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Review article

Unveiling Liquorice: A sweet journey through history, phytochemistry, and exceptional pharmacological activities

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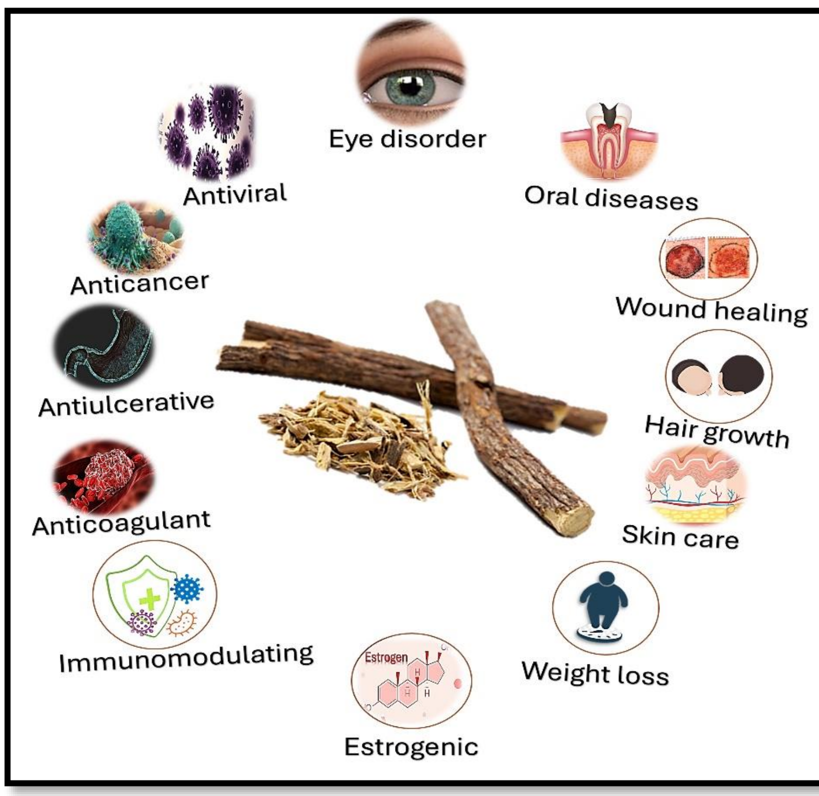
Abstract:

Radix Glycyrrhiza (liquorice), traditionally valued since old civilizations, continues to exhibit a wide range of beneficial properties across health, industry, and cosmetics. This sweet-tasting plant has been associated with numerous ancient cultures. It was used as a ritual beverage in ancient Egyptian tombs, described as the national treasure "Guo Lao" in Chinese medicine, and is featured in over 1250 Ayurvedic formulations under the Sanskrit name *Yashtimadhu*, meaning sweet stalk. Liquorice and its active compounds exhibit therapeutic potential across a wide spectrum of conditions, including those affecting the respiratory, digestive, nervous, cardiovascular, and immune systems. The broad spectrum of activities have been reported as antiviral, anticancer, anticoagulant, estrogenic, and many others. Recent research has also highlighted its applications in oral and eye diseases. Additionally, liquorice is extensively utilized in the cosmetics industry, with proven benefits for both skin and hair. This review provides a comprehensive overview of liquorice and its principal constituents, covering its historical significance, key phytochemicals, and diverse applications in the health and cosmetics fields as well.



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The safety profile of liquorice, along with potential risks associated with excessive consumption, is also addressed. Data for this review were sourced from scientific journals indexed in databases such as Web of Science, Springer, and Google Scholar, as well as pharmacopoeias, and theses. This work aims to serve as a foundational reference for ongoing research into the therapeutic potential of liquorice modern medicine.

Keywords: Liquorice, *Glycyrrhiza Glabra*, Pharmacology, Liquorice Safety Profile, Antiviral.

1. Introduction

Liquorice (*Glycyrrhiza glabra* L.) family Fabaceae and its varieties are composed of dried roots and rhizomes [(1)]. It is commonly known in Egypt as “erq soos”. Liquorice owes its Latin name to both Greek and Latin, as The Greek words "glykys," which means sweet, and "rhiza", which means root, are the sources of the name Glycyrrhiza while the species name “glabra” refers to the smooth husks of the plant where “glaber” in Latin means smooth. In China, the plant is referred to as "Guo Lao," meaning "a national treasure", where liquorice is considered one of the most widely used herbal medicines [(2)]. The plant is indigenous to the Mediterranean region and parts of Asia. It is grown in China, India, and Russia [(3)]. Liquorice is among the most renowned medicinal plants, with a long history of use in ancient civilizations and traditional medicine systems. For instance, the Egyptian and Chinese cultures have stated the use of liquorice in treating several ailments such as coughs and colds, and gastrointestinal disorders [(1, 4)]. Many therapeutic uses have been reported and proved for the plant extract as well as its isolated compounds. These include diseases of the gastrointestinal tract such as stomach and duodenal ulcers, respiratory conditions like cough and asthma, and effects resembling those of adrenocortical hormones. In addition, antiviral, anti-inflammatory, anticoagulant, and anti-microbial properties were identified. Remarkably, it has exhibited significant anticancer potential against various malignancies, including liver, breast, cervical, colorectal, prostate cancers, and others.

Liquorice also possesses numerous industrial applications, as a flavoring agent in food additives, tobacco flavors, and cosmetics due to its sweet taste and whitening properties [(5, 6)]. The plant extract and glycyrrhizin are used in flavoring tobacco, and candy. Additionally, liquorice is added to beer because it has good surfactant properties.

This review explores the pharmacological activities, phytochemical constituents, and safety profile of liquorice, emphasizing its medicinal value and potential applications.

2. Botanical description

Liquorice is a perennial shrub with many runners and a primary taproot, growing to a height of 1 to 2 meters. Rhizomes and roots grow in almost cylindrical segments, brownish grey to dark brown, and longitudinally wrinkled. Peeling reveals a bright, smooth, fibrous root with tiny striations.

Leaves are compound, alternate imparipinnate. Leaflets are oval with acute or obtuse apex.

The plant has axillary inflorescences that are upright, and spike-like. The individual flowers are 1 to 1.5 cm in length, bluish to pale violet, and have short pedicels. The calyx is short, glandular-haired. The fruit is a flat, glabrous pod with thick sutures that typically contains three to five brown, reniform seeds [(1)].

3. Traditional uses

It is one of the widely consumed drinks in Egypt and has a long history of use as a food flavoring throughout the world. During the

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Muslim fasting month of Ramadan, it is customary to have "erq soos", a famous traditional non-alcoholic beverage in Egypt that primarily consists of liquorice [7, 8]. Since the dawn of civilization, the plant has been used in both Eastern and Western cultures as one of the most well-known and traditional herbal remedies worldwide. One of the earliest proofs of the use of liquorice originates from its storage in the ancient tombs of ancient Egyptians as this was a ritual that permitted the spirits of the kings to prepare a sweet drink called *mai sus* in the afterlife [6]. In addition, liquorice drink was used by soldiers on the battlefields and travelers in the desert to quench their thirst. The ancient Egyptians consumed liquorice as a liquid drink, rather than as a food [8].

Code Humnubari (2100 BC) has the oldest known mention of its application in medicine. Several ancient civilizations mainly Egyptian and Chinese have stated the use of liquorice in treating many conditions of the respiratory and digestive systems. Folk uses of the plant include its use as expectorant and carminative. It is also used for the treatment of gastric and duodenal ulcers. As an anti-inflammatory agent. It is beneficial for allergic reactions, rheumatism, and arthritis. In addition, it is also used for the treatment of tuberculosis and the prevention of liver toxicity [1, 4, 9]. It is widely used in Unani medicine as roots (*Bikh-i-Asl-us-Sus*) and extract (*Rub al-Sus-extractum glycirrhiza*) in the treatment of cold, sore throat, and uvulitis due to its mucilaginous and expectorant effect. According to Ibn Baitar, the medication is particularly helpful for conditions affecting the lungs and bladder, such as chest burning, and burning micturition, respectively. Combining its extract with medications for liver conditions results in a synergistic effect. It strengthens the nerves and is beneficial for palpitations, as well as conditions affecting the brain and nervous system. Its temperament is believed to be hot and dry. However, Najmul Ghani claims that it is dry in the first degree and hot in the second. Meanwhile, it is advised to be taken after peeling to get rid of the toxic effect of the bark.

Liquorice also has been used as a laxative, in treating epilepsy, dizziness, tetanus, snake bites, hemorrhoids, and as an appetizer. Additionally, the plant was thought to have antiasthmatic and antiviral properties. In addition, it has been used as a contraceptive and galactagogue.

4. Phytoconstituents of *Glychrriza glabra* [10]

Different classes of compounds have been reported in *Glycyrrhiza glabra* as triterpenoid saponins, triterpenes, flavonoids, isoflavonoids, chalcones, coumarins, essential oil, polysaccharides, polyamine, fatty acids, and amino acids [11-13]. A summary of the main phytoconstituents of the plant and their structures is given in (**Table 1**) [10, 14, 15].

5. Pharmacological effect of liquorice in different diseases

Being a popular herbal medicine, liquorice extracts and their constituents have been extensively studied for their pharmacological effects proved by *in vitro*, *in vivo* and clinical studies. [6, 16-19]. Those pharmacological effects include the following, giving emphasis on the unconventional pharmacological activities of liquorice.

