Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/7d6r7a05

BIOAVAILABILITY AND PHARMACOKINETICS ,DRUG LIKELINESS PREDICTIONS OF BIOACTIVE COMPOUNDS OF LICORICE USING SWISS ADME SOFTWARE

Dr. N.V.V. Jagan Mohan Reddy[1]*, Varriswathi[2], Dr D.Narendra[3], A.Anusha[4], A.Uma Maheswari[5], B.Aparna[6], B.Lasya[7], B.Lakshmi Sreya[8].

[1*]Professor, Department of Pharmaceitics, VJ' College of Pharmacy, Rajahmundry, Andhrapradesh -India
[2]Assistant Professor, Department of Pharmaceutics, VJ's college of Pharmacy, Rajahmundry, Andhra Pradesh- India.
[3]Principal &Professor, Department of Pharmaceutical analysis, VJ's college of Pharmacy, Rajahmundry, Andhra Pradesh – India.
[4]Student, Department of Pharmacy, VJ's college of Pharmacy, Rajahmundry, Andhra Pradesh – India.
[5]Student, Department of Pharmacy, VJ's college of Pharmacy, Rajahmundry, Andhra Pradesh – India.
[6]Student, Department of Pharmacy, VJ's college of Pharmacy, Rajahmundry, Andhra Pradesh – India.
[7]Student, Department of Pharmacy, VJ's college of Pharmacy, Rajahmundry, Andhra Pradesh – India
[8]Student, Department of Pharmacy, VJ's college of Pharmacy, Rajahmundry, Andhra Pradesh – India

***Corresponding Author:** Dr. N.V.V. Jagan mohan reddy
[*]Professor, Department of Pharmaceitics, VJ' College of Pharmacy, Rajahmundry, Andhrapradesh - India

ABSTRACT

BACKGROUND:

Earlier research on licorice focused on documenting their bioactive compound profiles and traditional use. Before making a drug like substance prediction using information from in-silico experimental models. The current work aimed to examine and analyze the ADMET properties. This study assessed the drug-likeliness and ADMET characteristics of bioactive compounds from licorice.

MATERIALS AND METHODS:The current study will be the first to use the free online tool SWISS ADME to report the ADME characteristics of licorice. The ADME properties of five bioactive compounds from licorice were screened and the results were evaluated.

RESULT:Five bioactive compounds were identified to have good gastrointestinal absorption and can penetrate the brain . These compounds include Glycyrrhizic acid showing better lipophilicity, hydrogen bond donor and hydrogen bond acceptor.

CONCLUSION: This method is for determining the ADME characteristics of the bioactive compounds in Licorice. Based on the information, it was predicted that licorice would be effective in managing the disease. To validate these findings, it is advisable to conduct further controlled experimental research exploring the bioactive compounds' pharmacological effects.

KEYWORDS: ADMET LAB 3.0, licorice, bioactive compounds, medicinal plant, SWISS ADME, drug likeliness.

INTRODUCTION:

MEDICINAL PLANT : Medicinal Plants are the plants. These contains bioactive compounds. Medicinal plants are also known as medicinal herbs. These have been utilized in traditional and modern medicine since prehistoric times to treat or prevent a broad range of health conditions. The medicinal plant contain active ingredients including alkaloids , polyphenols, glycosides, and terpenes. Which can be have anti microbial,anti inflammatory, analgesic etc. These can be used for therapeutic purposes to develop pharmaceutical drugs. Plants containing compounds beneficial for health used for thousands of years[1,4].

Licorice is the root. It has been widely used as a medicinal herb since ancient times. Licorice is also spelled as" Liquorice " and also known as Glycyrrhizae Radix et Rhizoma in the Chinese Pharmacopoeia. Licorice is one of the oldest and most widely used herbal medicine in the world. Widely used in many countries to treat a variety of conditions and has made a great contribution to human health. It is also called as Glycyrrhiza, Sweet wood, Liquiritiae Radix in English. Sussholz and Lakritzenwarzel in German. Reglisse and bias doux in French. Shirin baian or Mak in Persian and Liquirizia Regaliz in Italian and Spanish languages. Licorice refers to the root of the Glycyrrhiza plant, most commonly Glycyrrhiza glabra,and is widely recognised for it's use as a sweet flavouring in food, beverages, medicine and traditional remedies, tobacco and marketed as a dietary supplement. Licorice is a flowering plant of the bean Family Fabaceae, from the root of which a sweet, aromatic, flavouring is extracted. The liquorice plant is an herbaceous perennial legume native to West Asia, North Africa, and Southern Europe[2,6].

