IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

SAFETY AND TOXICITY OF LICORICE IN CARDIOVASCULAR TREATMENT

[1]Yash.R.Kawale, [2]Akanksha.D.Chaudhari, [3]Karina.A.Ade, [4]Satyam.T.Shinde, [5]Amruta.A.Ade
Designation: Final year student of B-Pharm
Ishwar Deshmukh Institute of Pharmacy, Digras, Maharashtra

Abstract:

Because of its lipid-modulating, antioxidant, and anti-inflammatory qualities, licorice (Glycyrrhiza glabra), a popular medicinal herb, has shown promise for cardiovascular health. These therapeutic actions are caused by the bioactive molecule glycyrrhizin, which mainly modifies inflammatory pathways and lowers oxidative stress. Nevertheless, glycyrrhizin also inhibits 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which results in mineralocorticoid effects brought on by cortisol, including fluid retention, hypokalemia, and hypertension, which is referred to as pseudoaldosteronism. Adverse cardiovascular events, such as arrhythmias, heart failure aggravation, and severe electrolyte imbalances, have been associated with chronic or excessive licorice use. Although regulatory agencies such as the European Food Safety Authority (EFSA) advise against consuming more than 100 mg of glycyrrhizin per day, unregulated products that include licorice continue to be a major cause of toxicity .

A safer substitute that maintains therapeutic efficacy without having notable mineralocorticoid side effects is deglycyrrhizinated licorice (DGL).With a focus on its therapeutic potential, toxicity causes, clinical consequences, and safe usage techniques, this paper assesses licorice's dual role in cardiovascular therapy. In order to optimize benefits while reducing hazards, future research should concentrate on figuring out the best dosages, investigating safer formulations, and creating customized guidelines.

Ketwords: pseudoaldosteronism, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), deglycyrrhizinated licorice (DGL).

Overview

Licorice is an herb that grows in parts of Europe and Asia. Licorice root contains glycyrrhizin, which can cause side effects when eaten in large amounts.

The chemicals in licorice are thought to decrease swelling, decrease cough, and increase the chemicals in our body that heal ulcers. Many "licorice" products made in the U.S. actually don't contain licorice. They contain anise oil, which has the smell and taste of "black licorice".

Licorice is used for eczema, swelling of the liver, mouth sores, and many other conditions, but there is no good scientific evidence to support most of these uses. There is also no good evidence to support using licorice for COVID-19.

Fig 1. Diagrammatic Representation of Normal Licorice Plant.

Introduction:

Because of its anti-inflammatory, antioxidant, and antiviral qualities, licorice (Glycyrrhiza glabra) has been used for ages in traditional medicine, especially in Asia, the Middle East, and Europe. Glycyrrhizin, the active ingredient in licorice, is a triterpenoid saponin that gives it its pharmacological properties. Researchers have looked at the possible advantages of licorice and its derivatives in the treatment of cardiovascular disorders, namely in the areas of lipid metabolism, oxidative stress reduction, and inflammation attenuation.

Although licorice may have therapeutic benefits, excessive ingestion has been linked to serious side effects, mainly because glycyrrhizin inhibits the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). Pseudoaldosteronism, which is caused by this inhibition, is typified by increased blood pressure, potassium excretion, and retention of water and salt .These side effects have sparked questions regarding licorice's safety, especially for people who already have heart or kidney problems.

Severe hypertension, hypokalemia, and potentially fatal arrhythmias including torsades de pointes and QT prolongation have all been reported as side effects of licorice poisoning. Chronic use of licorice-containing items, such as herbal teas, dietary supplements, and confections, usually results in these dose-dependent adverse effects .

A thorough analysis of licorice's safety and toxicity profile is crucial, especially in light of its extensive usage in traditional medicine and the growing interest in its potential cardiovascular benefits. The purpose of this review is to assess the advantages and disadvantages of licorice in the treatment of cardiovascular disease, offering information on its modes of action, side effects, and safe usage guidelines.

Objective:

1. Examine the pharmacological characteristics of licorice, including the mechanisms of action of its bioactive components, especially glycyrrhizin, in relation to cardiovascular health.

2. To evaluate licorice's potential as a treatment for cardiovascular conditions: Examine preclinical and clinical research on the effects of licorice on blood pressure control, lipid metabolism, and anti-inflammatory reactions in cardiovascular diseases.

3. To review the toxicity and negative effects of licorice consumption: Examine glycyrrhizin's dose-dependent hazards, paying special attention to how it might cause arrhythmias, hypertension, hypokalemia, and Pseudoaldosteronism.

4. To investigate other licorice varieties, like deglycyrrhizinated licorice (DGL): Examine whether DGL can minimize the risks of toxicity while maintaining the therapeutic benefits of licorice.

