

Computational Studies on Drug Likeness and Pharmacokinetic Profile of Selected Phytoconstituents from Liquorice

Research Article

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Abstract

Liquorice consists of dried, unpeeled, roots and stolons of *Glycyrrhiza glabra* Linn., traditionally used as an expectorant, demulcent, antispasmodic, flavoring agent and also used in the treatment of rheumatoid arthritis inflammation and Addison's disease. It has reported for the presence of wide variety of simple and complex primary and secondary phytoconstituents. In the present investigation an attempt has been made to study the drug likeness properties and pharmacokinetic profile of selected phytoconstituents from Liquorice using computer and server based technology. We have selected Lihiritin, Isoliquiritin, Shinflavanone, Licopyranocoumarin, Methoxyficifolinol, Licoriphenon, Isoliquiritigenin, Ligquiritigenin, Prenyllicoflavone A, and Glisoflavone. PubChem database server is used for the find out the canonical smiles. Molsoft server is used for the drug likeness and molecular property prediction. The using the admetSAR server was used for the determination of pharmacokinetic profile along with some toxicity investigations. The results of investigation yield the drug likeness score of selected phytoconstituents along with its absorption, distribution, metabolism, and excretion profile along with some toxicity behaviors of selected phytoconstituents. The present investigation concludes that computer and server based screening play important role for identification of drug like candidates from Liquorice and also data obtained from admetSAR is valuable for research on Liquorice.

Key Words: *admetSAR*, Liquorice, Liquiritin, Molsoft, PubChem, Toxicity Investigation.

Introduction

Liquorice is the common name of *Glycyrrhiza glabra* consist of dried, unpeeled, roots and stolons of *Glycyrrhiza glabra* Linn, belonging to family Leguminosae contains not less than 3.0 per cent of glycyrrhonic acid. It is a unpeeled yellowish dark brown external and yellowish internally while peeled liquorice is pale yellow in color. It is faint and characteristics in odour and sweet in test. Size of plant is 20-50cm in length and 2cm in diameter, cylindrical pieces which are straight may be peeled or unpeeled. Peeled liquorice is angular. It is fibrous in bark and splintery in wood. (1-3).

Therapeutics Uses

Traditionally liquorice has been used as an expectorant and demulcent it is also used as flavoring agent in formulation with nauseous drugs like ammonium chloride, alkali, iodides, quinine, and cascara. Drug is also in antispasmodic this is due to the

flavonoid glycoside isoliquiritine the aglycone part of this glycoside has antispasmodic effect. The glycyrrhetic acid employed in place of corticosteroids for the treatment of rheumatoid arthritis inflammation and Addison's disease. Liquorice is used most commonly as flavoring agent for chewing tobacco and snuff tobacco.(4)

Phytoconstituents

The roots of *Glycyrrhiza glabra* linn. contain glycyrrhizin which is a saponins that is 60 times sweeter than cane sugar, flavonoids rich fraction includes liquiritin, isoliquiritin, liquiritigenin and rhamnoliquirilin and 5 new flavonoids like glucoliquiritin apioside prenyllicoflavone-A, shinflavanone, shinperocarpin and 1-methoxyphaseolin isolated from dried roots. Isolation and structure determination of licopyrano coumarin, licoaryl coumarin, glisoflavone and new coumarin-GU-12 also isolated. Four new isoprenoid-substituted phenolic constituents—semi licoiso flavone B, 1-methoxyficifolinol, isoangustone-A, and licoriphenone isolated from roots. A new prenylated isoflavan derivative, kanzonol-R was also isolated. (13) The presence of many volatile components such as pentanol, hexanol, linalool oxide A and B, tetramethyl pyrazine, terpinen-4-ol, α -terpineol, geraniol and others in the roots is reported. Presence of propionic acid, benzoic acid, ethyl linoleate, methyl ethylketine, 2,3-butanediol,

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furfuraldehyde, furfuryl formate, 1-methyl-2-formylpyrrole, trimethylpyrazole, maltol and any other compounds is also isolated from the essential oil¹³. The Indian roots show various 2-methyliso-flavones, and an unusual coumarin, C liquocoumarin, 6-acetyl-5-hydroxy-4-methylcoumarin. Asparagine is also found. Glycyrrhizin (glycyrrhizic acid; glycyrrhizinate) constitutes 10–25% of licorice root extract and is considered the primary active ingredient. Glycyrrhizin is a saponins class compound comprised of a triterpenoid aglycone, glycyrrhetic acid (glycyrrhetic acid; enoxolone) conjugated to a disaccharide of glucuronic acid.⁽¹⁾

Lipinski's rule of 5 also known as Pfizer's rule of 5, is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has chemical properties, physical properties that would make it a likely orally active drug in humans. The rule of 5 predicts that poor absorption or permeation is more likely when there are more than 5H bond donors, 10H bond acceptor, the molecular weight is greater than 500, and calculated logP is greater than 5. However Lipinski specifically state that the rule of 5 only holds for compounds that are not substrates for active transporter. The admetSAR server is used for describing the molecular properties important for a drug pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion.