BIOACTIVE COMPOUNDS:

There are some bioactive compounds from licorice.

1. Glycyrrhizin.
2. Glycycoumarin.
3. Licochalcone A .
4. Glabridin.
5. Licoricone.

1.GLYCYRRHIZIN: Glycyrrhizin is also called as Glycyrrhizinic acid. It is a sweet tasting compound found in licorice root and stolon (Glycyrrhiza glabra). Glycyrrhizinic acid is a teiterpenoid saponin that is the glucosidueonide derivative. Glycyrrhizin is 30 to 50 times sweeter than sucrose. It is a glycoside utilized for various ailments. It is a strong immunomodulator and maintain the liver functioning for detoxification of drugs. Also used in treating conditions like chronic hepatitis, allergic, asthma, and peptic ulcers.hern Europe[42].

2.GLYCYCOUMARIN: Glycycoumarin is a bioactive compound found in species of the genus Glycyrrhiza (commonly known as licorice), particularly Glycyrrhiza uralensis, which is widely used in traditional medicine. Glycycoumarin as a coumarin derivative. It shows potential hepatoprotective effect, demonstrates antioxidant activity, some studies indicate anti-inflammatory, anti-cancer, effects. Glycycoumarin is isolated from the roots and rhizomes of Glycyrrhiza uralensis and other licorice species[30,31].

3. LICOCHALCONE A: Licochalcone A is a chalconoid, a type of natural polyphenol . It can be isolated from the root of Glycyrrhiza glabra. It shows antimalarial, anti-cancer, antibacterial and antiviral properties in vitro, antiparasitic. It is used in cosmetics for it's soothing and skin protective effects and it's potential in treating various diseases, including cancer and inflammatory conditions. Licorice roots have a long history of use in traditional Chinese medicine and other complementary medicine systems to reduce toxicity and enhance the effects of other herbs[14,15].

4.GLABRIDIN: Glabridin is a prenylated isoflavan from the roots of Glycyrrhiza glabra Linne and has posee great impact on the areas of drug development and medicine, due to various biological

properties such as anti-inflammation, anti-oxidant, anti-tumor, anti-microorganism, bone protection, cardiovascular protection, neuroprotection, hepato protection, anti-obesity and anti-diabetes, anti-cancer, and anti-microbial. Glabridin is an isoflavane, a type of isoflavanoid[37,38].

5.LICORICONE: Licoricone appears to be related to "licorice"(Glycyrrhiza), known for multiple bioactive compounds including flavonoids and triterpenoids with health benefits and anti- microbial properties. One key active compound closely related to licorice metabolites is "Liquiritigenin", a flavanoid found in licorice with anti-microbial effects. It is widely studied for anti-viral, anti-inflammatory and other physiological properties[39].

MATERIALS AND METHODS :

Modelling platform The SwissADME and Admetlab3.0 were used to perform the computational analysis, which included absorption, distribution, metabolism, and excretion (ADME) toxicity; the operating system was Windows 10 Home single Language 64-bit with an Intel ® Core TM i5-6200U CPU @2.30 GHz. Biological data Chemsketch and PubChem https://pubchem.ncbi.nlm. nih.gov were used to find 10 bioactive compounds for this investigation .Two-dimensional (2D) images of the selected compound chemical structures of A. paniculata were obtained from PubChem, Chembank, and recognized indexed published publications Submission web page Accessing http://www.swissadme.ch/ in a web browser displays directly the submission page of SwissADME, where molecules to be estimated for ADME, physicalchemistry, drug-likeness, pharmacokinetics, and therapeutic chemistry properties and recommended value can be input.

ADME TOXICITY : The admetlab3.0 online server predicted the properties of ADME Toxicity https://admetlab3.scbdd.com/server/screening using the input of the bioactive substances Simplified Molecular Input Line Entry System (SMILES) string. We eliminated potentially harmful substances that were AMES carcinogens, mutagens, and inhibitors of the human ethera-go-go gene (hERG). The admtlab3.0 was used to create a collection of ADMET-related attributes for each of the 10 bioactive compounds in the usual mode.LICORICE (GLYCYRRHIZA GLABRA): An ancient medicinal herb used in traditional medicine, food & industry. Contains bioactive compounds like glycyrrhizin, flavonoids, saponins with multiple health benefits.