5.1. Antiviral effect

Liquorice possesses strong antiviral action, yet the exact mechanism is still unknown. In a recent review, Wang et al [20], summarized the antiviral activities of liquorice and its components stating that this activity is mainly due to glycyrrhizin and glycyrrhetinic acid. The proliferation and cytopathology of numerous unrelated DNA and RNA viruses are inhibited by liquorice with no effects on cellular replication. For example, two constituents of liquorice, isoliquiritigenin, and glycerol have shown neuroaminidase inhibitory activity and need further studies to

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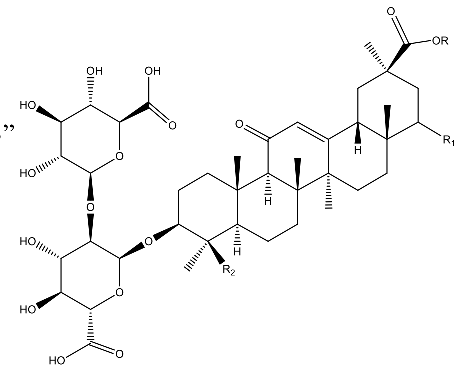
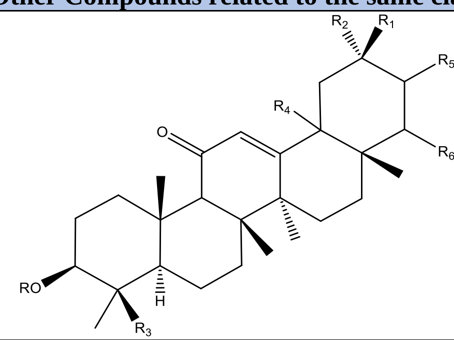
Table 1: Phytoconstituents previously isolated from the roots of *G. glabra*

Chemical class	Structures
A-Triterpenoid Saponins (10-13)	- **GL**"K^+, Mg^{+2}& Ca^{+2} salts of glycyrrhizic acid" **Major (parent compound)** - **GlycyrrhizicAcid 3-O-[β -D-g1ucuronopyranosyl-(1->2)- β -D-g1ucuronopyranosyl] glycyrrhetic acid**"R = H, R1= H, R2= CH3" - **24-HydroxyGL**"R = H, R1= H, R2= CH2OH " - 22- **β** -AcetoxyGL"R = H, R1= β -OCOCH3, R2= CH3" - **Liquorice saponin A3**"R = β -D-Glu**,** R1= H, R2= CH3" 

Other Compounds related to the same class



Compound Name	R	R1	R2	R3	R4	R5	R6
-Liquiritic acid	H	CH3	COOH	CH3	β -H	H	H
-Glycyrretol (Glycyrrhetol)	H	CH2OH	CH3	CH3	β -H	H	H
-24 hydroxyglycyrrhetic acid	H	COOH	CH3	CH2OH	β -H	H	H
-18 α-hydroxyglycyrrhetic acid	H	COOH	CH3	CH2OH	α-OH	H	H
- 18 α -glycyrrhetinic acid	H	COOH	CH3	CH3	α -H	H	H
- 18 β -glycyrrhetinic acid (Enoxolone)	H	COOH	CH3	CH3	β -H	H	H
-24-hydroxyliquiritic acid	H	CH3	COOH	CH2OH	β -H	H	H
- Glabric acid	H	CH3	COOH	CH3	β -H	α-OH	H

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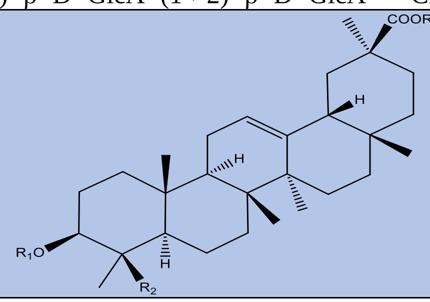
-Liquorice saponin G2	β-D- GlcA -(1->2)- β -D- GlcA	COOH	CH3	CH2OH	β -H	H	H
-RhaoGL	α-L Rha-(1->2)- β -D- GlcA -(1->2)- β -D- GlcA	COOH	CH3	CH3	β -H	H	H
-RhaoglucoGL	α-L Rha-(1->2) β - D-Glu -(1->2)- β -D-GlcA	COOH	CH3	CH3	β -H	H	H
-RhaogalactoGL	α-L Rha-(1->2)- β -D-Gal -(1->2)- β -D-GlcA	COOH	CH3	CH3	β -H	H	H
-30-Hydroxy GL	β -D- GlcA -(1->2)- β -D- GlcA	CH2OH	CH3	CH3	β -H	H	H
-GL-20-methanoate	β -D- GlcA -(1->2)- β -D- GlcA	CH2OCOH	CH3	CH3	β -H	H	H
-GlucoGL	β -D-Glu -(1->2)- β -D- GlcA	COOH	CH3	CH3	β -H	H	H
-24-HydroxyglucoGL	β -D-Glu -(1->2)- β -D- GlcA	COOH	CH3	CH2OH	β -H	H	H
-AraboGL	β -D-Ara-(1->2)- β -D- GlcA	COOH	CH3	CH3	β -H	H	H
-ApioGL	β -D-Api-(1->2)- β -D- GlcA	COOH	CH3	CH3	β -H	H	H
-Glycyrrhetinic acid-monoglucuronide	β -D- GlcA	COOH	CH3	CH3	β -H	H	H
-Liquorice saponin M3	β-D- GlcA -(1->2)- β -D- GlcA	CH3	CH3	CH3	β -H	H	O-α-L-Rha
-Liquorice saponin N4	α-L-Rha- (1->2)- β -D- GlcA -(1->2)- β -D- GlcA	CH3	CH3	CH3	β -H	H	O-α-L-Rha
- Liquorice saponin O4	α-L Rha-(1->2)- β -D- GlcA -(1->2)- β -D- GlcA	CH3	CH3	CH2OH	β -H	H	O-α-L-Rha
- Macedonoside A	β -D- GlcA -(1->2)- β -D- GlcA	CH3	COOH	CH3	β -H	α-OH	H
-20α-GalacturonoylGL	"R= β - D-Gal-(1->2)- β -D- GlcA	CH3	COOH	CH3	β -H	H	H
-20α-RhaoGL	α-L Rha -(1->2)- β -D- GlcA -(1->2)- β -D- GlcA	CH3	COOH	CH3	β -H	H	H



Compound Name	**R**	**R1**	**R2**
-11-deoxoglycyrrhetinic acid	H	H	CH3
-24-hydroxy-11 deoxoglycyrrhetic acid	H	H	CH2OH
-11-desoxoglycyrrhetic acid acetate methyl ester	CH3	COCH3	CH3
- 24-acetoxy-l 1-desoxoglycyrrheticacid acetate methyl ester	CH3	COCH3	CH2OCOCH3

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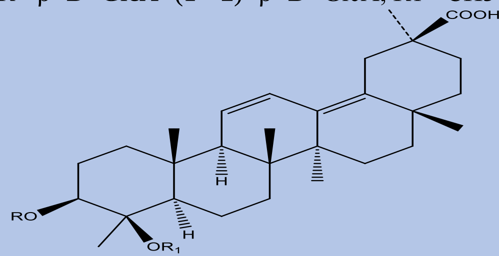
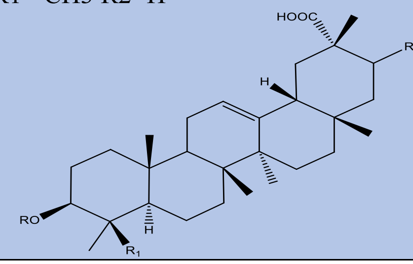
- 24-Hydroxy-11-desoxoglycyrrhetic acid methyl ester	CH3	H	CH2OH
-11-DeoxorhaoGL	H	α-L-Rha-(1->2)- β -D- GlcA -(1->2)- β -D- GlcA	CH3

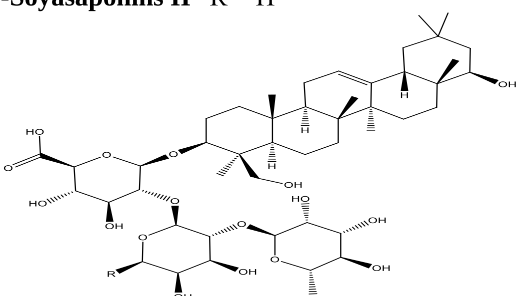
- Glypallidifloric acid; **(3 β -hydroxy-11, 13(18)-oleanadien-30-oic acid)** "R= H, R1= CH3"
- 3,24-dihydroxy-11, 13(18)-oIeanadien-30-oic acid"R= H, R1= CH2OH"
- 11-deoxo-11,13GLdiene"R= β -D- GlcA -(1->2)- β -D- GlcA, R1= CH3"



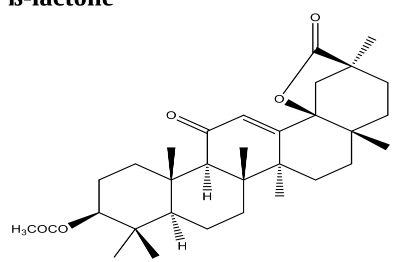
- Glyyunnansapogenin B(liquiridiolic acid) "R= H, R1= CH2OH, R2= α-OH"
- 11-Deoxo-20 α -GL"R= β-D- GlcA -(1->2)- β -D- GlcA, R1= CH3 R2=H"



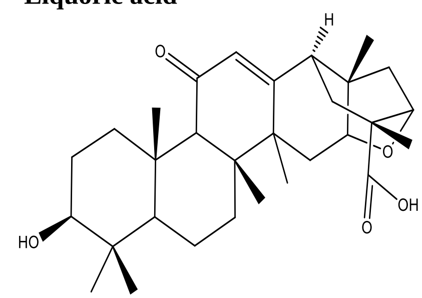
-Soyasaponins I "R = CH_2OH"
-Soyasaponins II "R = H"



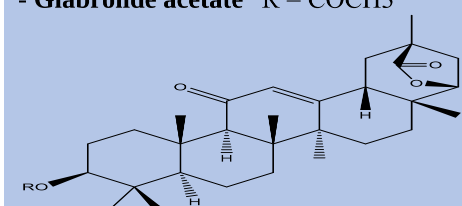
-3 β -acetoxy-18 ß-hydroxy-11-keto-olean-12-en-30-oic acid, 30,18 ß-lactone



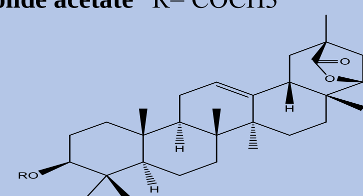
-Liquoric acid



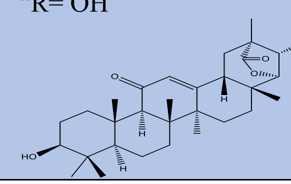
- Glabrolide"R = H"
- Glabrolide acetate "R = COCH3"



- 11-deoxoglabrolide"R= H"
-11-deoxoglabrolide acetate "R= COCH3"



- Isoglabrolide "R= H"
-21 α –hydroxyisoglabrolide "R= OH"



B-Phenolic compounds

I. Flavonoids
(10, 13, 14)

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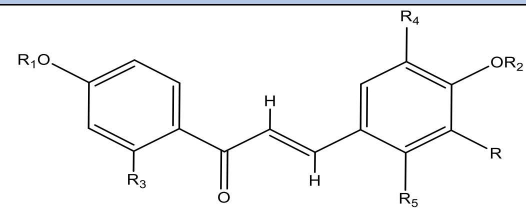
1- Chalcones

(10, 13, 14)



