase (SYK). (Wan et al., 2022). Isoliquiritin had been verified to have anti-depression effect by targeting the miRNA-27a. Isoliquiritin can strengthen this micorRNA to improve it inhibitory ability. After the administration of isoliquiritin, the symptoms like depression-like behaviour, inflammation response, and neuron pyroptosis are all reduced significantly (Li et al., 2021).

3.2.2 Use of Isoliquiritin in the Treatment of Other Neurodegenerative Diseases

The antioxidant effect and anti-neuroinflammatory activities of isoliquiritin indicates its potential in the treatment of neurodegenerative diseases, including Alzheimer's Disease (AD) and Parkinson's Disease (PD). In vitro test on rat adrenal pheochromocytoma PC12 cells had verified that isoliquiritin can protect neuron cells from 6-Hydroxydopamine (6-OHDA) and hydrogen peroxide (H_2O_2). It obviously lowers the rate of apoptosis induce by the dopaminergic neurotoxin or ROS (Wei et al., 2021). However, there is insufficient in vivo experimental evidence to support the therapeutic effect of isoliquiritin on neurodegenerative diseases. And due to the inability of isoliquiritin to cross the blood-brain barrier, it is difficult for the drug to reach its target and exert its effect. This limited the bioavailability of the drug.

3.3 Use of Isoliquiritin in the Treatment of Microorganism Infection

3.3.1 Use of Isoliquiritin in the Treatment of Helicobacter pylori (H. pylori) Infection

H. pylori is existed in the stomach of about half of global population (Grad et al., 2012). *H. pylori* is Gram-negative bacteria that can tolerant acidic environment, and it mainly infects the gastric mucosa of humans, leading to chronic gastritis. This is one of the main risk factors of developing gastric cancer (Malfertheiner et al., 2023). The extracts from *G. glabra* exhibit its ability as antiadhesive polymers. It reduced bacterial adhesion area by 30-40%, with concentration from 0.5 to 2 mg/mL respectively. The cytotoxic properties of the ingredients in the extract also allow them to inhibit the activity of *H. pylori* (Wittschier et al., 2009). the The molecular docking results shows that isoliquiritin have binding affinity of −8.0 kcal/mol with Lpp20 (HP1456) from *H. pylori* and −7.9 kcal/mol with *H. pylori* -carcinogenic TNF-alpha-inducing protein. This value is obviously higher than the controlled and standard mitomyosin (−6.3 kcal/mol and −7.0 kcal/mol, respectively), which indicated that isoliquiritin could more effectively inhibit the target protein. These two proteins are the target bacterial proteins responsible for gastric cancer, they enhance cell migration and lower the expression of E-cadherin (Akash et al., 2023).

3.3.2 Use of Isoliquiritin in the Treatment of Peronophythora litchi Chen Infection

P. litchi Chen is kind of fungus that mainly effect litchi (Litchi chinensis Sonn.), which is kind of fruit from Southeast Asia. Infection of the fungus will lead to litchi downy blight. Both pro-mature fruit, leaves, roots, and twigs of the infected plants will be damaged due to this disease. This brings serious problem to the production, storage, and transportation of litchi (Li et al., 2022). Isoliquiritin shows a dose-dependent inhibition on the activity of *P. litchi* Chen and other fungus that belongs to the same genus. The flavonoids compound can reach the EC50 of *P. litchi* Chen and *P. capsici* Leonian at a relatively low concentration (27.33 mg/L and 22.52 mg/L respectively). When the concentration of isoliquiritin over 500 mg/L, the activity of fungus will be completely

ISSN 2959-409X

inhibited. The relative electric conductivity test show that the membrane structure of *P. litchi* Chen is damaged after treated by isoliquiritin, and the amount of reducing sugar from *P. litchi* Chen is also decreased due to the existence of isoliquiritin. This indicate that isoliquiritin inhibit *P. litchi* Chen by damaging the cell structure of the fungi to kill it, and interrupt its metabolism to inhibit its growth (Luo et al., 2016).

3.3.3 Other Use of Isoliquiritin in the Treatment of Microorganisms

In traditional medicine, licorice extracts show their ability to inhibit many viruses, Gram-negative or Gram-positive bacterial. This includes Influenza A virus subtype H1N1, hepatitis B virus, candida albicans, and staphylococcus aureus (Ye et al., 2022).