MEDICINAL PROPERTIES: Anti-inflammatory – reduces inflammation (arthritis, gastric, skin irritation), Demulcent (soothing) – coats & soothes mucous membranes (throat, stomach, intestine), Expectorant – clears respiratory tract (cough, cold, asthma), Antiviral & Antimicrobial – active against herpes, hepatitis, influenza, bacteria, Hepatoprotective – supports liver health, Adrenal support – regulates cortisol, reduces fatigue & stress, Anti-ulcer – protects stomach lining (gastritis, peptic ulcers), Mild laxative – gentle bowel movement .Nutritional / Active Compounds: Glycyrrhizin – sweet, anti-inflammatory, immune boosting.Flavonoids – antioxidants, protect from oxidative stress, Isoflavones & Coumarins – hormonal & anti-inflammatory .USES: Digestive – indigestion, heartburn, ulcers.Respiratory – sore throat, cough, asthma relief.Anti-inflammatory – glycyrrhizin properties.Immune support – strengthens immunity.Skin conditions – psoriasis, skin lightening.Liver protection – protective effect on liver.Culinary – sweets, candies, teas, drinks, gum, tobacco.Other – cosmetics (skin brightening), Ayurveda, Unani, TCM.Benefits: Digestive health – indigestion, heartburn, gut lining support (DGL safer for long-term).Respiratory health – cough relief, loosens mucus, eases bronchitis/asthma.Anti-inflammatory & Antioxidant – joint pain, skin irritation relief.Immune & Antimicrobial – antiviral (herpes, hepatitis C), antibacterial, antifungal.Hormonal & Adrenal support – reduces stress, fatigue, supports PMS management.Caution – may ↑ blood pressure & ↓ potassium (avoid in BP, kidney, heart disease).Chemical constituents:Triterpenoid Saponins: Glycyrrhizin (main sweet compound, sweeter than sucrose), 18α & 18β-Glycyrrhetinic acid (glycone of glycyrrhizin), Licorice Saponins A–E.*Roles*: anti-inflammatory, antiviral, mineralocorticoid-like effects.Flavonoids & Isoflavonoids: Liquiritin, Iso-liquiritin, Liquiritigenin, Iso-liquiritigenin.Role: antioxidant, skin whitening.Coumarins: Herniarin, Glycycoumarin, Umbelliferone.Polysaccharides: Acidic polysaccharides – immunomodulatory.Other Constituents: Essential oil, starch, sugars, proteins, tannins, minerals (Ca, K, Fe, Mg).Major activity & therapeutic

action:Major activity –Glycyrrhizin (saponin), Coumarins, Flavonoids.Therapeutic action – Anti-inflammatory, Antiviral, Antioxidant.

IN-SILICO MODELLING:

INTRODUCTION OF SWISS ADME :The Swiss ADME is web-based tool that predicting the key properties of molecules like absorption, distribution, metabolism,& excretion they all together called as ADME. Based on the medicinal properties it can produce the structures. Developed by "Daina,Meichielin,&Zoete" at the 'SWISS INSTITUTE OF BIONORMATICS'. In vivo ADME testing is costly,time-consuming & put's animal lives at Risk. Where as in silico ADME testing is safer,simpler & faster. This study will use in silico methodologies from Swiss ADME & PKCSM as an integrated online platform for accurate & comprehensive predictions of artemisinin and it's derivative.Swiss ADME is a robust, It is a platform offering a wide array of predictive models, and also gives the strong visualization for the early stage drug discovery the batch processing is suitable.Used in the case of virtual screening.

The bioavailability radar are key visuals. In this software we give the inputs like SMILES (or) the drawn structure. It give the physicochemical,pharmacokinetic,Drug likeness ,synthetic accessibility, medicinal chemistry flags as the out put. There are some rules & limitations for this Swiss ADME software.

DRUG LIKENESS : lipinski, Ghose, Veber, Muegge. Synthetic accessibility: score -1 to 10. Medical alerts : structural alerts Integration & Batch capability Allows batch processing of many molecules usefull for virtual screening & library filtering. Swiss Drug design suite is a part of the SwissADME. It integrates with tools like Swiss similarity. The web servers are used in this work are free & several comparison trails show that ADME performed are better than a number of other frequently used methods. The designing (or) engineering of a novel drug molecule primarily requires knowledge of the features of ADME/T of the new drug compound. The bioavailability showed that the colored zone is the suitable Physicochemical space for oral bioavailability where the following properties were taken into consideration as flexibility, lipophilicity, saturation, size, polarity, & also solubility. By using Swiss ADME software we can also produce the 2D & 3D structures of TUG8.

INTRODUCTION OF ADMET LAB 3.0: It is the latest iteration of the ADMETlab platform a comprehensive online tool designed to predict and evaluate key properties related to drug absorption, distribution, metabolism, excretion, and toxicity (ADMET), alongside physicochemical and medicinal chemistry traits. It’s freely accessible without registration at its official site.