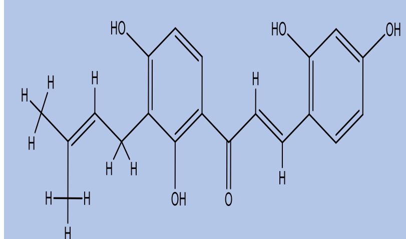
Major (parent compound)

- Isoliquiritin"R1= H, R2= -β-D Glu"

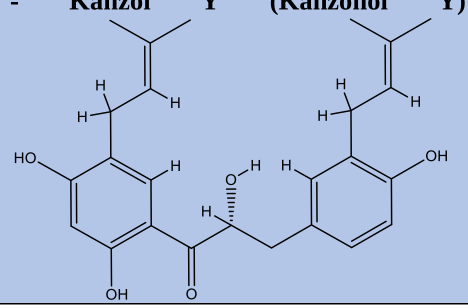
Compound Name	R	R1	R2	R3	R4	R5
- Isoliquiritigenin	H	H	H	OH	H	H
-Echinatin	H	H	H	H	H	OCH3
-2,4,4'-Trimethoxychalcone	H	CH3	CH3	H	H	OCH3
-Neoisoliquiritin	H	β -D-Glu	H	OH	H	H
-Rhamno-isoliquiritin	H	H	-Rha- β -D-Glu	OH	H	H
-Licuraside	H	H	β -D-Api-(1->2)- β -D-Glu	OH	H	H
-Isoliquiritigenin 4'-O-apiosylglucoside	H	β -D-Api-(***1***->***2***)-β -D-Glu	H	OH	H	H
- Licochalcone B	OH	H	H	H	H	OCH3

Other related compounds

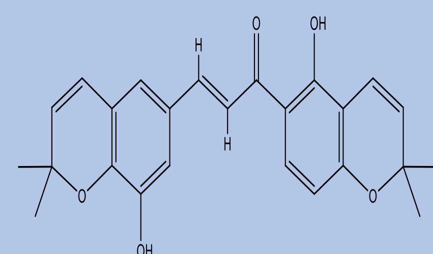
- Morachalcone A



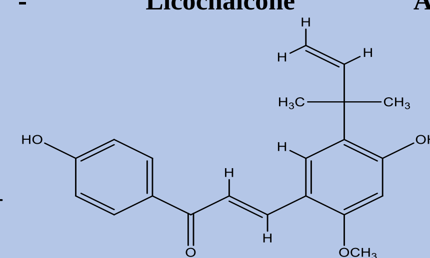
- Kanzol Y (Kanzonol Y)



- Glyinflanin G



- Licochalcone A



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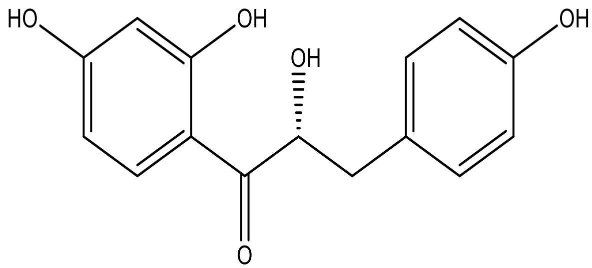
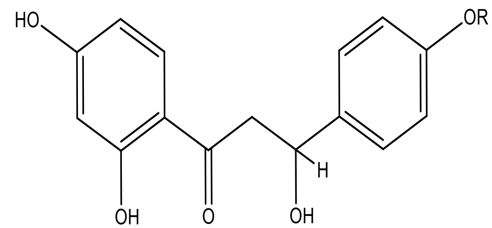
- (2R)-1-(2,4-Dihydroxyphenyl)-2-hydroxy-3-(4-hydroxyphenyl)-1-propanone



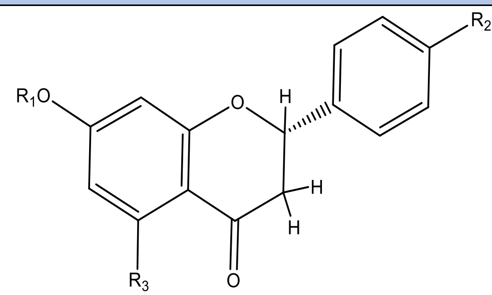
- 1-(2,4-Dihydroxyphenyl)-3-hydroxy-3-(4'-hydroxyphenyl)-1-propanone "R= H"

- 1-(2,4-Dihydroxyphenyl)-3-hydroxy-3-(4'-hydroxyphenyl-4'-*O*-β-D-glucopyranoside) -1-propanone "R= β-D-Glu"



2- Flavanone

(10, 13, 14)



Major (parent compound)

- Liquiritin"R1= H, R2= -β-D-Glu, R3= H"

Compound Name	R1	R2	R3
- Liquiritigenin	H	OH	H
- Neoliquiritin	β -D-Glu	OH	H
- Liquiritinapioside	H	-O- β -D-Api -(***1***->***2***)-β -D- Glu	H
- liquiritigenin 7-apiosylglucoside	β -D-Api -(1->2)-β -D- Glu	OH	H
- Rhamno-liquiritin	H	-O-Rha-Glu	H
- Glucoliquiritinapioside	β -D-Glu	-O- β -D-Api-(1->2)- β -D- Glu	H
-Choerospondin	H	-O- β -D-Glu	OH
- Pinocembrin	H	H	OH
-Liquorice glycoside D2	H	-O- [4-p-coumaroylapiosyl-(1->2)-glucoside]	H
- 5,7-Dihydroxyflavanone	H	H	OH

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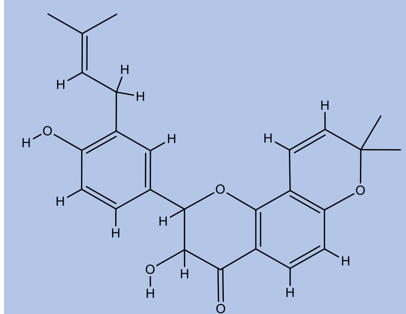
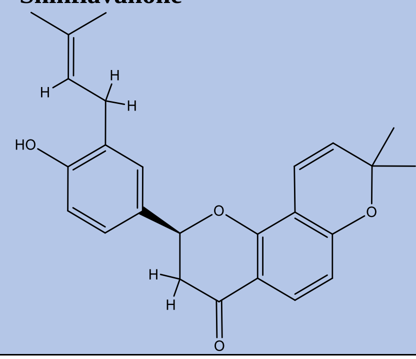
Other related compounds

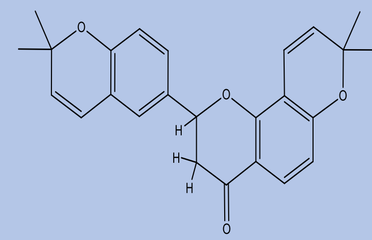
- KanzolZ(KanzonolZ)



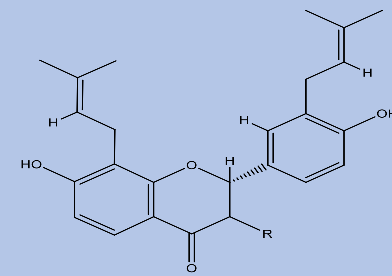
- Shinflavanone



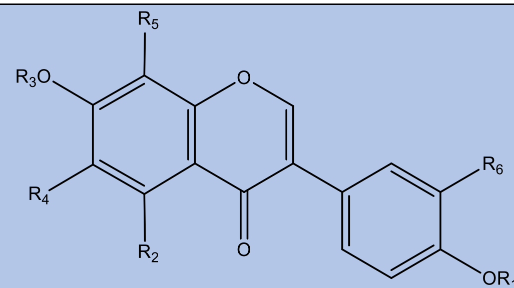
-Xambioona



- Glabrol"R= H"
- 3-Hydroxy glabrol"R= α -OH"



3- Isoflavone
(10, 13, 14)



Compound Name	R1	R2	R3	R4	R5	R6
- Genistein	H	OH	H	H	H	H
- Genistin	H	OH	β -D-Glu	H	H	H
- 3',6-Di-(dimethylallyl)-genistein	H	OH	H	Prenyl	H	Prenyl
- 6,8-Di-(dimethylallyl)-genistein	H	OH	H	H	Prenyl	Prenyl
-Formononetin	CH3	H	H	H	H	H
-Ononin	CH3	H	Glu	H	H	H
-Prunetin	H	OH	CH3	H	H	H
- Daidzein	H	H	H	H	H	H
- Daidzin	H	H	Glu	H	H	H