Isoliquiritin can act as adjuvant medicine to treat microorganisms. NDM-1-positive Enterobacteriaceae can cause serious infection with a high death rate. The development of New Delhi metallo-β-lactamase-1 (NDM-1) allow the bacterium to become tolerance to the antibiotic carbapenems. In vitro test shows that isoliquiritin have inhibitory effect on NDM-1. The combination of isoliquiritin and carbapenems can kill NDM-1-positive strains within 18 hours, while their killing efficacy is limited when used alone (Wang et al., 2020).

3.4 Use of Isoliquiritin in the Treatment of Osteoporosis

Osteoporosis is kind of chronic bone disease. The pathological mechanisms of this disease include the decline in osteoblast ability and enhancement of osteoclast ability, which result in a decrease in bone density (NIAMS, n.d.). The results of isoliquiritin administration on C57BL/6 female mice provide evidence that isoliquiritin can stimuli the formation of bone and inhibit its resorption. The average immunofluorescence intensity observed increasing production of osteogenic protein, Runx2 and OPN, after treated the bone marrow mesenchymal stem cells (BMSCs) by isoliquiritin. This indicate that isoliquiritin can promote the osteogenic differentiation of the stem cells. Isoliquiritin achieve this effect by strengthen the MAPK signal pathway to activate BMSCs by binding with MAPK8 (Alibakhshi et al., 2023). Isoliquiritin also induce the autophagy of BMSCs to maintain the homeostasis of the bone. The level of autophagy markers LC3 increased after treated with isoliquiritin (Su et al., 2024).

3.5 Use of Isoliquiritin in the Wounds Healing

In zebra fish wound model, 100 μg/ml or 200 μg/ml isoliquiritin significantly accelerated the recovery speed of the wound. The size of the wound reduced reach the peak at the third day. The rate of angiogenesis in the two isoliquiritin administrated group is also obviously higher than that of the control groups (Liu et al., 2020). According to the test result of ISL-treated human umbilical vein endothelial cells (HUVECs), the wound healing ability of isoliquiritin came from the inhibition of tyrosine kinase inhibitor II (VRL) induced apoptosis. The inhibitors of specific proteins on the pathway have been used to verified the mechanism of isoliquiritin on angiogenesis. The results shows that vasculotropin receptor tyrosine kinase (VEGFR2), Phosphoinositide 3-kinase (PI3K), Raf kinase, and mitogen-activated protein kinase kinase (MEK) may involve in the pro-angiogenesis ability of isoliquiritin (Zhang et al., 2019).

4. Discussion

Isoliquiritin has shown excellent therapeutic effects in a wide range of different types of diseases. Interestingly, isoliquiritin achieves different therapeutic goals under different contexts through opposite mechanisms. In the treatment of cancer, isoliquiritin can promote the content of Bax protein to induce apoptosis (Zhou and Ho, 2014). In the treatment of neurodegenerative disease and the elimination of chemotherapy side effects, isoliquiritin exhibits the ability to reduce apoptosis by lowering the content of pro-apoptosis proteins like Bax (Zhou et al., 2017; Pei et al., 2022). Both phenomena are supported by in vitro experimental evidence, and some have in vivo experimental data. However, the reasons for these two opposing mechanisms of isoliquiritin are still unclear. More research is needed to determine whether environmental factors will affect isoliquiritin to activate one of the opposite mechanisms and which specific targets isoliquiritin binds to and generates these mechanisms.

Another opposite phenomenon caused by isoliquiritin is the inhibition or promotion of angiogenesis. One research verified that isoliquiritin can inhibit angiogenesis to prevent cancer metastasis (Kobayashi et al., 1995). However, in the wound healing model of zebrafish, isoliquiritin shows the pro-angiogenesis ability to promote recovery (Zhang et al., 2019; Liu et al., 2020). Considering that the research on the inhibitory effect of isoliquiritin on angiogenesis is based on a 1995 study, there are almost no subsequent experiments to explain or validate this mechanism. The reliability of this literature needs further evaluation. While the researches about the pro-angiogenesis ability of isoliquiritin have higher timeliness, and it points out a few possible targets. This makes they have a higher credibility.

Despite promising funding for the use of isoliquiritin in the treatment of multiple diseases, several limitations

need more research to overcome before using the drug clinically. The majority of studies concentrated on cell models or animal models. Although isoliquiritin did not demonstrate excessive cytotoxicity in experiments, sufficient clinical trials are needed to determine its safety and efficacy in humans and to fund supported data such as therapeutic window for medication guidance. Additionally, the characteristics of insolubility and inability to cross the blood-brain barrier of isoliquiritin limited its therapeutic potential, especially in neurological disorders like depression, AD, and PD (Shi et al., 2022; Dotiwala et al., 2024). Unable to reach the brain means unable to achieve its therapeutic function. However, the development of hybrid membrane-camouflaged isoliquiritin nanoparticles can act as one solution to this problem (Shi et al., 2022). Although this membrane only improves the solubility of isoliquiritin, it indicates that other supramolecular transporters could be designed to help it to pass through the blood brain barrier.