Expanded Coverage & Data Volume: Predictable endpoints increased from 88 to 119—an addition of 31 new endpoints .Training dataset expanded to 1.5× the size of version 2.0, totaling over 400,000 entries .It includes the new Endpoints Include:Physicochemical: pKa (acid/base), melting point, boiling point.Absorption: human oral bioavailability (≥50%), PAMPA permeability. Distribution: transporter inhibitors.Metabolism: CYP enzyme inhibition, human liver microsomal stability. Toxicity: nephrotoxicity, neurotoxicity, ototoxicity, hematotoxicity, genotoxicity, plus several in vitro assays e.g : hERG blockers, cytotoxicity in A549 and HEK293 cells.Enhanced Modeling: DMPNN with Descriptors.ADMETlab 3.0 implements multi-task Directed Message Passing Neural Network (DMPNN) architectures, often combined with molecular descriptors (DMPNN-Des). This fusion allows for deep molecular graph analysis plus descriptor-based insights, improving both accuracy and robustness across tasks .Model performance metrics: Regression tasks: R^2 values mostly between 0.75 and 0.95; even for challenging endpoints like LC50FM, $R^2 \approx 0.68$. New endpoints achieve R^2 between 0.8 and 0.9; $T_{1/2}$ model scores near 0.7 .Classification tasks: AUC values range from 0.72 to 0.99 for established endpoints; newly added ones also score between 0.73 and 0.96 .Comparatively, DMPNN and DMPNN-Des outperform older MGA-based models in most tasks—

DMPNN-Des shows slightly better overall performance, albeit at a minor runtime cost .ADMETlab 3.0 introduces a full-featured API, making the platform far more versatile for developers and researchers.Features include: Molecule Wash: automatic standardization, fragment handling, tautomer and stereochemistry management, charge assignment, isotope correction .Batch prediction: submit multiple molecules and retrieve all 119 predicted endpoints, along with structure (SVG) and task IDs. Uncertainty data is available only via API .Rate limit: recommended up to 5 requests per second to maintain server stability .Users can choose between DMPNN or DMPNN-Des models depending on preference for accuracy or performance .Uncertainty Estimation:A standout addition in this version is the integration of uncertainty quantification for each prediction:Regression models: employ an evidential deep learning approach to estimate both epistemic and aleatoric uncertainty (via "evidential_total") .Classification models: utilize Monte Carlo dropout to generate prediction variances. Outcomes are interpreted using thresholds based on Youden's index, classifying results into 'high confidence' or 'low confidence' predictions .This feature enhances decision support, especially in virtual screening where understanding model reliability is critica .

Comparison with Other Tools: ADMETlab 3.0 stands out among peer platforms (e.g., SwissADME, admetSAR 2.0, pkCSM, ADMET-boost, Interpretable-ADMET).Key differentiators: Feature ADMETlab 3.0 Other Tools; Endpoint coverage Very comprehensive Varies; often narrower Batch/API support Full support Limited or none . Uncertainty estimation: Yes / No.Interpretation & decision support: Colour-coded outputs, uncertainty, alert sub structures generally minimal. Speed (1,000 molecules)~87 seconds Often slower (e.g., SwissADME: ~1560s). These capabilities make ADMETlab 3.0 a highly competitive and practical tool for early-stage drug development. Summary at a Glance.Expanded endpoint set: 119 total, including new pharmacologically significant properties.Massive dataset: 400,000+ entries, 1.5× larger than version 2.0.Advanced modeling: Multi-task DMPNN and DMPNN-Des architectures with strong metrics.API-enabled batch processing: Molecule standardization, SVG outputs, uncertainty access.Uncertainty-aware predictions: Confidence metrics improve result interpretation.Superior performance: Faster and more comprehensive than many counterparts.We use it as a: Via web interface: Manually submit molecules (e.g., SMILES, SDF) for single-molecule or small-batch predictions. Ideal for one-offs or quick checks.Via API: Programmatically submit larger datasets, retrieve structured CSV outputs with predictions, uncertainties, and optionally molecular structures. Choose between DMPNN or DMPNN-Des based on your priority.External Insight (Optional): While ADMETlab 3.0 boasts impressive coverage and accuracy, some studies (e.g., for CYP450 isoforms) note that performance may plateau or not always exceed earlier versions under certain evaluation conditions . That said, the broader improvements in endpoint scope, API access, and uncertainty handling make version 3.0 a substantial leap forward overall. ADMETlab 3.0 is a major upgrade over its predecessors and many peer tools—offering expanded endpoint coverage, deeper models, batch/API capabilities, and crucial uncertainty quantification. It's especially valuable for medicinal chemists and computational researchers seeking reliable, interpretable, and high-throughput ADMET assessments.