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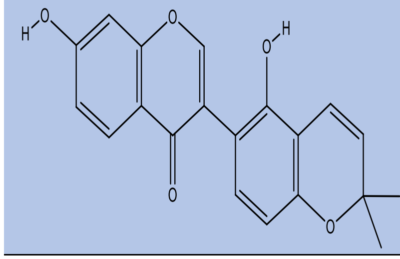
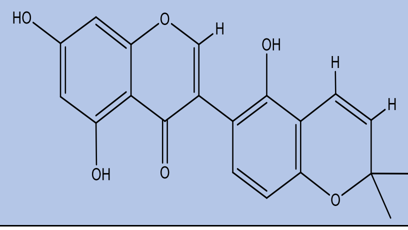
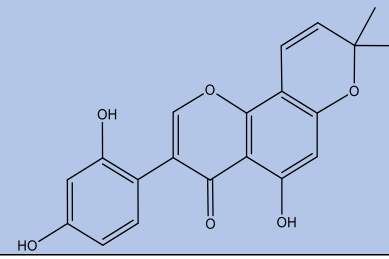
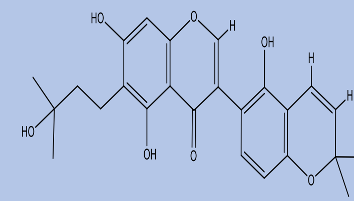
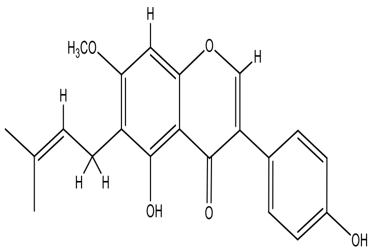
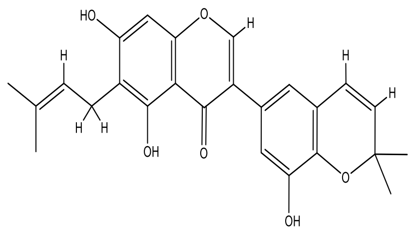
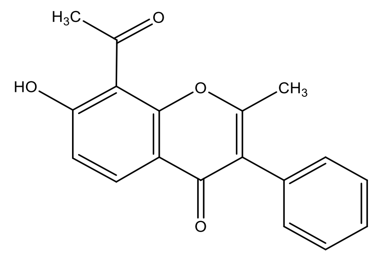
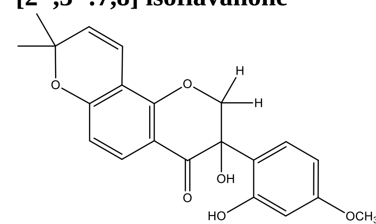
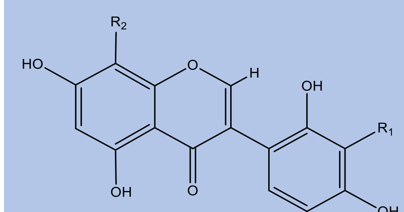
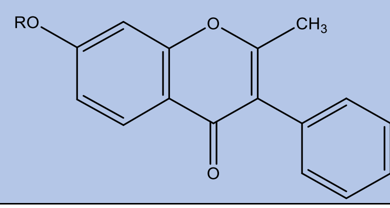
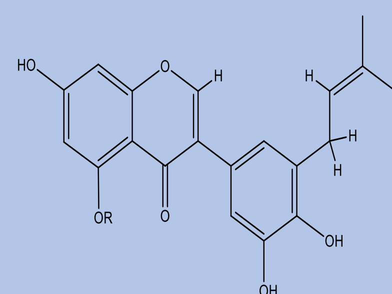
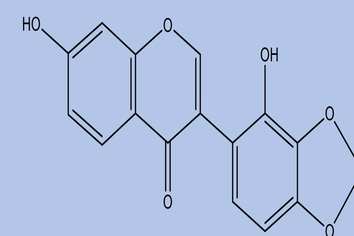
Other related compounds			
- Glabrone 	**- Licoisoflavone B** 	**- Parvisoflavone A** 	**- Kanzol T (Kanzonol T)** 
- Gancaonin G 	**- Gancaonin H** 	**- Glyzarin** 	**-2',3-Dihydroxy-4'-methoxy-3'',3''-dimethylpyrano [2'',3'':7,8] isoflavanone** 
- LicoisoflavoneA“R1=Prenyl , R2= H” **- GancaoninL**“R1=OH, R2= Prenyl” 	**-7-Hydroxy-2-methylisoflavone“**R= OH” **-7-Methoxy-2-methylisoflavone“**R=CH3” **-7-Acetoxy-2-methylisoflavone“**R= COCH3” 	**-Glycyrrhisoflavone“**R= H” **- Glisoflavone**“R= CH3” 	**- Glyzaglabrin isoflavone** 

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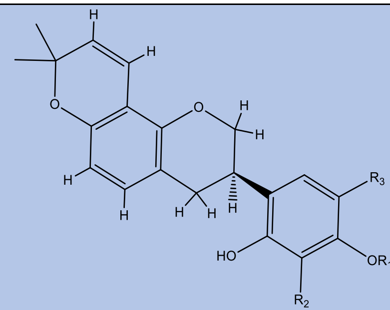
4- Isoflavane, Isoflavene

(10, 13, 14)



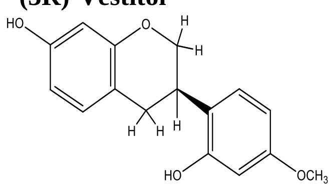
Major (parent compound)

- Glabridin"R1= H, R2= H, R3=H"

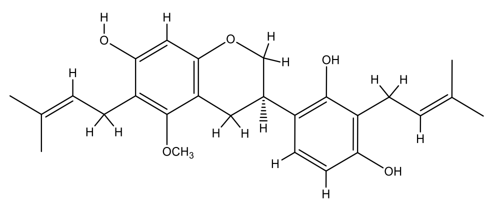
Compound Name	R1	R2	R3
- 4'-O-methyl glabridin	CH3	H	H
- 3'-hydroxy-4'-O-methylglabridin	CH3	OH	H
-5'-Formyl glabridin	H	H	CHO

Other related compounds

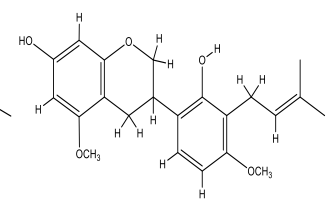
- (3R)-Vestitol



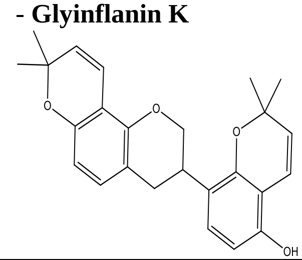
-Licoricidin



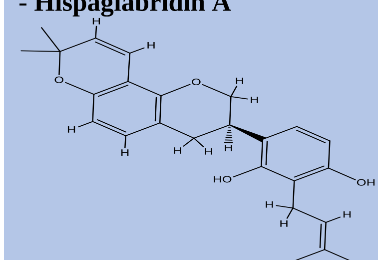
- Kanzol R (Kanzonol R)



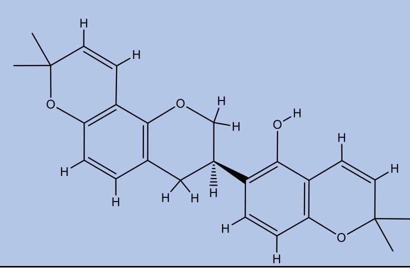
- Glyinflanin K



- Hispaglabridin A

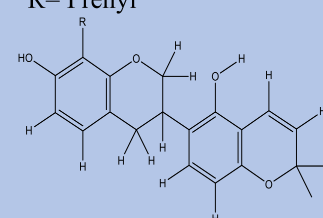


- Hispaglabridin B

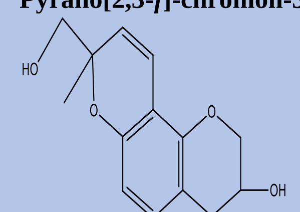


- Phaseollinisoflavan "R= H"

- 8-Prenyl- Phaseollinisoflavan "R= Prenyl"



- 8-Hydroxymethyl-8-methyl-3,4-dihydro-2H,8H-Pyrano[2,3-*f*]-chromon-3-ol



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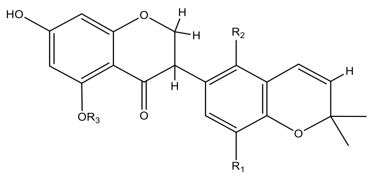
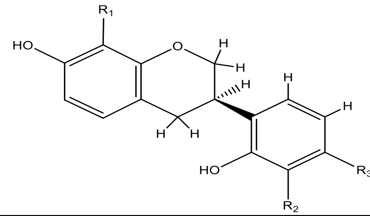
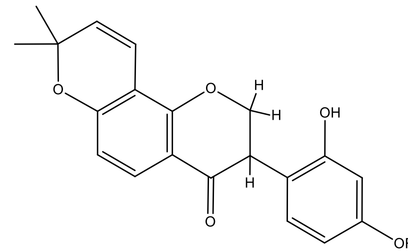
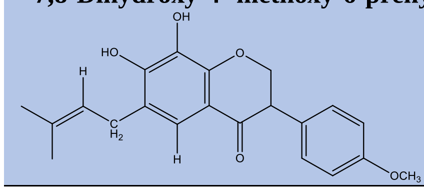
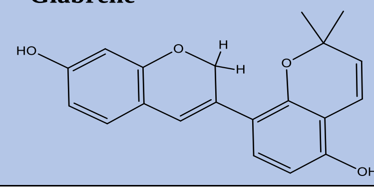
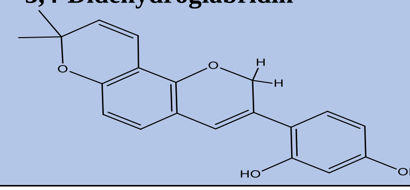
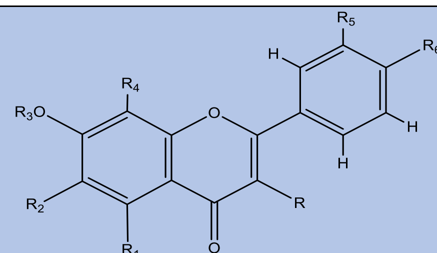
-**Licoisoflavanone**"R1= H, R2=OH, R3=H" -**Glycyrrhisoflavanone**"R1= OH, R2=H, R3=CH3" -**GlyasperinM**"R1= H, R2=OH, R3=CH3" 	- **Kanzol X(KanzonolX)**"R1= Prenyl, R2=Prenyl, R3=OH" - **(3R)-2',3',7-Trihydroxy-4'-methoxyisoflavan**"R1= H, R2=OH, R3=OCH3" 	-**GlabroisoflavanoneA**"R= H" -**GlabroisoflavanoneB**"R= CH3" 
- **7,8-Dihydroxy-4'-methoxy-6-prenylisoflavanone** 	- **Glabrene** 	-**3,4-Didehydroglabridin** 

5- Flavone

(10, 14)



Compound Name	R	R1	R2	R3	R4	R5	R6
-4',7-Dihydroxyflavone	H	H	H	H	H	H	OH
-Isovitexin	H	OH	C-β-Glu	H	H	H	OH
-Genkwanin	H	OH	H	CH3	H	H	OH
- Quercetin 3,3'-dimethyl ether	OCH3	OH	H	H	H	OCH3	OH
- Quercetin-3-glucobioside	-O-β-Glu-(1->2)- β- Glu	OH	H	H	H	OH	OH
-Glychionide A	H	OH	H	β- GlcA	OH	H	H
-Glychionide B	H	OH	H	β- GlcA	OCH3	H	H
- Isoviolanthin	H	OH	C-α -L-Rha	H	C-β-Glu	H	OH