Therapeutic Uses in the Management of Cardiovascular Disease:

Because of its anti-inflammatory and antioxidant properties, licorice has been studied for its ability to enhance cardiovascular health. According to studies, licorice may improve endothelial function, lower inflammation, and lessen lipid peroxidation, all of which could lead to better cardiovascular outcomes .Licorice extract decreased cholesterol and prevented the development of atherosclerotic plaque in animal experiments .Furthermore, by lowering oxidative stress, its flavonoids have been demonstrated to guard against cardiac ischemia-reperfusion injury.

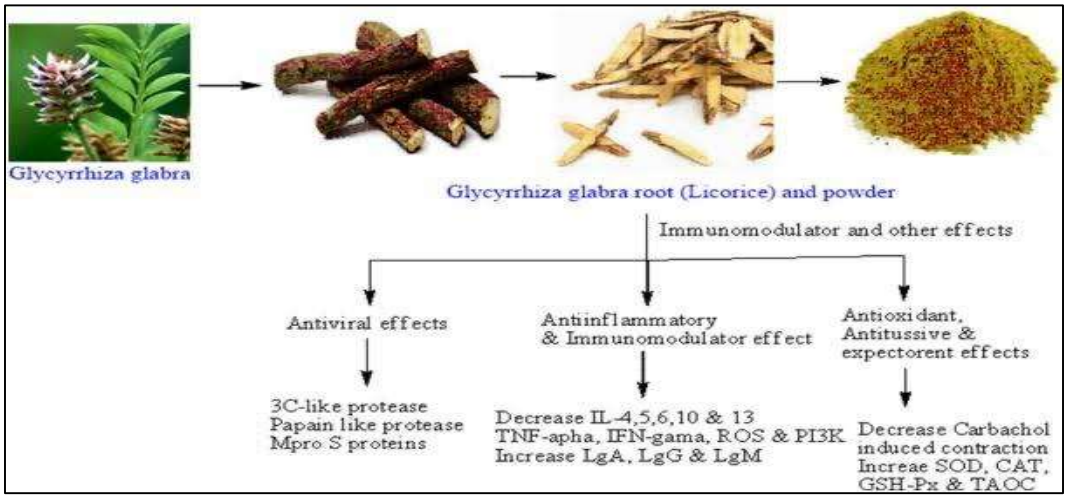

Fig 2. Diagrammatic Representation of Pharmacological Uses of Licorice.

❖ **Adverse Effect and Toxicology :**

Despite its possible advantages, licorice raises serious safety issues, especially with regard to cardiovascular health. Chronic licorice use is linked to pseudoaldosteronism, which manifests as arrhythmias, hypokalemia, and hypertension .Consuming licorice increased blood pressure by an average of 6.6 mmHg in the systolic and 3.9 mmHg in the diastolic, according to a meta-analysis . Muscle weakness, exhaustion, and arrhythmias, such as QT prolongation and torsades de pointes, might result from hypokalemia brought on by glycyrrhizin-induced potassium excretion .

1. Hypertension and pseudoaldosteronism:

Long-term licorice use inhibited 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which raised cortisol levels and caused potassium excretion, salt retention, and cortisol activity to rise. This process led to pseudoaldosteronism, which was typified by hypokalemia and hypertension .

Cardiac Arrhythmias:

Torsades de pointes and QT prolongation have been associated with excessive glycyrrhizin intake. Several examples of severe arrhythmias brought on by licorice ingestion were found in a systematic study, especially in individuals who already had cardiovascular disease .

2. Dependent on Dosage Toxicity:

Licorice has very dose-dependent effects. Significant side effects, including cardiac arrest, have been linked to glycyrrhizin consumption in doses greater than 100 mg per day .

❖ **Mechanism of Toxicity :**

Glycyrrhizin, the active ingredient in licorice (Glycyrrhiza glabra), interacts with the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) to produce serious side effects.
Cortisone, the inactive form of cortisol, is produced by this enzyme. Because glycyrrhizin inhibits 11β-HSD2, elevated cortisol levels mimic the actions of aldosterone, causing water retention, potassium excretion, and salt retention . The disorder known as pseudoaldosteronism, which presents as edema, hypokalemia, and hypertension, is caused by this process.

Toxic Effects In Cardiovascular Health:

1. Hypokalemia and Hypertension: Long-term licorice use is linked to dose-dependent elevations in blood pressure. Consuming licorice increased systolic blood pressure by an average of 6.6 mmHg and diastolic blood pressure by 3.9 mmHg, according to a meta-analysis.Muscle weakness, exhaustion, and cardiac arrhythmias, including potentially fatal conditions like torsades de pointes, can result from hypokalemia brought on by excessive potassium loss .
2. Arrhythmias: Prolonged QT intervals, ventricular arrhythmias, and sudden cardiac death have all been linked to glycyrrhizin-

induced hypokalemia. Patients who consume significant amounts of items containing licorice have been reported to experience severe arrhythmias .