Isoliquiritin has demonstrated specific disease treatment capabilities and better absorption in drug mixing trials (Shi et al., 2014; Zhou and Ho, 2014; Han et al., 2024). This proves the existence of drug-drug interactions between these chemical components. Another research had verified the drug-protein interactions of isoliquiritin. Isoliquiritin is also able to interact with trypsin in the protein, which may lead to a decreased activity of the enzymes that are responsible for the metabolism of the drugs. This will result in an interference on the plasma concentration of the drug (Li et al., 2020). The interaction between drugs and other components is a complex process that is influenced by factors such as drug concentration and internal environment. More systematic research is needed on the interaction between isoliquiritin and other ingredients to maximize its efficacy and avoid adverse effects during use.

The use of isoliquiritin as the model for the design of a new drug is also a potential use of the drug due to its various medical functions. By adjusting its structure with the addition of new functional groups, isoliquiritin can have a new surface chemistry. In this case, both the delivery, affinity, and efficacy of the new drugs developed can be improved from isoliquiritin. New structures can be designed to fit specific targets in certain diseases, which can improve the affinity of the drugs. The introduction of hydrophilic functional groups into isoliquiritin by nanotechnology can increase the solubility of new drugs developed, improving their volume of distribution. Strong electron-withdrawing functional groups can enhance lipid solubility and drug action time, which gives isoliquiritin-derived new drugs the potential to pass the blood brain barrier to achieve their medical function (Mittal et al., 2022). The recent advancement of artificial intelligence and deep learning bring significant assistance to this process. More efficient and accurate toxicity prediction, structural design, drug activity identification, administration monitoring, and other capabilities enable artificial intelligence to highly accelerate and realize these prospects (Gupta et al., 2021).

5. Conclusion

Isoliquiritin has demonstrated extensive potential in clinical applications in recent years. Research has shown that isoliquiritin not only exhibits significant antioxidant, anti-inflammatory, and anti-tumor activities, but also demonstrates positive effects in the treatment of microbial infections and neurodegenerative diseases. However, despite the encouraging preliminary results, the clinical application of isoliquiritin still faces many challenges, such as improving bioavailability, describing specific mechanisms, and evaluating long-term safety. More researches are needed to clarify the mechanism of isoliquiritin, such as its targets and pathways of action in different diseases, and its interaction with other drugs and enzymes. Additionally, large-scale clinical trials are needed to explore the safety and effectiveness of its long-term use will be an important step in promoting the clinical application of isoliquiritin. Moreover, optimizing the administration method to improve its clinical efficacy will have a profound impact on its widespread application.

References

Akash, S., Bayıl, I., Mahmood, S., Mukerjee, N., Mili, T.A., Dhama, K., Rahman, M.A., Maitra, S., Mohany, M., Al-Rejaie, S.S., Ali, N., Semwal, P., Sharma, R., 2023. Mechanistic inhibition of gastric cancer-associated bacteria Helicobacter pylori by selected phytocompounds: A new cutting-edge computational approach. Heliyon 9, e20670. https://doi.org/10.1016/j.heliyon.2023.e20670

Alibakhshi, A., Malekzadeh, R., Hosseini, S.A., Yaghoobi, H., 2023. Investigation of the therapeutic role of native plant compounds against colorectal cancer based on system biology and virtual screening. Sci Rep 13, 11451. https://doi.org/10.1038/s41598-023-38134-5

Alsaadi, D.H.M., Raju, A., Kusakari, K., Karahan, F., Sekeroglu, N., Watanabe, T., 2020. Phytochemical Analysis and Habitat Suitability Mapping of Glycyrrhiza glabra L. Collected in the Hatay Region of Turkey. Molecules 25, 5529. https://doi.org/10.3390/molecules25235529

Cassidy, A., Minihane, A.-M., 2017. The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids. Am J Clin Nutr 105, 10–22. https://doi.org/10.3945/