FLOW CHART OF LICORICE:

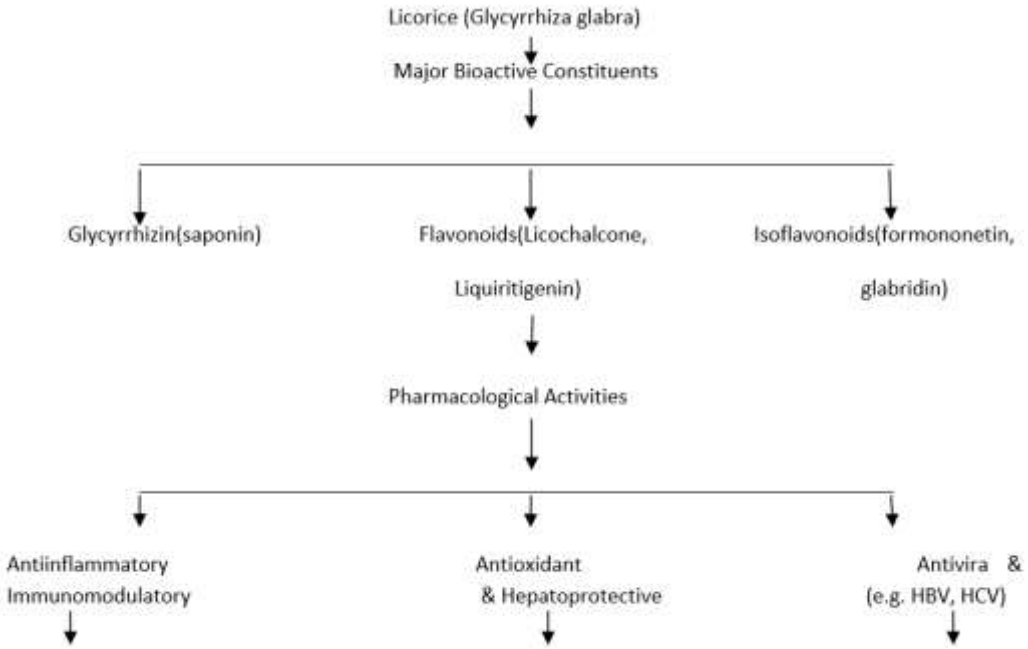
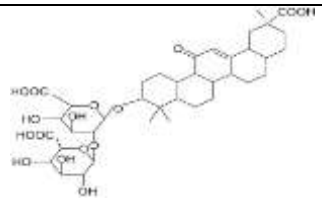
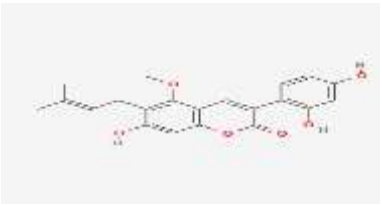
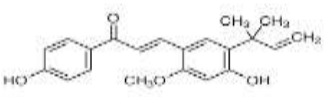
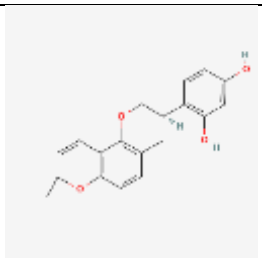
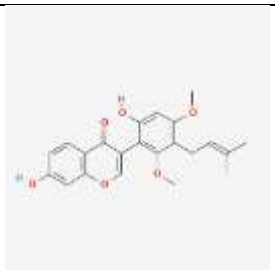


Table 1: General characteristics and PubChem ID of the bioactive compounds of licorice :

S.no	Bioactive compound	Pubchem ID(CID)	Plant part	Structure
1	Glycyrrhizic acid	14982	Root	
2	Glycycoumarin	5317756	Root	
3	Licochalcone A	5318998	Root	

4	Glabridin	124052	Root	
5	Licoricone	5319013	Root	

METHODOLOGY:

Bioactive compounds smiles are copied by using Pubchem software. That smiles are pasted in the Swiss ADME software in http://www.swissadme.ch/. Physicochemical properties of the bioactive compounds obtained as well as pharmacokinetics, water solubility, druglikeliness and boiled eggs, lipophilicity are also obtained and they are shown in below figure.