3. Edema and Volume excess: Glycyrrhizin-induced sodium and water retention can worsen heart failure and other diseases by causing fluid excess.

4.Dependent on Dosage Toxicity:

Licorice has very dose-dependent effects. Significant side effects, including cardiac arrest, have been linked to glycyrrhizin consumption in doses greater than 100 mg per day .

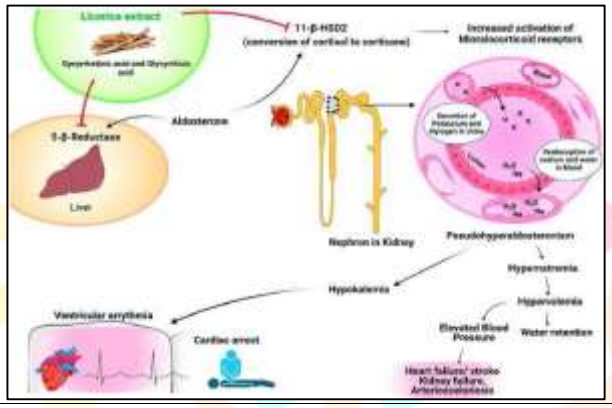

Fig 3. Diagrammatic Representation of Mechanism Of Action Of Licorice Toxicity.

Risk Factors and Toxic Doses:

To reduce toxicity risks, the European Food Safety Authority (EFSA) advises consuming no more than 100 mg of glycyrrhizin per day . However, individual characteristics including age, pre-existing cardiovascular problems, and concurrent use of drugs like corticosteroids or diuretics may affect toxicity thresholds.

Clinical Proof of Toxicology:

Numerous clinical investigations and case reports demonstrate licorice's dose-dependent toxicity. For instance, patients with underlying cardiovascular illness have experienced
life-threatening arrhythmias and cardiac arrest as a result of consuming herbal supplements or confections containing licorice in excess. To reduce toxicity hazards, the European Food Safety Authority (EFSA) advises consuming no more than 100 mg of glycyrrhizin per day

1) Case Reports:

After drinking licorice tea every day for two weeks, a 54-year-old male experienced severe hypokalemia and arrhythmias.

2) Population Studies:

People with hypertension who regularly eat licorice have higher blood pressure and a higher risk of cardiovascular events.

Deglycyrrhizinated licorice (DGL) :

DGL was created by eliminating glycyrrhizin while keeping other advantageous substances in order to lessen toxicity. Particularly in gastrointestinal disorders, DGL has demonstrated promise in offering therapeutic advantages without the negative side effects linked to glycyrrhizin; its possible application in cardiovascular health also merits more research.

Safety Of DGL:

Deglycyrrhizinated Licorice (DGL) Safety By eliminating glycyrrhizin while keeping other beneficial substances, deglycyrrhizinated licorice (DGL) provides a safer substitute. DGL may be used therapeutically because it has shown anti-inflammatory and antioxidant properties without producing pseudoaldosteronism . Its effectiveness in cardiovascular applications is still being studied, albeit.

Efficacy Of DGL:

1. Less Toxicity:

DGL, which is devoid of glycyrrhizin, maintains the majority of licorice's medicinal benefits, such as its anti-inflammatory and antioxidant qualities, without producing pseudoaldosteronism. DGL may be a safer substitute for long-term use, according to studies.

2. Limited Cardiovascular Data:

Although DGL has demonstrated effectiveness in treating gastrointestinal disorders, more clinical research is necessary before it may be used to treat cardiovascular diseases.

Knowledge Gaps and Upcoming Studies:

There are still a lot of unanswered questions about the safe use of licorice in the treatment of cardiovascular disease, despite its well-established pharmacological profile. Future studies should concentrate on determining acceptable dosages, investigating the glycyrrhizin toxicity pathways, and assessing DGL's long-term safety in human populations.

Glycyrrhizin's pharmacokinetic properties:

After being absorbed in the intestines, intestinal bacteria hydrolyze glycyrrhizin to glycyrrhetinic acid (GA). The active metabolite GA is in charge of blocking 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which results in mineralocorticoid effects brought on by cortisol. Due to variations in gut flora, glycyrrhizin's absorption varies greatly between people, making dosage recommendations even more challenging.

Pharmaceutical Interactions Licorice :

Increase the risk of hypokalemia and arrhythmias by intensifying the effects of drugs that affect potassium levels, such as corticosteroids and diuretics. Additionally, it may change the efficiency of anticoagulants such warfarin by interfering with them.

Populations at Risk Pregnant Women:

Preterm labor, hypertension, and possible neurological consequences in the fetus have all been linked to licorice use during pregnancy. Elderly People: Glycyrrhizin's actions put older persons with compromised renal function at greater risk for electrolyte imbalances and hypertension. Patients with Pre-existing Conditions: Individuals who have kidney problems, cardiovascular diseases, or adrenal insufficiency are more vulnerable to the negative effects of licorice.