ISSN 2959-409X

ajcn.116.136051

Chien, P.-S., Tseng, Y.-F., Hsu, Y.-C., Lai, Y.-K., Weng, S.-F., 2013. Frequency and pattern of Chinese herbal medicine prescriptions for urticaria in Taiwan during 2009: analysis of the national health insurance database. BMC Complement Altern Med 13, 209. https://doi.org/10.1186/1472-6882-13-209

Dai, J., Yang, J., Li, C., 2008. Transport and metabolism of flavonoids from Chinese herbal remedy Xiaochaihu-tang across human intestinal Caco-2 cell monolayers 1. Acta Pharmacologica Sinica 29, 1086–1093. https://doi.org/10.1111/j.1745-7254.2008.00850.x

Dotiwala, A.K., McCausland, C., Samra, N.S., 2024. Anatomy, Head and Neck: Blood Brain Barrier, in: StatPearls. StatPearls Publishing, Treasure Island (FL).

Gold, J.M., Raja, A., 2024. Cisplatin, in: StatPearls. StatPearls Publishing, Treasure Island (FL). https://www.ncbi.nlm.nih.gov/books/NBK547695/

Grad, Y.H., Lipsitch, M., Aiello, A.E., 2012. Secular trends in Helicobacter pylori seroprevalence in adults in the United States: evidence for sustained race/ethnic disparities. Am J Epidemiol 175, 54–59. https://doi.org/10.1093/aje/kwr288

Gupta, M., Sarwat, M., 2022. Protective effects of plant-derived natural products against hepatocellular carcinoma, in: Herbal Medicines. Elsevier, pp. 609–627. https://doi.org/10.1016/B978-0-323-90572-5.00009-3

Gupta, R., Srivastava, D., Sahu, M., Tiwari, S., Ambasta, R.K., Kumar, P., 2021. Artificial intelligence to deep learning: machine intelligence approach for drug discovery. Mol Divers 25, 1315–1360. https://doi.org/10.1007/s11030-021-10217-3

Han, Y.J., Song, K.-S., Song, I.-S., 2024. Beneficial Interaction between Isoliquiritigenin and Liquiritigenin in their Pharmacokinetics in Rats Following Oral Intake of Glycyrrhizae Radix Extract Compared with Oral Intake of an Individual Component. DTT 3, 39–50. https://doi.org/10.58502/DTT.23.0029

Hardwick, J.M., Soane, L., 2013. Multiple functions of BCL-2 family proteins. Cold Spring Harb Perspect Biol 5, a008722. https://doi.org/10.1101/cshperspect.a008722

Hasler, G., 2010. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiatry 9, 155–161. https://doi.org/10.1002/j.2051-5545.2010.tb00298.x

Johnson-Arbor, K., Dubey, R., 2024. Doxorubicin, in: StatPearls. StatPearls Publishing, Treasure Island (FL). https://www.ncbi.nlm.nih.gov/books/NBK459232/

Kobayashi, S., Miyamoto, T., Kimura, I., Kimura, M., 1995. Inhibitory effect of isoliquiritin, a compound in licorice root, on angiogenesis in vivo and tube formation in vitro. Biol Pharm Bull 18, 1382–1386. https://doi.org/10.1248/bpb.18.1382

Li, X., Peng, Y., Liu, H., Xu, Y., Wang, X., Zhang, C., Ma, X., 2020. Comparative studies on the interaction of nine flavonoids with trypsin. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 238, 118440. https://doi.org/10.1016/j.saa.2020.118440

Li, Y., Song, W., Tong, Y., Zhang, X., Zhao, J., Gao, X., Yong, J., Wang, H., 2021. Isoliquiritin ameliorates depression by suppressing NLRP3-mediated pyroptosis via miRNA-27a/SYK/NF-κB axis. J Neuroinflammation 18, 1. https://doi.org/10.1186/s12974-020-02040-8

Li, J., Wu, J., Lin, J., Li, C., Lu, H., Lin, C., 2022. Nondestructive Identification of Litchi Downy Blight at Different Stages Based on Spectroscopy Analysis. Agriculture 12, 402. https://doi.org/10.3390/agriculture12030402

Liu, Y.-Y., Wu, J.-Q., Fan, R.-Y., He, Z.-H., Li, C.-Y., He, M.-F., 2020. Isoliquiritin promote angiogenesis by recruiting macrophages to improve the healing of zebrafish wounds. Fish & Shellfish Immunology 100, 238–245. https://doi.org/10.1016/j.fsi.2020.02.071