Literature search revealed that till date no computational studies have been reported on computer based screening on Liquorice to investigate its drug likeness properties and profile of ADME along with some toxicity investigations. Hence in the present investigation an attempt has been made to study drug likeness properties and ADME profile of selected phytoconstituents from Liquorice using computer applications and servers.

Materials and Methods

Server used

PubChem database, Molsoft, admetSAR

Phytoconstituents used

Liquiritin, Isoliquiritin, Shinflavanone, Licopyranocoumarin, Methoxyflicifolinol, Licoriphenon, Isoliquiritigenin, Ligquiritigenin, Prenyllicoflavone A, and Glisoflavone.

Role of Servers used in study

PubChem database is used for the find out the canonical SMILES. PubChem is the give freely accessible chemical information like molecular formula, structure, chemical and physical properties, biological activities, safety and toxicity information. Molsoft server is used for the drug likeness and molecular property prediction. The molecular properties like molecular weight, hydrogen bond acceptor, hydrogen bond donor, drug likeness score is found out. The admetSAR server used for the determination of pharmacokinetic profile.

Determination of Physicochemical Properties and Drug Likeness Score

In this present investigation we have identified and taken around 10 phytoconstituents from Liquorice for determining drug likeness score according to Lipinski's Rule of Five. Lipinski's rule of five was followed so as to find out drug likeness property of each phytoconstituents. The data about drug likeness was complied with adherence of Lipinski's rule. The canonical SMILES (Simplified Molecular Line Entry System) were obtained from PubChem and in order to apply them in Molsoft server to gather data.⁽⁶⁾

Determination of Absorption, Distribution, Metabolism and Excretion (ADME) Profile

The pharmacokinetic property such as absorption, distribution, metabolism and excretion of phytoconstituents play important role in drug development process. We have used the online server admetSAR to predict several pharmacokinetic aspects. admetSAR evaluates pharmacokinetic properties such as plasma protein binding, skin permeability, P-glycoprotein, Blood Brain Barrier (BBB), Human intestinal absorption and buffer solubility along with other important aspects of ADME. ⁽⁷⁾

Results and Discussion

Liquorice consists of various phytoconstituents and found to exert many pharmacological and biological actions. In the present computational screening, we have selected Liquiritin, Isoliquiritin, Shinflavanone, Licopyranocoumarin, Methoxyflicifolinol, Licoriphenon, Isoliquiritigenin, Ligquiritigenin, Prenyllicoflavone A, and Glisoflavone as important constituents based on Lipinskies Ro5. Lipinski's rule of 5 also known as Pfizer's rule of 5, is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has chemical properties, physical properties that would make it a likely orally active drug in humans. The rule of 5 predicts that poor absorption or permeation is more likely when there are more than 5H bond donors, 10H bond acceptor, the molecular weight is greater than 500, and calculated logP is greater than 5. However Lipinski specifically state that the rule of 5 only holds for compounds that are not substrates for active transport. The molecular weight, hydrogen bond acceptor, hydrogen bond donor, log P value and drug likeness score of identified and selected phytoconstituents were presented in Table 1.

The admetSAR server is used for describing the molecular properties important for a drug pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion. The pharmacokinetic property such as absorption, distribution, metabolism and excretion of phytoconstituents play important role in drug development process. The admetSAR evaluates pharmacokinetic properties such as plasma protein binding, skin permeability, P-glycoprotein, Blood Brain Barrier (BBB), Human intestinal absorption and buffer

solubility along with some toxicity prediction. The admetSAR profile of Liquiritin, Isoliquiritin, Shinflavanone, Licopyranocoumarin, Methoxyficifolinol, Licoriphenon, Isoliquiritigenin,

Ligquritigenin, Prenyllicoflavone A, and Glisoflavone is presented in Table 2. The Heat map is generated from data obtained from AdmetSAR and presented in Figure 1.