International Regulatory Standards:

Glycyrrhizin has been categorized by the World Health Organization (WHO) as "possibly unsafe" when used in significant amounts over an extended length of time. Food safety agencies of the European Union advise that goods containing licorice should clearly disclose their glycyrrhizin content and potential hazards.

New Research:

Recent research is looking into how licorice affects gut flora, which could have an indirect impact on cardiovascular health. Nevertheless, additional information is required to validate these effects. In order to better understand individual sensitivity to licorice toxicity, genetic studies are investigating polymorphisms in genes linked to cortisol metabolism (e.g., HSD11B2).

Alternative Uses for Medicine:

In addition to cardiovascular health, licorice has been researched for its hepatoprotective, antiviral, and anti-ulcer effects. Nevertheless, these uses frequently necessitate weighing the advantages against any possible negative consequences. Although DGL has a limited function in cardiovascular therapy, it is still a safer choice for non-cardiovascular applications, especially the treatment of gastrointestinal diseases.

T**oxicity Dependent on Dosage Low Doses:**

Most people can safely consume tiny doses of licorice (less than 100 mg/day glycyrrhizin), which can have anti-inflammatory and antioxidant effects. Moderate to High Doses: The risk of pseudoaldosteronism, hypokalemia, and high blood pressure is increased by daily ingestion of more than 200–600 mg of glycyrrhizin. Cases of Severe Toxicity: Extended use of high-dose licorice products has been linked to acute cardiac events, such as ventricular arrhythmias and myocardial infarction .

Pseudoaldosteronism Pathophysiology:

Because glycyrrhizin inhibits 11β-HSD2, mineralocorticoid receptors are activated by cortisol. This process results in: Water and sodium retention raise blood volume and cause hypertension. loss of potassium, which raises the risk of cardiac arrhythmias and causes hypokalemia. renin-angiotensin-aldosterone system suppression, which makes fluid and electrolyte balance even more difficult.

Comparative Study Of Licorice derivatives:

Glycyrrhizin is present in whole licorice extracts, which are linked to an increased risk of toxicity. Glycyrrhizin is absent from deglycyrrhizinated licorice (DGL), which lowers toxicity while maintaining its antioxidant and anti-inflammatory qualities. Nevertheless, nothing is known about DGL's cardiovascular effectiveness. Licorice Flavonoids: New research indicates that licorice fractions high in flavonoids may have cardiovascular advantages without posing a serious risk.

Advantages and of Cardiovascular Disease Benefits:

1. Anti-inflammatory and Antioxidant Effects:

Glycyrrhizin and its metabolites are responsible for the notable anti-inflammatory and antioxidant qualities of licorice. These substances lessen pro-inflammatory cytokines and oxidative stress, two important elements in the etiology of cardiovascular disorders. Licorice extracts decreased oxidative stress indicators and enhanced endothelial function, according to studies conducted on animal models.

2. Improvement of Lipid Profile:

Preclinical research showed that licorice flavonoids could raise HDL cholesterol levels while lowering LDL and triglycerides . Licorice administration significantly decreased total cholesterol and LDL levels in a clinical investigation including patients with hyperlipidemia.

3. Anti-Atherosclerotic Effects:

By preventing lipid peroxidation and lowering inflammation in the arterial walls, licorice extract decreased the development of atherosclerotic plaque in animal models.

Certain Product's Toxicity Candies and Drinks:

High concentrations of glycyrrhizin found in licorice-flavored candies and beverages can cause poisoning in unwary consumers. Herbal Supplements: Glycyrrhizin content may not always be disclosed by supplements that are advertised for their detoxifying or anti-inflammatory qualities, which raises the risk of poisoning.

Clinical Recommendations and Guidelines Nutritional Limitations:

Licorice, especially products with an unknown glycyrrhizin content, should be avoided or consumed in moderation by patients with cardiovascular disorders. Parameters for Monitoring: People who consume licorice or products containing licorice should have their blood pressure, potassium levels, and ECG changes regularly monitored. Patient Education: It is important to inform consumers about the possible dangers associated with licorice, particularly when taken with drugs such as ACE inhibitors or diuretics.

New Treatments:

Scientists are looking into artificial glycyrrhizin derivatives that lessen toxicity while maintaining its medicinal benefits. These substances might provide safer alternatives for the management of heart conditions. To lessen licorice-induced pseudoaldosteronism in people with hereditary predispositions, gene-targeted treatments are being investigated.

Public Health Concerns:

Bodies find it difficult to strike a balance between licorice's medicinal potential and public safety due to its extensive use in food and traditional medicine. To educate the public on the dangers of excessive consumption, especially for vulnerable groups like the elderly and expectant mothers, awareness programs are crucial.