Liu, Y., Xu, X., Xu, R., Zhang, S., 2019. Renoprotective Effects Of Isoliquiritin Against Cationic Bovine Serum Albumin-Induced Membranous Glomerulonephritis In Experimental Rat Model Through Its Anti-Oxidative And Anti-Inflammatory Properties. Drug Des Devel Ther 13, 3735–3751. https://doi.org/10.2147/DDDT.S213088

Luo, J., Li, Z., Wang, J., Weng, Q., Chen, S., Hu, M., 2016. Antifungal Activity of Isoliquiritin and Its Inhibitory Effect against Peronophythora litchi Chen through a Membrane Damage Mechanism. Molecules 21, 237. https://doi.org/10.3390/molecules21020237

Malfertheiner, P., Camargo, M.C., El-Omar, E., Liou, J.-M., Peek, R., Schulz, C., Smith, S.I., Suerbaum, S., 2023. Helicobacter pylori infection. Nat Rev Dis Primers 9, 19. https://doi.org/10.1038/s41572-023-00431-8

Miao, Z., Gu, M., Raza, F., Zafar, H., Huang, J., Yang, Y., Sulaiman, M., Yan, J., Xu, Y., 2024. Isoliquiritin Ameliorates Ulcerative Colitis in Rats through Caspase 3/HMGB1/TLR4 Dependent Signaling Pathway. Curr Gene Ther 24, 73–92. https://doi.org/10.2174/1566523223666230731115236

Mittal, K.R., Pharasi, N., Sarna, B., Singh, M., Rachana, null, Haider, S., Singh, S.K., Dua, K., Jha, S.K., Dey, A., Ojha, S., Mani, S., Jha, N.K., 2022. Nanotechnology-based drug delivery for the treatment of CNS disorders. Transl Neurosci 13, 527–546. https://doi.org/10.1515/tnsci-2022-0258

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), n.d.. Osteoporosis. https://www.niams.nih.gov/health-topics/osteoporosis

National Center for Biotechnology Information, 2024. PubChem Compound Summary for CID 5318591, Isoliquiritin. Retrieved August 18, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Isoliquiritin.

National Institute of Biomedical Imaging and Bioengineering (NIBIB), 2024. Ultrasound. https://www.nibib.nih.gov/science-education/science-topics/ultrasound

Nishida, N., Yano, H., Nishida, T., Kamura, T., Kojiro, M., 2006. Angiogenesis in cancer. Vascular Health and Risk Management