Table 1: Phytoconstituents and Molecular Properties Prediction by Molsoft Analysis

Sl. No.	Phytoconstituents	Mol. Weight	HBA (>10)	HBD (>5)	Log P (>5)	Drug Likeness Score
1	Liquiritin	418.13	9	5	0.2	0.33
2	Isoliquiritin	256.07	4	2	2.4	0.79
3	Shinflavanone	390.18	4	1	5.86	0.51
4	Licopyranocoumarin	384.12	7	3	3.25	0.37
5	Methoxyficifolinol	257.11	3	1	2.68	0.29
6	Licoriphenon	372.16	6	3	4.64	0.72
7	Isoliquiritigenin	256.07	4	3	2.91	0.34
8	Ligquritigenin	256.07	4	2	2.4	0.79
9	Prenyllicoflavone A	390.18	4	2	7.5	0.51
10	Glisoflavone	368.13	6	3	3.89	0.34

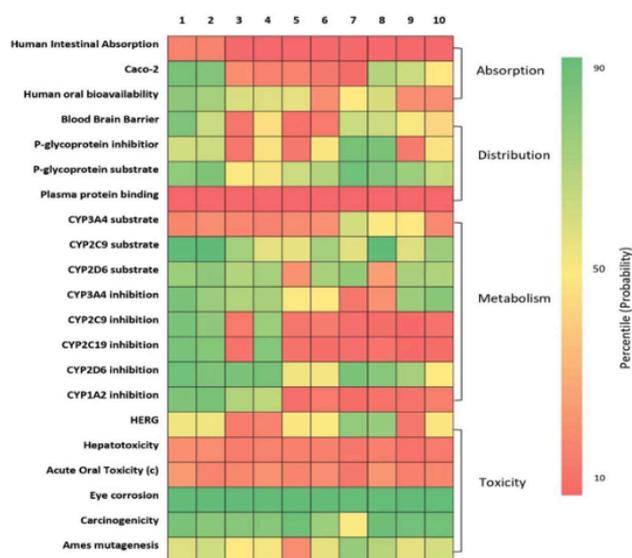
Table 2: The admetSAR profile of selected phytoconstituents

		1	2	3	4	5	6	7	8	9	10
ABSORPTION	HIA	+	+	+	+	+	+	+	+	+	+
	Caco-2	-	-	+	+	+	+	+	-	-	-
	HOB	-	-	-	-	-	+	-	-	+	+
DISTRIBUTION	BBB	-	-	+	-	+	+	-	-	-	-
	P-glycoprotein (i)	-	-	+	-	+	-	-	-	+	-
	P-glycoprotein (s)	-	-	-	-	-	-	-	-	-	-
	PPB	0.91	0.83	0.94	0.89	0.97	0.82	0.62	0.85	0.8	0.95
METABOLISM	CYP3A4 (s)	+	+	+	+	+	+	-	-	-	+
	CYP2C9 (s)	-	-	-	-	-	-	-	-	-	-
	CYP2D6 (s)	-	-	-	-	+	-	-	+	-	-
	CYP3A4 (i)	-	-	-	-	-	-	+	+	-	-
	CYP2D6 (i)	-	-	-	-	-	-	-	-	-	-
	CYP1A2 (i)	-	-	-	-	+	+	+	+	+	+
EXCRETION	Plasma t1/2	NA	NA	NA							
	Renal clearance	NA	NA	NA							
TOXICITY	HERG	-	-	+	+	-	-	-	-	+	-
	Hepatotoxicity	+	+	+	+	+	+	+	+	+	+
	AOT	III	III	III							
	Eye corrosion	-	-	-	-	-	-	-	-	-	-
	Carcinogenicity	-	-	-	-	-	-	-	-	-	-
	Ames mutagenesis	-	-	-	-	+	-	-	-	-	-

1-Liqhiriti, 2-Isoliquiritin, 3- Shinflavanone, 4-Licopyranocoumarin, 5-methoxyficifolinol, 6- Licoriphenon, 7- Isoliquiritigenin, 8- Ligquritigenin, 9- Prenyllicoflavone A, 10- Glisoflavone.

Human ether-a-go-go inhibition: HERG, Plasma protein binding: PPB, Blood Brain Barrier: BBB, Human Intestinal Absorption: HIA, Human Oral Bioavailability: HOB, Acute Oral Toxicity: AOT, (i): Inhibiter, (s): Substrate.

Figure 1: Heat Map of AdmetSAR profile of selected phytoconstituents



Conclusion

The present investigation concludes that computer and server based screening play important role for identification of drug like candidates from Liquorice and also data obtained from admetSAR is valuable for research on Liquorice. The selected constituents such as Lihiritin, Isoliquiritin, Shinflavanone, Licopyranocoumarin, Methoxyficyfolinol, Licoriphenon, Isoliquiritigenin, Ligquiritigenin, Prenyllicoflavone A, and Glisoflavone are found to be good drug like candidates.

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