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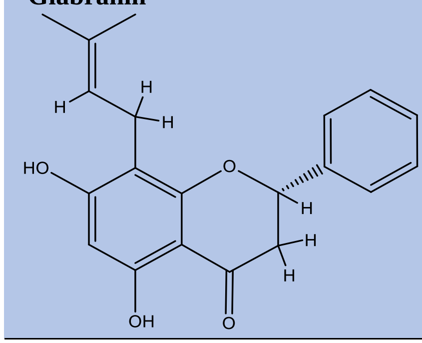
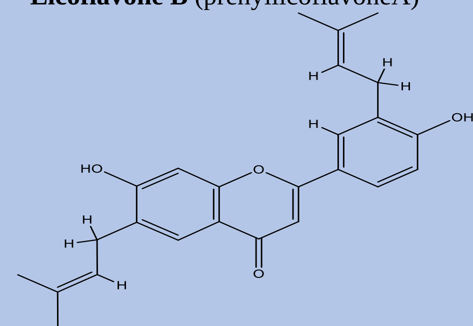
- Violanthin	H	OH	C-β-D-Glu	H	C-6-deoxy-α-L mannopyranosyl	H	OH
-Luteolin	H	OH	H	H	H	OH	OH
- Apigenin	H	OH	H	H	H	H	OH
- Isoschaftoside	H	OH	C-α -L-Ara	H	C-β-D-Glu	H	OH
- Schaftoside	H	OH	C-β-D-Glu	H	C-β-D-Rib	H	OH
- Licoflavonol	OH	OH	Prenyl	H	H	H	OH
- Astragalin (kaempferol-3-glucoside)	O- β -D-Glu	OH	H	H	H	H	OH
-Isokaempferide (Kaempferol 3-O-methyl ether)	OCH3	OH	H	H	H	H	OH
- Kumatakenin	OCH3	OH	H	CH3	H	H	OH

Other related compounds

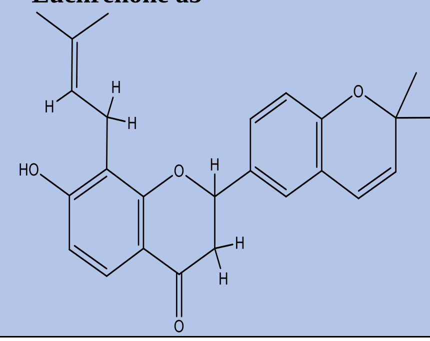
-Glabranin



- Licoflavone B (prenyllicoflavoneA)

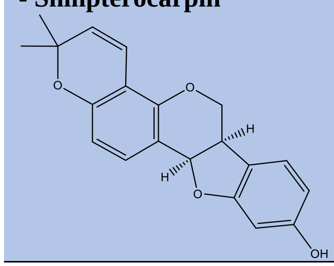


- Euchrenone a5

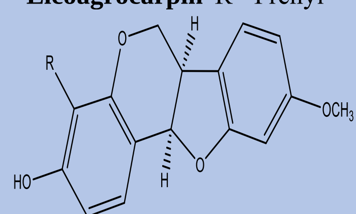


6- Pterocarpans [14]

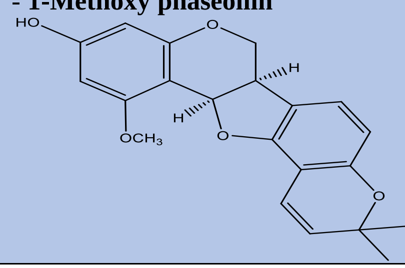
- Shinpterocarpin



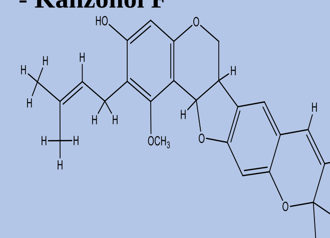
- Medicarpin“R= H”
- Licoagrocarpin“R= Prenyl”



- 1-Methoxy phaseollin



- Kanzonol F



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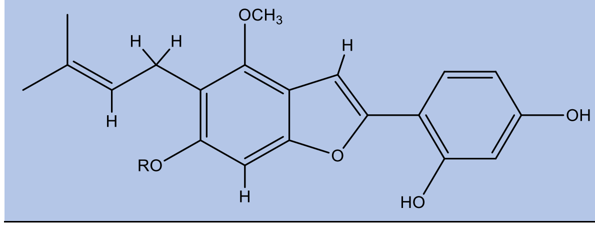
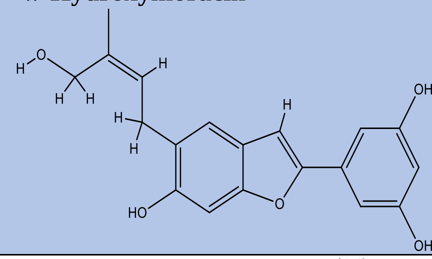
7- (2-Arylbenzofuran flavonoids) [14]

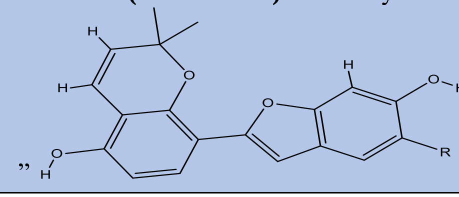
-Licocoumarone"R= H"
- GancaoninI"R= CH3"



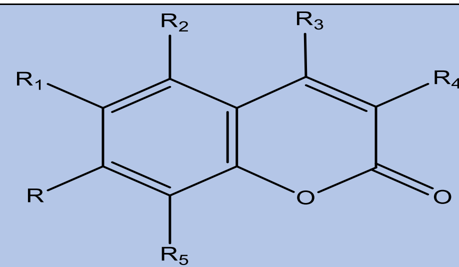
-w-Hydroxymoracin **N**



- Kanzol U (Kanzonol U)(GlabrocoumaroneA)"R= H"
- KanzolV(KanzonolV)"R= Prenyl



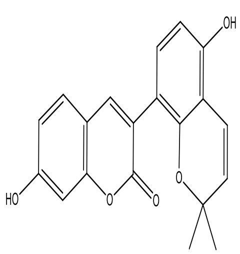
II. Coumarins [14]



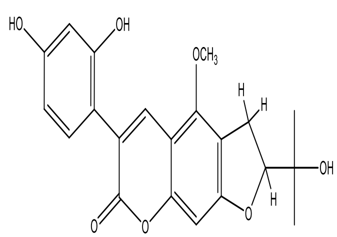
Compound Name	R	R1	R2	R3	R4	R5
-Umbelliferone	OH	H	H	H	H	H
-Herniarin (7-Methoxycoumarin)	OCH3	H	H	H	H	H
- Liqcoumarin	H	COCH3	OH	CH3	H	H
-Glycocoumarin	OH	Prenyl	OCH3	H	(2,4-DHP)	H
-Glycyrin	OCH3	Prenyl	OCH3	H	(2,4-DHP)	H
-Licoarylcoumarin	OH	H	OCH3	H	(2,4-DHP)	2-methylbut-3-en-2yl

Other related compounds

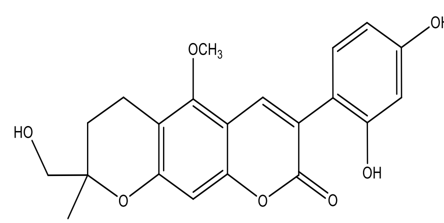
-Glabrocoumarin



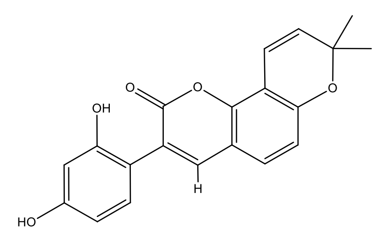
-Licofuranocoumarin



-Licopyranocoumarin



- Kanzonol W (Kanzol W)



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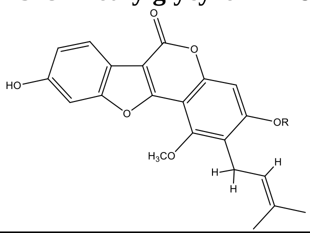
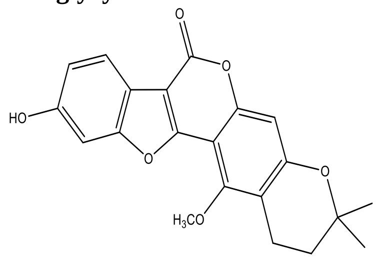
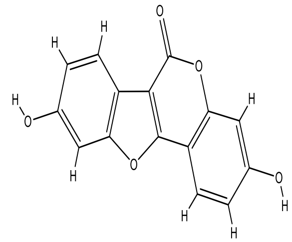
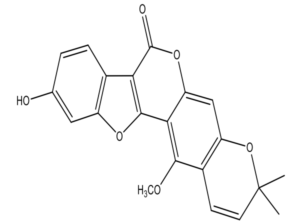
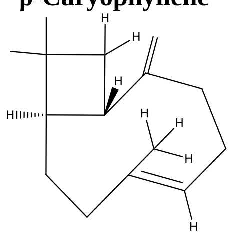
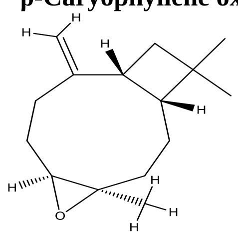
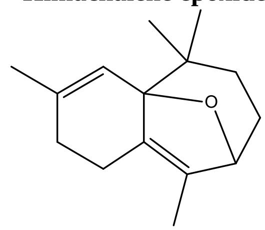
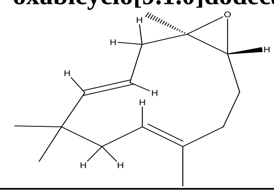
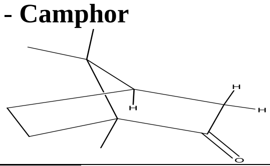
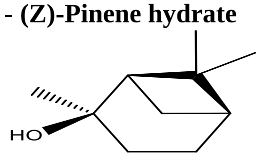
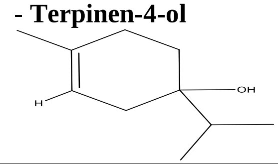
C- Coumestan derivative [14]			
- Glycyrol“R= H” **- 5-O-Methylglycyrol**“R= CH3” 	**- Isoglycyrol** 	**- Coumestrol** 	**-Gancaonin F** 

D- Sesquiterpenes [14]			
- β-Caryophyllene 	**- β-Caryophyllene oxide** 	**- Himachalene epoxide** 	**- Humulene epoxide II (1R,3E,7E,11R)-1,5,5,8-tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene)** 