2, 213–219. https://doi.org/10.2147/vhrm.2006.2.3.213
PlantNet (n.d.) Glycyrrhiza glabra L. https://identify.plantnet.org/k-world-flora/species/Glycyrrhiza%20glabra%20L./data
Pastorino, G., Cornara, L., Soares, S., Rodrigues, F., Oliveira, M.B.P.P., 2018. Liquorice (Glycyrrhiza glabra): A phytochemical and pharmacological review. Phytother Res 32, 2323–2339. https://doi.org/10.1002/ptr.6178
Pei, Z., Wu, M., Yu, H., Long, G., Gui, Z., Li, X., Chen, H., Jia, Z., Xia, W., 2022. Isoliquiritin Ameliorates Cisplatin-Induced Renal Proximal Tubular Cell Injury by Antagonizing Apoptosis, Oxidative Stress and Inflammation. Front Med (Lausanne) 9, 873739. https://doi.org/10.3389/fmed.2022.873739
Shi, W., Cao, X., Liu, Q., Zhu, Q., Liu, K., Deng, T., Yu, Q., Deng, W., Yu, J., Wang, Q., Xu, X., 2022. Hybrid Membrane-Derived Nanoparticles for Isoliquiritin Enhanced Glioma Therapy. Pharmaceuticals (Basel) 15, 1059. https://doi.org/10.3390/ph15091059
Shi, X., Zou, M., He, J., Xie, H., Li, X., 2014. Studies on the identification of constituents in ethanol extract of Radix Glycyrrhizae and their anticancer activity. Afr J Tradit Complement Altern Med 11, 334–338. https://doi.org/10.4314/ajtcam.v11i2.18
Sosa, M.B., Chang, M.C.Y., 2024. Solving the mystery of enediyne biosynthesis. Nat Chem Biol. https://doi.org/10.1038/s41589-024-01686-2
Su, Z., Chen, D., Huang, J., Liang, Z., Ren, W., Zhang, Z., Jiang, Q., Luo, T., Guo, L., 2024. Isoliquiritin treatment of osteoporosis by promoting osteogenic differentiation and autophagy of bone marrow mesenchymal stem cells. Phytotherapy Research 38, 214–230. https://doi.org/10.1002/ptr.8032
Wan, T., Li, X., Fu, M., Gao, X., Li, P., Guo, W., 2022. NLRP3-Dependent Pyroptosis: A Candidate Therapeutic Target for Depression. Front. Cell. Neurosci. 16, 863426. https://doi.org/10.3389/fncel.2022.863426
Wang, G., Pan, J., Chen, S.-D., 2012. Kinases and kinase signaling pathways: Potential therapeutic targets in Parkinson's disease. Progress in Neurobiology 98, 207–221. https://doi.org/10.1016/j.pneurobio.2012.06.003
Wang, J., Li, Y., Zhang, J., Luo, C., 2023. Isoliquiritin modulates ferroptosis via NF-κB signaling inhibition and alleviates doxorubicin resistance in breast cancer. Immunopharmacol Immunotoxicol 45, 443–454. https://doi.org/10.1080/08923973.2023.2165943
Wang, W., Hu, X., Zhao, Z., Liu, P., Hu, Y., Zhou, J., Zhou, D., Wang, Z., Guo, D., Guo, H., 2008. Antidepressant-like effects of liquiritin and isoliquiritin from Glycyrrhiza uralensis in the forced swimming test and tail suspension test in mice. Prog Neuropsychopharmacol Biol Psychiatry 32, 1179–1184. https://doi.org/10.1016/j.pnpbp.2007.12.021
Wang, Y., Sun, X., Kong, F., Xia, L., Deng, X., Wang, D., Wang, J., 2020. Specific NDM-1 Inhibitor of Isoliquiritin Enhances the Activity of Meropenem against NDM-1-positive Enterobacteriaceae in vitro. Int J Environ Res Public Health 17, 2162. https://doi.org/10.3390/ijerph17062162
Wei, G., Da, H., Zhang, K., Zhang, J., Fang, J., Yang, Z., 2021. Glycoside Compounds From Glycyrrhiza uralensis and Their Neuroprotective Activities. Natural Product Communications 16, 1934578X2199298. https://doi.org/10.1177/1934578X21992988
Wittschier, N., Faller, G., Hensel, A., 2009. Aqueous extracts and polysaccharides from Liquorice roots (Glycyrrhiza glabra L.) inhibit adhesion of Helicobacter pylori to human gastric mucosa. Journal of Ethnopharmacology 125, 218–223. https://doi.org/10.1016/j.jep.2009.07.009
Yan, B., Hou, J., Li, W., Luo, L., Ye, M., Zhao, Z., Wang, W., 2023. A review on the plant resources of important medicinal licorice. J Ethnopharmacol 301, 115823. https://doi.org/10.1016/j.jep.2022.115823
Zhang, C., Liu, X., Jin, S., Chen, Y., Guo, R., 2022. Ferroptosis in cancer therapy: a novel approach to reversing drug resistance. Mol Cancer 21, 47. https://doi.org/10.1186/s12943-022-01530-y
Zhang, X.-H., Li, C.-Y., Lin, Q.-H., He, Z.-H., Feng, F., He, M.-F., 2019. Pro-angiogenic activity of isoliquiritin on HUVECs in vitro and zebrafish in vivo through Raf/MEK signaling pathway. Life Sciences 223, 128–136. https://doi.org/10.1016/j.lfs.2019.03.026
Zhou, Y., Ho, W.S., 2014. Combination of liquiritin, isoliquiritin and isoliquirigenin induce apoptotic cell death through upregulating p53 and p21 in the A549 non-small cell lung cancer cells. Oncology Reports 31, 298–304. https://doi.org/10.3892/or.2013.2849
Zhou, Y., Li, X., Gong, W., Tian, J., Gao, X., Gao, L., Zhang, X., Du, G., Qin, X., 2017. Protective effect of isoliquiritin against corticosterone-induced neurotoxicity in PC12 cells. Food Funct. 8, 1235–1244. https://doi.org/10.1039/C6FO01503D
华会明 , 娄红祥主编 ., 2022. 天然药物化学 , 8 ban. ed. 人民卫生出版社 , Beijing.
叶敏 , 秦路平主编 ., 2022. 生药学 , 8 ban. ed. 人民卫生出版社 , Beijing.
黄宝康主编 ., 2022. 药用植物学 , 8 ban. ed. 人民卫生出版社 , Beijing.
国家药典委员会编 ., 2020. 中华人民共和国药典 , 2020 年版 , Di 1 ban. ed. 中国医药科技出版社 , Beijing Shi.