Historical Use of Licorice:

Licorice incorporates a long history of utilize in conventional Chinese, Ayurvedic, and
Greco-Arab pharmaceutical frameworks. Verifiably, it was endorsed as an anti-inflammatory, demulcent, and expectorant. The "sweet root," because it is commonly called, picked up acknowledgment not as it were for its therapeutic applications but too for it utilize as a flavoring specialist in nourishments and refreshments.

Bioactive Components and Pharmacology

The pharmacological impacts of licorice are fundamentally ascribed to its auxiliary metabolites, counting:

- **Glycyrrhizin:**

A triterpenoid saponin dependable for licorice's sweet taste and its most broadly examined bioactive compound.

- **Flavonoids:**

Compounds such as liquiritigenin and isoliquiritigenin, which contribute to its anti-inflammatory and antioxidant properties.

- **Polysaccharides:**

These components exhibit immunomodulatory impacts.

Glycyrrhizin metabolizes into glycyrrhetinic corrosive within the intestine, which restrains
11β-hydroxysteroid dehydrogenase sort 2 (11β-HSD2). This restraint disturbs cortisol digestion system, driving to mineralocorticoid-like impacts such as sodium maintenance, potassium excretion, and increased blood weight.

Cardiovascular Applications of Licorice:

Later thinks about recommend that licorice may advantage cardiovascular wellbeing through the taking after instruments:

1. Anti-inflammatory Impacts:

Unremitting aggravation plays a key part in atherosclerosis and other cardiovascular infections. Licorice decreases the generation of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor corruption factor-alpha (TNF-α).

2. Antioxidant Properties:

Oxidative push may be a major supporter to endothelial brokenness and cardiovascular illnesses. Flavonoids in licorice rummage free radicals and diminish oxidative harm .

3. Lipid-Modulating Impacts:

Glycyrrhizin and its metabolites have been appeared to lower add up to cholesterol and triglyceride levels in test ponders.

Security and Harmfulness Concerns:

In spite of its restorative potential, licorice postures noteworthy security dangers when expended in abundance. Glycyrrhizin-induced pseudoaldosteronism can result in hypertension, hypokalemia, and liquid maintenance, expanding the chance of cardiovascular complications such as arrhythmias and heart disappointment. These impacts are dose-dependent, with constant utilization of more than 100 mg/day glycyrrhizin related with unfavorable results.

Administrative and Open Wellbeing Challenges:

Administrative bodies, counting the European Nourishment Security Specialist (EFSA) and the
U.S. Nourishment and Medicate Organization (FDA), have issued notices around the overconsumption of licorice, especially in unregulated items like home grown supplements, candies, and refreshments. Open mindfulness campaigns are required to teach customers around the dangers related with licorice, particularly among powerless populaces such as pregnant ladies, the elderly, and people with pre-existing cardiovascular or renal conditions.

Licorice's Mode of Action in the Treatment of Heart Disease:

Glycyrrhizin, glycyrrhetinic acid, and flavonoids are among the bioactive substances that provide licorice (Glycyrrhiza glabra) its numerous pharmacological effects on the circulatory system.
These substances assist the cardiovascular system by interacting with different biological pathways.
An outline of the mechanisms is provided below:

1. Inhibition of Inflammation In cardiovascular illnesses, chronic inflammation is important, especially in the development of atherosclerosis. Pro-inflammatory cytokines like interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) are suppressed by glycyrrhizin. Additionally, it suppresses nuclear factor-kappa B (NF-κB), a transcription factor that plays a crucial role in inflammation. Flavonoids: Lessen vascular inflammation by reducing leukocyte adherence and infiltration.

2. The Activity of Antioxidants Cardiovascular disorders and endothelial dysfunction are significantly influenced by oxidative stress. Reactive oxygen species (ROS) scavenging: Licorice's flavonoids counteract free radicals and lessen endothelial cell oxidative damage. Improvement of Antioxidant Enzymes: Substances such as isoliquiritigenin raise the activity of antioxidant enzymes including glutathione peroxidase (GPx) and superoxide dismutase (SOD).

3. Effects of Lipid Modulation A significant risk factor for cardiovascular disorders is dyslipidemia, which is defined by increased triglycerides and cholesterol. LDL Cholesterol Reduction: Glycyrrhizin and flavonoids lower LDL cholesterol and stop it from oxidizing, which is a sign of atherosclerosis. Enhancement of Lipid Profiles: Research indicates that licorice extracts raise levels of high-density lipoprotein (HDL) while lowering triglycerides and total cholesterol.

4. Effects on Vasoprotection Because of its effects on vascular smooth muscle and endothelial cells, licorice improves vascular health. Enhancement of Endothelial Activity: By encouraging the synthesis of nitric oxide (NO), glycyrrhizin improves vasodilation and lowers blood pressure
. Stopping the Growth of Smooth Muscles: Flavonoids lower the risk of arterial thickening and stenosis by inhibiting the development of vascular smooth muscle cells.