E- Monoterpenes [14]		
- Camphor 	**- (Z)-Pinene hydrate** 	**- Terpinen-4-ol** 

*DHP: Dihydroxyphenyl

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be used in order to prevent or treat influenza A and B[16].
Glycyrrhizic acid showed activity against the reproduction of the Epstein Barr virus. Licochalcone A, isolicoflavonol, glycycoumarin, glycyrrhisoflavone, and licopyranocoumarin represent five phenolics isolated from liquorice that suppressed human immunodeficiency virus [21].
Liquorice and its components, particularly glycyrrhizin (GL) have shown antiviral efficacy against a variety of viruses such as Hepatitis A virus (HAV), Herpes simplex, Herpes zoster, and Varicella zoster. It acts by inhibiting viral replication and infectivity [22]. GL was effective against enterovirus 71 (EV71) and coxsackievirus A16 (CVA16) infection because it directly activated CVA16. Also, it affected the virus's ability to enter cells and reduced the replication of the Newcastle disease virus [23]. Glycyrrhizin (GL) had antiviral action on three Japanese encephalitis viruses [24]. Furthermore, GL expressed immunostimulant properties by promoting T cell proliferation where it acted synergistically with the duck hepatitis virus (DHV) vaccine [25]. Thus, GL is a potent antiviral chemical that inhibits the activity of various viruses, including HCV, HIV, CVB3, DHV, EV71, CVA16, HSV, and H5N1. It does this by decreasing the adhesion force, stress, and gene expression of the viruses [21].
A recent study adopting an *in vitro* with chemometric approaches identified the following compounds as prospective antivirals against adenoviruse-7 (HAdV-7); violanthin, rhamnoliquiritin, isoliquiritigenin isomer, licoagro-side B, and liquiritin apioside. The high antiviral activity of kaempferol-3-O-rutinoside was further validated by the *in vitro* adenovirus inhibitory assay, which showed IC 50 and CC 50 values of 54.7 ± 1.93 μM and 655.7 ± 2.22 μM, respectively [26].
During the coronavirus crisis in 2019, Chinese health authorities recommended herbs for preventing COVID-19 with liquorice at the top of the list. GL was found to act as an inhibitor of SARS-COV-2 replication compared to ribavirin as it hinders virus reproduction slowing its spread. An *in-silico* studies have shown several phytoconstituents, on top of which the triterpenoidal saponin Glabranin B may be functioning as an inhibitor of cathepsin L, preventing the entry and reproduction of 2019-NCOV host cells [27].
A recent study using the innovative technique of deep learning-based network pharmacology revealed that glabrone and vestitol can inhibit COVID-19 viral replication by inhibiting the activation of the main protease (Mpro), the spike protein (S-protein) and the angiotensin-converting enzyme 2 (ACE2) [28].

5.2.Anticancer effects

Different liquorice extracts are active against intestinal carcinoma cell lines, prostate carcinoma cell lines, colon cancer cell lines, and human monoblastic leukemia, as reported in various studies. Moreover, long-term liquorice administration for hepatitis C infection has been effective in preventing hepatocellular carcinoma (HCC). Intravenous GL improves liver histology and decreases the incidence of hepatic cirrhosis in HCC patients [29]. Isoliquiritigenin also prevented the incidence of 1,2-dimethylhydrazine-induced colon and lung tumors in mice [30]. Many compounds present in liquorice have been identified to exhibit anti-cancer effects by inhibiting cancer cell proliferation and metastasis. The three compounds; glycyrrhetinic acid, isoliquiritigenin, and licochalcone A, stand out as promising modalities for anticancer agents [31]. Furthermore, combinations of liquorice -derived compounds with synthetic antineoplastic agents would be valuable for reducing unwanted side effects. For instance, GL has shown favorable action in counteracting cisplatin resistance in HCC cell

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lines. Wang and Nixon have published a comprehensive review of the anticancer activity of liquorice [32].

5.3. Antiulcerative effects

Many compounds isolated from liquorice as GL, carbenoxolon Na, hemisuccinate Na have anti-ulcerative effects, especially against gastric and duodenal ulcers. A double-blind, placebo-controlled research found that other substances have inhibitory effects against *H. pylori* and could be employed as chemoprotective treatments for *H. pylori* peptic ulcers. To eliminate hypertension caused by liquorice, a processed form of the drug was created in which the GL was removed. This type of liquorice may be used successfully to treat peptic ulcer illness for an extended period of time disease [33].

5.4. Anticoagulant activity

Several studies indicated the anticoagulant activity for the plant since 1997. The effects were mainly due to plant extract or some of its isolated compounds. A previous study indicated that *Glycyrrhiza glabra* aqueous extract exhibits significant antithrombotic activity *in vivo* as it produced an increase in bleeding when given intravenously to rats. The same study also showed that concomitant use of the plant extract decreases the effects of vitamin K and increases the effects of heparin [34]. Glycyrrhizin (GL) is the first plant-based selective thrombin inhibitor [35]. It is found to prolong the thrombin and fibrinogen clotting time. It also increases plasma recalcification duration. Its mechanism of action is believed to take place through interaction with the enzyme's anion binding exosite I without blocking the thrombin catalytic site. Moreover, GL was found to be an effective thrombin inhibitor *in vivo* in agreement with the previously reported *in vitro* results [35]. The antithrombotic activity was tested in two experimental models of induced thrombosis in rats (the stasis model of venous thrombosis and the arteriovenous model). As observed for other direct thrombin inhibitors, such as hirudin and medications derived from hirudin, this compound was more effective in the first study than the second [36]. IV injection of GL (300 mg kg^{-1} body weight) given to rats was shown to prevent venous thrombosis formation without altering the intrinsic or extrinsic pathways. This study was performed in a rat model of inferior vena cava ligation. The reported effects were due to the blockade action of GL on P-selectin lowering neutrophil adhesion and stopping the development of venous thrombosis as a result. These findings imply that GL may be helpful in clinical settings to avoid deep vein thrombosis [37]. A recent study showed the anticoagulant effect of glycyrrhetinic acid and explained it due to its direct inhibitory effect of FXa ; an important coagulation enzyme for thrombin generation [36]. The compound has IC_{50} of 32.6 µmol L^{-1} as tested *in vitro*. Moreover, the *in vivo* experiments confirmed this effect where glycyrrhetinic acid administered intragastric reduced thrombus weight in a dose-dependent manner in a rat venous stasis model [36]. Another study described the biologically guided separation of particular FXa inhibitors from liquorice root and identified liquirtin as a potent inhibitor, with an *in vitro* IC_{50} value of 5.15 µM [38],

Additionally, a study utilizing a mass spectrometry-based chemoproteomic assay combined with molecular docking suggested that licochalcone A can bind to thrombin at both exosite I and the catalytic site. Glabridin effectively inhibits the phospholipase protein kinase c cascade and prevents the activation of the mitogen-activated protein kinase pathways. This reduces [Ca^{+2}] ion mobilization, which in turn limits platelet aggregation [39].

All these studies explain the reported hemorrhagic tendency and herb-drug

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interaction of liquorice with warfarin and other anticoagulant medications [40].

5.5. Estrogenic activity

Liquorice extract exhibited moderate estrogenic activity, which may be beneficial for menopausal women. This effect is primarily attributed to the dihydroflavanone, liquiritigenin, and its parent chalcone, isoliquiritigenin. Liquiritigenin acts as a selective agonist of estrogen receptor beta (ERβ), while isoliquiritigenin exhibits general estrogenic activity. Together, these compounds may help mitigate menopausal symptoms by avoiding stimulation of reproductive tissues and enhancing resilience to estrogen deficiency [41]. Additionally, the extract can promote ovulation and menstruation in amenorrhoeic women [42]. In Japan, liquorice is frequently used in conjunction with peony to treat polycystic ovaries syndrome (PCOS) using a herbal remedy known as Shakuyaku-Kanzo-To, which is believed to decrease the high level of testosterone [43], high-fat diet-induced metabolic syndrome, and obesity [44,45]. Liquorice possesses estrogenic characteristics that may cause aromatase-stimulating activity, which may lower serum testosterone in PCOS women. In a study on PCOS-induced mice, the intake of a daily dose of 100 mg kg^{-1} body weight potentially improves oocyte fertilization rate, reduces ovarian cysts, and enhances embryo development [46]. Another study on Leptazole pellet induced-PCOS rats showed that daily intake of liquorice controlled levels of serum FSH, LH to FSH ratio, irregular follicular phase, and abnormal historical changes in the ovaries [47].

Liquorice can decrease the incidence of intermenstrual bleeding, which affects approximately 20–50% of women taking spironolactone. This effect may be attributed to the enhancement of aromatase activity or the oestrogenic properties of the flavonoid glabridin [48].

In women with hyperprolactinemia caused by the antipsychotic drug risperidone, the combination of peony and glycyrrhiza has been demonstrated to lower high prolactin [49].

5.6. Effect on Body weight and mobility function

Daily intake of root extract decreased total body fat mass in obese diabetic mice, decreased the size of adipocytes, and improved the fate degenerative of hepatocytes [50]. In hypercholesterolaemic rats, the plant extract caused a significant decrease in plasma, hepatic total lipids, cholesterol, triglycerides, and low-density lipoprotein accompanied by a notable rise in the generation of bile acid and the activity of the liver's HMG-CoA reductase, as well as a notable increase in the excretion of bile acid [51].

In a study performed on healthy subjects, daily intake of liquorice suppressed aldosterone and decreased body fat mass without affecting body mass index (BMI) [52]. A randomized clinical trial suggests that its use along with a low-calorie diet can help ameliorate the lipid profile. Consuming liquorice root extract in hypercholesterolemic patients was linked to a decrease in the atherogenic alterations of low-density lipoprotein (LDL), such as decreased oxidation, chondroitin sulfate (CS) binding capacity (retention), and aggregation. These effects were accompanied by moderate decreases in plasma LDL concentrations, total cholesterol levels, and blood pressure [53].

In addition, liquorice flavonoid oil supplementation was shown to improve body balance function and reduce fall risk as demonstrated in a randomized double-blind, placebo-controlled trial on the Japanese population. This was evidenced by a significantly increased one-leg standing time in the intervention group compared to the control group. The observed effects were

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attributed to liquorice's role in reducing body mass index (BMI) and its antioxidant properties, which may improve skeletal muscle function and thereby mitigate fall risk [54].

5.7. Hair growth stimulating activity

Female rats treated with the petroleum ether extract of liquorice proved promising as a hair growth stimulant. Compared to minoxidil and a placebo, the liquorice-treated group exhibited longer hair and a higher proportion of hair follicles in the anagen phase (76%) (active growth stage), compared to 65% in the minoxidil group and 45% in the control group [55].

The same effect was also observed upon using 2% hydroalcoholic extract of liquorice to treat alopecia in female albino rats compared to minoxidil [56]. Glycyrrhetic acid when applied to the skin surface of fur model mice induced by H_2O_2 caused a marked increase in the number of hair follicles and hair blackening and an increment in the β-catenin, and tyrosinase expression levels in the skin tissue [57]. 18-β-glycyrrhetinic acid may have therapeutic promise for androgenetic alopecia as it increases the proliferation of outer root sheath cells and dermal papilla cells isolated from human hair follicles. Indicating that it encourages the growth of hair. Additionally, it reduced the activity of testosterone 5α-reductase, an enzyme that converts androgen to dihydroandrogen. The expression of transforming growth factor-β1 (TGF-β1), which is responsible for transitioning the hair cycle from the anagen to the telogen phase, was likewise inhibited by 18-β-Glycyrrhetinic acid [58].