Figure:1

Bioactive compounds smiles are copied by using Pubchem software. That smiles are pasted ADMET-lab-3.0 software in https://admetlab3.scbdd.com/. Toxicity of the bioactive compounds

was obtained i.e., Ames toxicity, Carcino toxicity, Geno toxicity, and Oto toxicity are shown in the

below figure

Figure:2-physicochemical properties of glycyrrhizic acid

Figure:3-Toxicity of glycyrrhizic acid

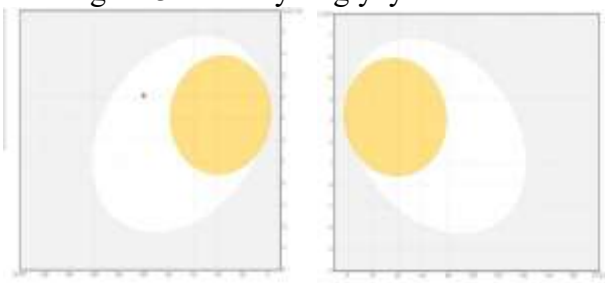


Figure:A Figure:B

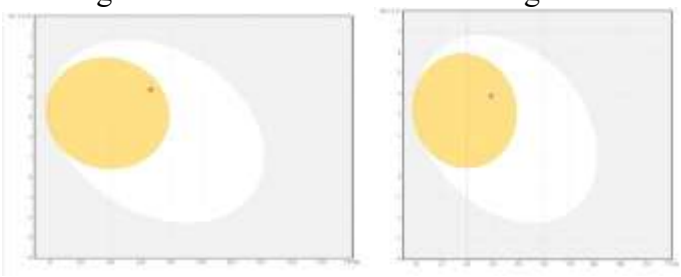


Figure:C Figure:D

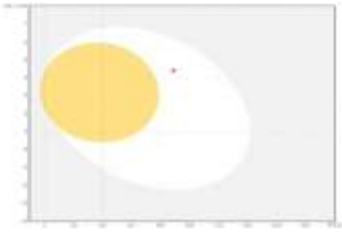


Figure:E

Figure-4:a-glycyrrhigic acid,b-glycycoumarin,c-licochalcone-a,d-glabridin,e-licoricone

Figure:A **Figure:B**

Figure :C **Figure:D**

Figure:E

Figure:5-glycyrrhiza glabra(licorice) Tabel:2 Physicochemical properties of the bioactive compounds of Licorice

Table:2 physicochemical properties of the bioactive compounds of licorice:

Bioactive compounds	Molecular weight	Lipophilicity	No.H-bond donor	No.H-bond acceptor	TPSA	No.of Lipinski rule violation
Glycyrrhizic acid	822.93g/mol	1.49	8	16	267.04A^2	3
Glycycoumarin	368.38g/mol	3.53	3	6	100.13A^2	0
Licochalcone A	338.40g/mol	3.93	2	4	66.76A^2	0
Glabridin	324.37g/mol	3.45	2	4	58.92A^2	0
Licoricone	382.41g/mol	3.67	2	6	89.13A^2	0

Table:3 Drug likeliness of the bioactive compounds of Licorice:

Bioactive compounds	Pgp substrate	CYP_1A_2	CYP_2C_{19}	CYP_2C_9	CYP_3A_4	CYP_2D_6
Glycyrrhizic acid	Yes	No	No	No	No	No
Glycycoumarin	No	No	No	Yes	No	No
Licochalcone A	No	Yes	No	Yes	Yes	No
Glabridin	Yes	Yes	Yes	Yes	Yes	Yes
Licoricone	No	No	No	Yes	No	No

Table:4 Pharmacokinetics of the bioactive compounds of Licorice :

Bioactive compounds	Molecular Formula	Water solublility	GI Absorption	BBB Permeant	Abbot bioavalibility score
Glycyrrhizic acid	$C_{42}H_{62}O_{16}$	Poorly soluble	Low	No	0.11
Glycycoumarin	$C_{21}H_{20}O_6$	Moderately soluble	High	No	0.55
Licochalcone A	$C_{21}H_{22}O_4$	Moderately soluble	High	Yes	0.55
Glabridin	$C_{20}H_{20}O_4$	Moderately soluble	High	Yes	0.55
Licoricone	$C_{22}H_{22}O_6$	Moderately soluble	High	No	0.55

Table:5 Ames mutagen and carcinogen toxicology properties of the bioactive compounds of licorice:

Bioactive compound	Ames toxicity	Oto toxicity	Carcino toxicity	Genotoxicity
Glycyrrhizic acid	Non-toxic	No toxic	Non-toxic	Toxic
Glycycoumarin	Moderate	No toxic	Moderate	Toxic
LicochalconeA	Non-toxicity	No toxic	Moderate	Moderate
Glabridin	Toxic	No toxic	Moderate	Toxic
Licoricone	Moderate	No toxic	Moderate	Toxic