5. Mineralocorticoid Activity Regulation Because licorice can mimic the effects of aldosterone, it can have both positive and negative effects on cardiovascular health. Elevenβ-Hydroxysteroid Dehydrogenase Type 2 Inhibition: This enzyme is inhibited by glycyrrhetinic acid, which raises cortisol activity at mineralocorticoid receptors. Blood pressure management may be impacted by this action, which can increase potassium excretion and sodium retention. Possible Risk of High Blood Pressure: Overindulging in licorice can result in pseudoaldosteronism, which is typified by low potassium levels, hypertension, and fluid retention.

6. Antithrombotic and Antiplatelet Actions Liquiritigenin and other flavonoids inhibit platelet aggregation, which lowers the risk of thrombosis. Prevention of Thrombus Formation: By regulating fibrinogen levels, licorice chemicals help to keep blood arteries from clotting.

7. Cardioprotective Impacts Mitigation of Myocardial Damage: By lowering oxidative stress and apoptosis in heart cells, licorice flavonoids guard against ischemia-reperfusion injury. Enhancement of Cardiac Function: In animal models of heart failure, glycyrrhizin reduces ventricular remodeling and increases cardiac output.

Effects of Lipid Modulation A significant risk factor for cardiovascular disorders is dyslipidemia, which is defined by increased triglycerides and cholesterol. LDL Cholesterol Reduction: Glycyrrhizin and flavonoids lower LDL cholesterol and stop it from oxidizing, which is a sign of atherosclerosis. Enhancement of Lipid Profiles: Research indicates that licorice extracts raise levels of high-density lipoprotein (HDL) while lowering triglycerides and total cholesterol.

1. Effects on Vasoprotection Because of its effects on vascular smooth muscle and endothelial cells, licorice improves vascular health. Enhancement of Endothelial Activity: By encouraging the synthesis of nitric oxide (NO), glycyrrhizin improves vasodilation and lowers blood pressure
. Stopping the Growth of Smooth Muscles: Flavonoids lower the risk of arterial thickening and stenosis by inhibiting the development of vascular smooth muscle cells.

2. Mineralocorticoid Activity Regulation Because licorice can mimic the effects of aldosterone, it can have both positive and negative effects on cardiovascular health. Elevenβ-Hydroxysteroid Dehydrogenase Type 2 Inhibition: This enzyme is inhibited by glycyrrhetinic acid, which raises cortisol activity at mineralocorticoid receptors. Blood pressure management may be impacted by this action, which can increase potassium excretion and sodium retention. Possible Risk of High Blood Pressure: Overindulging in licorice can result in pseudoaldosteronism, which is typified by low potassium levels, hypertension, and fluid retention.

3. Antithrombotic and Antiplatelet Actions Liquiritigenin and other flavonoids inhibit platelet aggregation, which lowers the risk of thrombosis. Prevention of Thrombus Formation: By regulating fibrinogen levels, licorice chemicals help to keep blood arteries from clotting.

4. Cardioprotective Impacts Mitigation of Myocardial Damage: By lowering oxidative stress and apoptosis in heart cells, licorice flavonoids guard against ischemia-reperfusion injury. Enhancement of Cardiac Function: In animal models of heart failure, glycyrrhizin reduces ventricular remodeling and increases cardiac output.

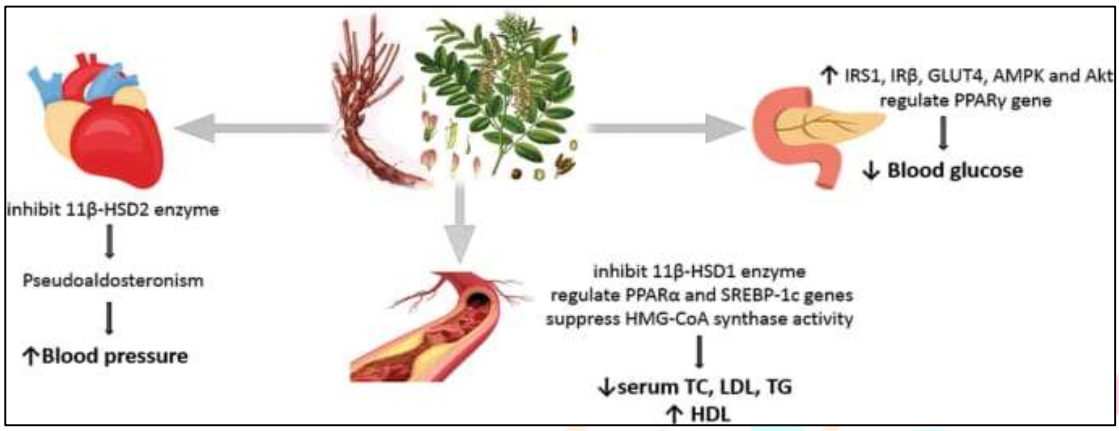

Fig 4: Diagrammatic Representation of Licorice's Mode of Action in the Treatment of Heart Diseases.