5.8. Dermatocosmetic activity

Studies showed the efficacy of ethanolic extract of heat-treated liquorice cultivar as anti-melanogenic, tested by reduction of intracellular tyrosinase and melanin content in B16F10 melanoma cells [59, 60]. Glabridin has been highlighted as one of the compounds responsible for the tyrosinase inhibition activity without affecting DNA synthesis along with glabrene, isoliquiritigenin, licuraside, isoliquiritin, and licochalcone A [61]. A formulation of 20% liquiritin cream applied at 1 g/day for 4 weeks was reported effective in melasma disease without affecting tyrosinase [62]. Ciganovic et al. [63], highlighted for *G. glabra* extract, has excellent anti-aging properties because of its good anti-oxidant activity, tyrosinase, and elastase inhibitory activity as well as anti-inflammatory activity [64]. While Prenylflavonoids dehydroglyasperin C, dehydroglyasperin D, and isoangustone prevent wrinkles through their superoxide scavenger activity. Moreover, eicosanyl caffeate and docosyl caffeate, displayed a potent elastase inhibitory activity [65].

5.9. Wound healing

A cream containing aqueous extract of liquorice was a potent healing agent in open wound healing in rabbits [66]. In both normal and diabetic mice, glycyrrhizin-based hydrogels promote the healing of cutaneous wounds via affecting keratinocyte migration. The primary cause of this impact is an increase in antioxidant biomarkers such as glutathione peroxidase activity superoxide dismutase, and reduced glutathione levels, together with a significant decrease in the oxidative stress marker malondialdehyde. On the other hand, liquorice extract used at 10% concentration was not effective in the healing of *Pseudomonas aeruginosa* infected burn wounds [67]. In a study on Wister rats when compared to the control group, the addition of liquorice extract supplementation increased angiogenesis and collagen deposition by up-regulating the expression levels of the genes bFGF, VEGF, and TGF-β [68]. In a comparative clinical trial on patients with second-degree burns, hydrogel containing hydroalcoholic extract of liquorice root can accelerate the healing process of burns compared to the control

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group which was treated with only hydrogel [69]. The glyrrhizin-based hydrogel also accelerated wound healing when compared to commercial hydrogel when applied on normoglycemic and diabetic rats as wounds were fully re-epithelialized with less granulation tissue and longer epithelial tongues [66].

5.10. Immunomodulating effect

Oral glycyrrhizin tablet administration stopped HIV-positive individuals' illness from progressing and kept their CD4/CD8 levels high [70]. Glycyrrhizin increased the survival rate in mice infected with influenza virus A2 by 70% and this effect is not attributed to the anti-viral effect as the compound did not inhibit viral replication *in vitro* [71, 72]. The effect of glycyrrhizin was inhibited by giving infected mice interferon monoclonal antibody. This confirms that glycyrrhizin's antiviral effect stems from its stimulation of γ interferon production by T-cells.

5.11. Effect on neurological problems, age-related disorders, and learning and memory

Liquorice in Ayurveda and Persian ethnomedicine as well is generally used as a rejuvenator and for boosting memory [73]. A combination of anti-inflammatory, and antioxidant can be the cause of its neuroprotective role [74]. In a study on diazepam-induced amnesia rats using the elevated plus maze method liquorice extract showed a significant enhancement in learning and memory as indicated by a decrease in Transfer latency TL [75]. In a similar study, the aqueous extract when given in a daily dose of 150 mg/kg improved spatial learning and memory retention of mice measured via Elevated plus-maze (Transfer latency) and passive avoidance paradigm [74]. In a study on children aged 14-16 years, liquorice granules when given daily for 12 weeks helped in improving functional aspects of IQ, several aspects of quality of life parameters, and health [73, 76]. This effect may be due to improving acetylcholine levels in the brain and also by mediating gamma-aminobutyric acid (GABA). Oral intake of liquorice for six months helped in improving The Parkinson's patients' situation for the Unified Parkinson's rating scale expressed significantly better motor test and rigidity scores [77, 78]. Administration of liquorice extract in a prenatal valproic acid model of autism spectrum disorder in Wistar rat offspring was beneficial in increasing motor activity, reducing recurrent behavior, and reducing anxiety-related behaviors [79].

Glycyrrhizic acid (GA) of liquorice root enhanced superoxide dismutase activity and reduced lipid peroxidation in vascular dementia rats leading to the reduction of oxidative stress and consequently may help in the treatment of cognitive deficits caused by stroke, Alzheimer's disease, or brain injury [80]. It was found that intraperitoneal administration of GA helped to increase superoxide dismutase and decrease cerebral edema, vacuolization, degeneration, and destruction of neurons in a rat model with cerebral ischemia induced by middle cerebral artery occlusion [81, 82]. A limited study on mice for 3 days suggested that glabridin in a relatively high dose (2 and 4 mg kg (-1), P. O.) significantly antagonized the amnesia induced by scopolamine (2 and 4 mg kg (-1), P. O.) [82]. Isoliquiritigenin has proved to inhibit neurotoxicity and reduce stress mediators, and liquiritigenin isolated from liquorice root has the potency to reverse the glutamate-induced apoptosis in HT22 cell line [83]. Sarkar *et al.* [81] have published a review article on the mechanistic insights for neurological disorders of liquorice.

5.12. Antidepressant effect

As per the principles of Ayurveda, the strength of your ojas, the essential fluid of life and the source of energy, determines your immunity, vitality, and emotional resilience.

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Liquorice is thought to be rich in prana, or life energy, and possess a deeply relaxing, and renewing effect [84]. The antidepressant effect of liquorice was tested on mice using the widely used methods forced swim test and tail suspension test and it was found to reduce the immobility times of mice in both, this effect was not reduced by p-chlorophenyl alanine while prazocin did suggesting its mechanism is due to increase of brain norepinephrine and dopamine, but not by increase of serotonin [85], the same authors conducted a similar experiment using glycyrrhizin and concluded same mechanism of action for the compound [86]. A similar study conducted on adult rats using liquorice total flavonoids showed a significant reduction in immobility time [87], particularly liquiritin which additionally increased grid crossings, and uprights in rats. Both total liquorice flavonoids (LF) and liquiritin were found to decrease serum corticosterone the stress hormone related to hypothalamic-pituitary-adrenal axis dysfunction thus it can be speculated that controlling the HPA axis may be the mechanism by which LF and liquiritin exert their antidepressant effects [87, 88]. According to studies, liquorice flavonoid greatly enhances each other's ability to induce head shaking following 5-HT injection. The enhancement of brain 5-HT neurological function in mice may be the reason behind liquorice flavonoid treatment of depressed behaviour, as evidenced by the fact that monoamine oxidase (MAO) activity in the cortex, hippocampus, and thalamus of the mice did not differ from that of normal controls, same results were found concerning the effect of liquiritin [88]. In brief, LF and liquiritin are the material basis of liquorice in treating Major depressive disorder as suggested by Wang *et al.* in their review on the antidepressant effect of total flavonoid and liquiritin [89].

5.13. Xanthine oxidase inhibition

Several fractionation steps of liquorice alcoholic extract followed by orthogonal projection to latent structures (OPLS) model implemented to correlate *in vitro* xanthine oxidase inhibitory activity to their chemical profile presented by their chromatographic fingerprints lead to the identification of 3,3´,4,4´-tetrahydroxy-2 methoxychalcone (IC50=28.29 mM) and 7,4´-dihydroxyflavone (IC50=32.86 mM) as potent xanthine oxidase inhibitors [90].

5.14. Effect on Eye disorders

In Ayrevida, liquorice is used with ghee for degenerative eye conditions and dry eyes. *In vitro* studies showed that Glabridin stopped the progression of retinal degeneration and decreased the production of deposits on the retinal pigment epithelial (RPE) layer caused by NaIO3, therefore preventing retinal damage significantly [91]. In a pilot study conducted on 37 patients with a dry eye condition, an eye drop containing 2.5 %glycyrhhizin improved the condition through binding to pro-inflammatory protein found in the tear fluid during conjunctivitis, blepharitis, and DED. And thus inhibiting cytokine activities [92]. Isoliquiritigenin has also an antiangiogenic impact using different experimental models of ocular neovascularization and may be beneficial in case of vision loss due to the growth of abnormal blood vessels in the eye in people with the wet form of age-related macular degeneration [73, 93].

5.15. Effect on periodontal diseases

Liquorice can be beneficial in treating periodontal disease because of its antimicrobial, anti-inflammatory effect, it minimizes the development of plaque, decreases the diameter of the ulcer, and inhibits osteoclastogenesis [94]. Studies showed that liquorice demonstrates considerable potential as a natural therapeutic agent for the treatment of various oral diseases [95] when incorporated into patient's treatment as mouthwashes or as bio-adhesive

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patches [96, 97]. Dental caries are mainly caused by microbial infection S*treptococcus sanguis*, *Lactobacillus* spp. and *Actinomyces* spp., pterocarpenes namely glycyrrhizol A and glycyrrhizol B in addition to the isoflavonoids, 5-O-methylglycryol, isoglycyrol, 6,8-diisoprenyl-5,7,4′-trihydroxyisoflavone and gancaonin G have shown activity against *S. mutans*. In addition, glycyrrhizic acid can inhibit the growth of these bacteria *in vitro* [98]. A sugar-free liquorice lollipop containing glycyrrhizol A has been formulated and found to decrease salivary *S. mutans* when consumed [99-101]. Strong anti-adhesive activities against *P. gingivalis* have been demonstrated by aqueous extracts of raw polysaccharides from *G. glabra* [95]. Licochalcone A inhibits *P. gingivalis* biofilm formation suggesting that using liquorice in oral hygiene products can help preserve the health of the gingiva and oral tissues [102, 103]. Liquorice extract has a significant inhibitory effect on *E. faecalis* while retaining the periodontal ligament cells viability and hence can help as a root canal irrigant and medicament [104]. Liquorice bioadhesive hydrogel patches were proven effective in reducing pain and inflammation and speeding up the healing process of recurring aphthous ulcers [103].

5.16. Hepatoprotective properties

Studies conducted on patients with chronic hepatitis and liver cirrhosis have demonstrated that liquorice formulations can effectively reduce liver inflammation and improve liver function [105]. Glycyrrhizic acid and 18α-glycyrrhetinic are responsible for these effects [2, 106]. Glycyrrhizin was proved also to alleviate CCl_4-induced liver injury, which may be due to the induction of heme oxygenase-1 and the downregulation of proinflammatory mediators [107]. A study suggests that the hepatoprotective effect of the roots may be due to the inhibitory effects of glycyrrhizin and glycyrrhetinic acid on immune-mediated cytotoxicity against hepatocytes and on nuclear factor (NF)-kappa B, which activates genes encoding inflammatory cytokines in the liver [108].