Result:

The ideal molecular weight range should be more than 500g/mol (<500g/mol). The Glycyrrhizic acid having molecular weight is 822.93g/mol.So,Glycyrrhizic acid has more molecular weight more than ideal molecular weight i.e., said to be better compound.According to Lipinski rule the lipophilicity

of compound should be more than 3 than it shows high lipophilicity.The Glycyrrhizic acid shows low lipophilicity,because it has less than 3.According to Lipinski rule the number of hydrogen bond donor should be more thsn 5. So, the Glycyrrhizic acid shows hihgh number of hydrogen bond donors it indicates better compound when compared to other four compounds.According to Lipinski rule the number of hydrogen bond acceptor should be more than 10. The Glycyrrhizic acid shows more than 10 number of hydrogen bond acceptor i.e., it is better compound than other compounds.According to Lipinski rule of TPSA(Technological polar surface area) is above 0 to 140A^2 so, glycyrrhizic acid having more TPSA value while compare to bother bioactive compounds . the number of Lipinski rule violation should be less than 3 so, the compounds Glycycoumarin , Licochalcone A , Glabridin , Licoricone having less than 3 no.of violation i.e. they shows better compound while comparing to glycyrrhizic acid. The water solubility of glycyrrhizic acid showing poor water solubility when compared to other compounds .Glycyrrhizic acid shows low GI absorption when compared to other compounds . Licochalcone A and Glabridin are penetrated blood brain barrier when compared to the other compounds.

Discussion and conclusion:

Incorporating in silico profiling provides a rapid method for identifying active compounds,predictind their biological action and refining then for traditional drug development.This study used SWISSADME and ADMETLAB3.0 web serves to assess the ADMET and drud likeness properties of bioactive compounds derived from (glycyrrhiza glabra) licorice.five specific compounds ,namely Glycyrrhizic acid , Glycycoumarin, Licochalcone A, Glabridin, Licoricone were selected and found to show promising drug like attribute and improved safty profile based on their chemical characteristics,drug likeness score ,ADMET models.Inaddition insilico pharmacophore models were employed to predict potential therapeutic targets,revealing various associated therapeutic possibilities.Based on the available data,licorice shows promise in treating the mentioned disorders nonetheless,controlled experimental research is essential to validate the pharmacological effects of these bioactive compounds. Glycyrrhizic acid shows better lipophilicity and glabridin show high GI absorption and BBB permeant.

REFERENCES:

1. Blumenthal M, Goldberg A, Brinckmann J. Herbal medicine: expanded Commission E monographs. Boston: Integrative Medicine Communications; 2000.
2. Amani M, Mostoufi RS, Kashani HA. Optimal extraction of glycyrrhetinic acid from licorice root. J Food Technol. 2005;3(4):576-80.
3. Awad V, Kuvalekar A, Harsulkar A. Microbial elicitation in root cultures of *Taverniera cuneifolia* (Roth) Arn. for elevated glycyrrhizic acid production. Ind Crops Prod. 2014;54:13-6.
4. Simon JE, Chadwick AF, Craker LE. Herbs: an indexed bibliography, 1971-1980: the scientific literature on selected herbs, aromatic, and medicinal plants of the temperate zone. Connecticut: Shoe String Press; 1984.
5. Evans WC. Trease and Evans' pharmacognosy. London: Elsevier Health Sciences; 2009.
6. Abe H, Ohya N, Yamamoto KF, et al. Effects of glycyrrhizin and glycyrrhetinic acid on growth and melanogenesis in cultured B16 melanoma cells. Eur J Cancer Clin Oncol. 1987;23:1549-55.
7. Abudayyak M, Özdemir Nath E, Özhan G. Toxic potentials of ten herbs commonly used for aphrodisiac effect in Turkey. Turk J Med Sci. 2015;45:496-506.
8. Agarwal R, Mukhtar H. Inhibition of mouse skin tumor-initiating activity of DMBA by chronic oral feeding of glycyrrhizin in drinking water. Nutr Cancer. 1991;15:187-93.
9. Akasaka Y, Hatta A, Sato T, et al. Chronic toxicity study of monoammonium glycyrrhizinate by repeated subcutaneous administration to CD rats for 26 weeks. Jpn Pharmacol Ther. 2008;36:1025-37.