Comparing Licorice With Digoxin:

Comparing licorice (Glycyrrhiza glabra) to digoxin, a well-known cardiac glycoside used in the treatment of heart failure and arrhythmias, involves weighing their pharmacological properties, safety profiles, and clinical applications. Licorice offers certain advantages over digoxin in specific contexts, although the two serve different primary purposes. Below is an analysis of why licorice might be considered beneficial in some aspects:

1. Broader Mechanisms of Action

Licorice:
Licorice has multifaceted effects, including antioxidant, anti-inflammatory, lipid-lowering, and vasodilatory properties. These actions address multiple pathways in cardiovascular disease, such as reducing oxidative stress, controlling inflammation, and preventing atherosclerosis.
Example: Licorice flavonoids like glabridin improve endothelial function and reduce LDL oxidation, which are pivotal in preventing atherosclerosis.
Broader Application: Licorice supports general cardiovascular health and may be beneficial in early-stage conditions like hypertension, mild heart failure, or prevention of ischemic heart disease.

Digoxin:
Digoxin specifically targets cardiac contractility by inhibiting the sodium-potassium ATPase pump, leading to increased intracellular calcium and improved myocardial contractility. This makes it particularly effective in managing systolic heart failure and atrial fibrillation but limited in broader cardiovascular benefits.

2. Safety Profile and Toxicity

Licorice:
In moderate doses, licorice is safer for long-term use and has fewer severe side effects compared to digoxin. Overdose or prolonged use may cause pseudoaldosteronism, leading to hypertension, hypokalemia, and fluid retention. However, deglycyrrhizinated licorice (DGL) eliminates glycyrrhizin, reducing these risks.
Advantage: It is less likely to cause life-threatening toxicity compared to digoxin.

Digoxin:
Digoxin has a narrow therapeutic index, meaning small changes in dose can result in toxicity. Digoxin toxicity can cause arrhythmias, nausea, visual disturbances (e.g., yellow halos), and even death. Regular monitoring of drug levels and kidney function is required to minimize risks.

3. **Lipid-Lowering Effects**

Licorice:
Licorice reduces LDL cholesterol and triglycerides, helping to prevent atherosclerosis and coronary artery disease. This is an added benefit not associated with digoxin.

Digoxin:
Digoxin has no lipid-lowering or plaque-preventing properties. Its primary function is to improve cardiac contractility and manage arrhythmias.

4. **Antioxidant and Anti-Inflammatory Effects**

Licorice:
The antioxidant properties of licorice protect cardiomyocytes from oxidative damage, particularly during ischemia-reperfusion injury. Its anti-inflammatory effects reduce cytokine production and prevent chronic inflammation in the cardiovascular system.
Example: Glycyrrhizin inhibits NF-κB and reduces TNF-α levels, both of which are implicated in myocardial damage.

Digoxin:
Digoxin does not possess antioxidant or anti-inflammatory properties and is therefore less protective against the underlying causes of cardiovascular disease.

5. **Risk of Arrhythmias**

Licorice:
At appropriate doses, licorice stabilizes cardiac rhythm through its effects on potassium channels. However, excessive consumption can cause hypokalemia, predisposing patients to arrhythmias.

Digoxin:
While digoxin is used to manage certain arrhythmias (e.g., atrial fibrillation), it can also induce arrhythmias at toxic levels, particularly ventricular arrhythmias, making it a double-edged sword in cardiac care.

6. **Accessibility and Cost**

Licorice:
Licorice is widely available as an herbal remedy and is generally more affordable. It is suitable for individuals seeking natural, complementary therapies for cardiovascular support.

Digoxin:
Digoxin requires a prescription, regular medical supervision, and monitoring of serum drug levels, which can increase treatment costs.

7. **Suitability for Long-Term Use**

Licorice:
In its deglycyrrhizinated form (DGL), licorice is suitable for long-term use in preventing cardiovascular diseases.

Digoxin:
Long-term use of digoxin requires careful dose adjustments and monitoring due to its toxicity risk.

Conclusion:

Licorice (Glycyrrhiza glabra) holds significant therapeutic potential in cardiovascular medicine, attributed to its anti-inflammatory, antioxidant, and lipid-modulating properties. These effects, driven by bioactive compounds like glycyrrhizin and flavonoids, make licorice a promising candidate for addressing oxidative stress, endothelial dysfunction, and atherosclerosis.
However, its benefits must be weighed against the risks of glycyrrhizin-induced toxicity, including pseudoaldosteronism, hypertension, and life-threatening cardiovascular complications.

Despite extensive historical and clinical evidence supporting licorice's medicinal value, its safety profile demands careful regulation and public awareness. The development of deglycyrrhizinated licorice (DGL) offers a safer alternative, but further research is required to validate its efficacy in cardiovascular applications. Additionally, personalized approaches, such as genetic risk assessment and tailored dosing, could optimize its use in clinical practice.