5.17. Antidiabetic effects

Long-term Glycyrrhizin treatment in non-insulin-dependent diabetic model mice significantly lowered blood insulin level without affecting the food intake or body weight and improved the tolerance to oral glucose loading [109]. Another study showed the suppression effect of the ethyl acetate extract of liquorice on the receptors targeted by insulin-sensitizing drugs eg: Pioglitazone. The results indicated that liquorice extract suppresses the increased blood glucose level in mice after sucrose loading. These effects were attributed to six phenolic compounds with glycyrin possessing potent binding activity to these receptors [3, 110, 111].

5.18. Anti-inflammatory activities as well as Antioxidative activities

Evidence has shown that glabridin and isoliquiritigenin are linked to *G. glabra*'s inhibition of the inflammatory enzymes lipoxygenase and cyclooxygenase synthesis. GL also exhibited steroid-like anti-inflammatory activity. Hispaglabridin B, isoliquiritigenin, and paratocarpin B present in *G. glabra* extract were found to be potent antioxidant agents in peroxynitrite antioxidant assay. Another study proved the protective effects of isoliquiritigenin from reactive oxygen species (ROS) produced by arachidonic acid and iron. Moreover, polysaccharides of *G. glabra* have antioxidant activity and reduced oxidative stress in mice with high-fat diets [112].

5.19. Antimicrobial and antiprotozoal activities

Many studies confirmed the antimicrobial activities of liquorice extracts against many Gram -positive and Gram-negative bacteria. Glicophenone and glicoisoflavanone present in the plant have potential activity to control Methicillin-resistant Staphylococcus aureus

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(MRSA) infection [113]. Licochalcone A isolated from the plant has an inhibitory effect against food-borne pathogens like *Clostridium* species and *Bacillus subtilis* [114]. Moreover, it alters the ultrastructure of parasite mitochondria and selectively blocks the respiratory chain of Leishmania parasites, making it a potential target for antileishmanial medications [33].

Table 2 summarizes the most important pharmacological activities reported for the individual compounds isolated from *G. glabra*.

5.20. Other well-known pharmacological activities

Other activities reported for liquorice include antitussive, bronchodilator, demulcent effects, insecticidal, anti-inflammatory, activities [116-118].

Table 2: An overview of the major research involving compounds derived from liquorice

Activity	Compound	Method	Major finding	Reference
Antiviral effect	Licochalcone A, isolicoflavonol, glycycoumarin, glycyrrhisoflavone, and licopyranocoumarin	*In vitro*	-suppress human immunodeficiency virus	[21]
	Glycyrrhizin	*In vitro*	-antiviral action on three Japanese encephalitis virus -inhibits the activity of various viruses, including HCV, HIV, CVB3, DHV, EV71, CVA16, HSV, and H5N1	[24] [21]
	Glabranin B	*In silico*	-prevent the entry and reproduction of 2019-NCOV host cells	[27]
Anticancer effects	Glyrrhizin	*In vivo*	-decreases the hepatic cirrhosis in Hepatic cellular carcinoma patients	[29]
	Isoliquiritigenin	*In vivo*	-Prevent colitis-associated colorectal cancer in mice	[30]
	glycyrrhetinic acid, isoliquiritigenin, and licochalcone A	*In vivo*	-promising modalities for anticancer agents	[31]
Anticoagulant	-Glycyrrhizin	*In vivo*	-GL demonstrated strong antithrombotic action, and this capacity was unrelated to heparin cofactor II or antithrombin III potentiation.	[36]
	-Glycyrrhetinic acid	*In vitro* *In vivo*	-direct inhibitory effect of FXa -reduced thrombus weight	[40]
	-Liquirtin	*In vivo*	-FXa inhibitor	
	-licochalcone A	*In vitro* & *In silico* studies	-can bind to thrombin both exosite I and the catalytic site.	[40]
	-Glabridin	*In vitro* & *In silico* studies	-limits platelet aggregation	[71]
Hair growth stimulating activity	Glycyrrhetic acid	*In vivo*	-It caused marked increase in the number of hair follicles	[57]
	18-β-glycyrrhetinic acid	*In vivo*	-it encourages the growth of hair	[58]
Dermatocosmetic activity	Glabridin	*In vitro*	-anti-melanogenic activity via tyrosinase inhibition [61]	[61]
	Prenylflavonoids		-superoxide scavenger and prevent wrinkles	[64]
Wound healing	Glyrrhizin	*In vivo*	-accelerated wound healing[66]	[115]

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Immunomodulating effect	Glycyrrhizin	Clinical *In vivo*	-stopped HIV-positive individuals' illness from progressing. -increased the survival rate in mice infected with influenza virus A2	(57, 71, 72)
Neurological problems	Glycyrrhizic acid	*In vivo*	-may help in the treatment of cognitive deficits	(79)
	Glabridin	*In vivo*	-antagonized the amnesia induced by scopolamine	(82)
	Isoliquiritigenin		-Inhibit neurotoxicity	(83)
Antidepressant effect	Liquiritin	*In vivo*	-Has antidepressant effect via controlling the HPA axis	(87)
Eye disorders	Glabridin	*In vitro*	-It stopped the progression of retinal degeneration	(91)
	glycyrhhizin	Clinical	-Improved dry eye condition	(92)
	Isoliquiritigenin	*In vivo*	-potential antiangiogenic molecule	(93)
In periodontal diseases	Pterocarpenes and isoflavonoids	*In vitro*	-Have antibacterial activity against those causing dental caries	(97)
	Glycyrrhizic	*In vitro*	-Inhibit growth of these bacteria	(98)
	Licochalcone A	*In vitro*	-inhibits *P. gingivalis* biofilm formation	(102)
Hepatoprotective properties	Glycyrrhizin	*In vivo*	-alleviate CCl_4-induced liver injury	(106)
Antioxidative activities	Hispaglabridin B, isoliquiritigenin, and paratocarpin B	*In vitro*	-potent antioxidant agents	(33, 112)
Antimicrobial and antiprotozoal activities	Glicophenone and glicoisoflavanone	*In vitro*	-May control Methicillin-resistant Staphylococcus aureus (MRSA) infection	(113)
	Licochalcone A	*In vitro*	-have inhibitory effect against food-borne pathogen	(33, 114)
	Glycyrrhetinic acid	In vitro	-Active against *Helicobacter pylori*	(33)

6. Common side effects of liquorice

Glycyrrhizin mimics the hormone aldosterone, There are several reports that liquorice increases cystolic and diastolic pressure and decreases serum potassium level [119], high consumption that is, over 200 mg can lead to serious problems for people with high blood pressure. Glycyrrhizin, 3-monoglucuronyl glycyrrhetinic acid, and Glycyrrhizic acid have been implicated in these negative consequences. Therapeutic dosages of liquorice have been considered safe in humans with close monitoring of blood pressure and potassium levels during chronic consumption [120].

Cases of toxicity due to black liquorce, a confectionary made mainly from liquorice, have been reported, where consumption of an amount way above average leads to hypotension, tachycardia, tarry stool, and INR 5.5 in 80-year-old lady on warfarin [120, 121], in addition to the death of a 54-year-old man after ventricular fibrillation-related cardiac arrest after consumption of big amount of black liquorice [122].

Liquorice influences the cytochrome P450 family of enzymes, potentially leading to a reduction in the bioavailability of various medications, including phenprocoumon. Additionally, liquorice flavonoids and isoflavonoids may exhibit estrogenic effects. Liquiritigenin has demonstrated a strong binding affinity for the bovine uterine estrogen receptor. Moreover, glycyrrhizic acid (GA) has been associated with an increased risk of miscarriage, and should therefore be avoided in patients taking hydrocortisone, prednisone, or oral contraceptives [117].

7. Safety of liquorice

The Food and Drug Administration (FDA) has labeled liquorice as “Generally Recognized as Safe. Several studies on rats and mice have shown no toxic effect on the death rate, body weight, haematological [119], and histopathological data, no teratogenic

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effect was observed as measured via fetal mortality rate, inhibition of fetal growth, and deformities. A recent review covered the toxic effects of liquorice [122, 123].

Concerning the daily maximum dose, The Dutch Nutrition Information Bureau restricts the usage of liquorice to 200 mg/d, despite the World Health Organization's recommendation that 100 mg/d be used safely without any negative effects. This agrees with the study conducted by Sontai et al where half of the 14 participants in research that consumed 100–200 mg/d of liquorice had to be removed from the study early because of edema or hypokalaemia [71]. Numerous genotoxic investigations have demonstrated that glycyrrhizin is neither mutagenic nor teratogenic, and under some circumstances, it may even have anti-genotoxic qualities [10]. Both the UK Food Additive and Contaminants Committee and the Council of Europe determined a limit of less than 50 ppm glycyrrhizin.

8. Conclusion

Radix Glycyrrhiza is one of nature's gifts that contributes to plenty of benefits on both nutritional and medicinal levels. Besides, its sweet taste has contributed to its high demand and extensive use across various commercial applications. It is one of the oldest herbs employed in traditional medicine across various cultures. Comprehensive reports and research have been carried out on the biological activity of liqourice, encompassing *in silico*, *in vitro*, *in vivo*, and human clinical studies. The plant extract and its isolated compounds showed anticancer, antiviral, anti-inflammatory, antioxidant, anti-ulcerative potential, and many other activities. The common side effects linked to liquorice are few mainly hypertension and fluid retention. Liquorice is rich in phytoconstituents, with glycyrrhizin being the most extensively investigated for its pharmacological actions among them. Furthermore, the chemical constituents of the plant present substantial potential for generating novel molecules with diverse medicinal applications, informed by its traditional uses. This promise holds significant implications for modern drug discovery and development.

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Competing Interests

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Author Contribution

RI and HF provided the main conceptual ideas and contributed to discussing the data. RM and HF did the data gathering. All authors contributed to the manuscript writing revised the manuscript draft and reviewed the final version of the manuscript.

Highlights

- Liquorice is one of the most well-known traditional herbal remedies worldwide.
- Numerous chemical classes as triterpene saponins, flavonoids, and polysaccharides.
- It is well-reputed for its antiviral, expectorant, and antiulcer activities.
- Less known activities are anticoagulant, immunomodulating, and antidepressant.

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