Future studies should aim to clarify the long-term safety of licorice consumption, establish standardized dosing protocols, and explore novel formulations to maximize therapeutic benefits while minimizing risks. By addressing these gaps, licorice can transition from a traditional remedy to a modern, evidence-based adjunct in cardiovascular care.

Licorice may complement or prevent cardiovascular conditions, while digoxin remains the treatment of choice for advanced heart failure and certain arrhythmias. Careful use of licorice, particularly in deglycyrrhizinated form, can mitigate its potential side effects

References:

1.Isbrucker, R. A., & Burdock, G. A. (2006). Risk and safety assessment on the consumption of licorice root (Glycyrrhiza sp.). Regulatory Toxicology and Pharmacology, 46(3), 167–192.

2. Shibata, S. (2000). A drug over the millennia: Pharmacognosy, chemistry, and pharmacology of licorice. Yakugaku Zasshi, 120(10), 849–862.

3. Stormer, F. C., et al. (1993). Glycyrrhizic acid in licorice—Evaluation of health hazard. Food and Chemical Toxicology, 31(4), 303–312.

4. Omar, H. R., et al. (2012). Licorice abuse: Time to send a warning message. International Journal of Cardiology, 156(3), 330–332.

5. Mattarello, M. J., et al. (2006). Licorice consumption and pseudoaldosteronism. American Journal of Hypertension, 19(10), 1082–1083.

6. Pandit, S., et al. (2020). Glycyrrhizin-induced arrhythmias: A systematic review. Heart Rhythm Case Reports, 6(5), 258–262.

7. Revers, W., & Ammon, H. P. (2000). The toxicity of glycyrrhizin: A review. Phytotherapy Research, 14(8), 557–563.

8. EFSA Panel. (2008). Opinion on the use of glycyrrhizin in food. EFSA Journal, 6(6), 229–250.

9. Tack, J., et al. (2012). Deglycyrrhizinated licorice in functional dyspepsia: A randomized trial. Digestive Diseases and Sciences, 57(7), 1536–1545.

10. Hodge, G., et al. (2021). Licorice: Understanding its health benefits and risks. Journal of Medicinal Food, 24(8), 789–799.

11. FDA. (2017). The dangers of black licorice. FDA Consumer Update

12. van Gelderen, C. E., et al. (2000). Clinical and toxicological aspects of glycyrrhizin (licorice): A review. Phytomedicine, 7(6), 365–375.

13. Nomura, T., et al. (2002). Licorice and aldosterone metabolism. Steroids, 67(8), 655–659.

14. Rosenbloom, A. L., & Mendoza, S. A. (2002). Licorice-induced hypokalemia. Journal of Pediatrics, 140(4), 453–454.

15. Krentz, A. J., et al. (2013). Safety considerations with herbal medicine in cardiovascular disease. Current Pharmaceutical Design, 19(32), 5731–5742.

16. Sigurjonsdottir, H. A., et al. (2001). Hypertension and hypokalemia in a woman consuming licorice. The Lancet, 358(9288), 1558–1559.

17. Thurnham, D. I., et al. (2011). Licorice: Pros and cons. Nutrition Bulletin, 36(4), 378–383.

18. Yamamoto, T., et al. (2017). Licorice-induced torsades de pointes. Journal of Electrocardiology, 50(5), 694–696.

19. Sharma, A., et al. (2023). Safety of herbal products in cardiovascular disease. Herbal Medicine Research, 2(3), 115–122.

20. Strandberg, T. E., et al. (2001). Adverse effects of licorice consumption during pregnancy. American Journal of Epidemiology, 153(11), 1085–1092.

21. WHO. (2004). Monographs on Selected Medicinal Plants. World Health Organization Press.

22. European Commission. (2006). Directive 2006/52/EC. Official Journal of the European Union.

23. Hsu, Y. W., et al. (2011). Protective effects of glycyrrhizin against myocardial ischemia-reperfusion injury. Molecular Medicine Reports, 4(2), 417–423.

24. Baker, W. L., et al. (2009). Digoxin in heart failure: An overview of use, pharmacology, and monitoring. Therapeutics and Clinical Risk Management, 5, 1261–1273

25. Takahashi, T., et al. (2008). Flavonoid glabridin inhibits LDL oxidation and attenuates atherosclerosis in rabbits. Atherosclerosis, 201(2), 307–313.

26. Bleske, B. E., et al. (2004). Digoxin's role in clinical cardiology. American Journal of Health-System Pharmacy, 61(7), 662–669.

27. Dong, Z., et al. (2015). Licorice-derived flavonoids and heart protection. Food & Function, 6(1), 3–10.

28. Mount Sinai Health Library (2021). Licorice Information. Mount Sinai Hospital. (mountsinai.org)