10. Akasaka Y, Hatta A, Sato T, et al. Studies on genotoxicity of monoammonium glycyrrhizinate. Jpn Pharmacol Ther. 2009;37:49-60.
11. Zhao Z, Luo L, Wang Z, Guo B, Gao C. Biomimetic “Trojan Horse” delivery of traditional Chinese medicine with immunogenic hybrid vesicles of bacterial outer membrane and tumor cell membrane for synergistic chemo-immunotherapy of liver cancers. Mater Today Bio. 2025;34:102251. doi:10.1016/j.mtbio.2025.102251
12. Sivakumar H, Brintha Jei J, Muthukumar B. In vitro evaluation of tear strength, antifungal effect, and polymicrobial resistance in *Glycyrrhiza glabra*–incorporated maxillofacial silicone. J Oral Biol Craniofac Res. 2025;15(5):1071-6. doi:10.1016/j.jobcr.2025.07.010
13. Xue W, Fan X, Hui Y, Yu J. Active compounds of licorice ameliorate microplastics-induced intestinal damage by targeting FADD. Food Chem Toxicol. 2025;203:115570. doi:10.1016/j.fct.2025.115570
14. Labrie F, Cusan L, Gomez JL, Diamond P, Candas B. Can combined androgen blockade provide long-term control or possible cure of localized prostate cancer? Urology. 2002;60(3):115-9. Available from: [https://www.sciencedirect.com/science/article/pii/S0090429502016394](https://www.sciencedirect.com/science/article/pii/S009042950201639 4)
15. de la Taille A, Hayek OR, Burchardt M, Melamed J, Buttyan R, Katz AE. Herbal therapy PC-SPES: in vitro effects and evaluation of its efficacy in 69 patients with prostate cancer. J Urol. 2000;164(4):1229-34. Available from: [https://www.sciencedirect.com/science/article/pii/S0022534705671467](https://www.sciencedirect.com/science/article/pii/S002253470 5671467)
16. Pirani JF. The effects of phytotherapeutic agents on prostate cancer: an overview of recent clinical trials of PC-SPES. Urology. 2001;58(2 Suppl 1):35-8. Available from: [https://www.sciencedirect.com/science/article/pii/S0090429501012407](https://www.scienced irect.com/science/article/pii/S0090429501012407)
17. Oh WK, Kantoff PW, Weinberg V, Jones HW, Rini BI, Derynck MK, et al. Activity of the herbal combination, PC-SPES, in the treatment of patients with androgen-independent prostate cancer. Urology. 2001;57(1):122-6. Available from: [https://www.sciencedirect.com/science/article/pii/S0090429500009869](https://www.sciencedirect.com/science/article/pii/S00 90429500009869)
18. Oh WK, Bubley GJ, Balk SP. PC-SPES and prostate cancer. Urol Clin North Am. 2002;29(1):107-18. Available from: [https://www.sciencedirect.com/science/article/pii/S0094014302000174](https://www.sciencedirect.com/science/article/pii/S00940143 02000174)
19. Ye L, Wang ZL, Xu ZQ, Tian YG, Zhang M, Abe I, Ye M. Elucidating the biosynthetic pathway and mechanisms of retrochalcones. J Am Chem Soc. 2025;147(32):29205-14. doi:10.1021/jacs.5c08070
20. Zhao C, Zhang Q, Li H, Wang R, Fan J, Ting JU, Zou J, Ye M. Isolation, structural characterization, and hepatoprotective activities of isopentenylphenols from the root barks of *Glycyrrhiza uralensis*. J Agric Food Chem. 2025;73(25):15741-50. doi:10.1021/ac s.jafc.5c04426
21. Çevik D, Masullo M, Lauro G, Napolitano A, Martucciello S, Paolella G, et al. Dihydroaurones and isoflavan derivatives from the roots of *Glycyrrhiza asymmetrica*. J Nat Prod. 2025;88(2):294-305. doi:10.1021/acs.jnatprod.4c00878
22. Alhusban M, Pandey P, Ahn J, Avula B, Haider S, Avonto C, et al. Computational tools to expedite the identification of potential PXR modulators in complex natural product mixtures: a case study with five closely related licorice species. ACS Omega. 2022;7(30):26824-43. doi:10.1021/acsomega.2c03240
23. Kang Y, Pezzuto J. Induction of quinone reductase as a primary screen for natural product anticarcinogens. Methods Enzymol. 2004;382:380-414. doi:10.1016/S0076-6879(04)82021-4

24. Kape R, Parniske M, Brandt S, Werner D. Isoliquiritigenin, a strong nod gene- and glyceollin resistance-inducing flavonoid from soybean root exudate. Appl Environ Microbiol. 1992;58:1705-10. doi:10.1128/aem.58.5.1705-1710.1992
25. Cao Y, Wang Y, Ji C, Ye J. Determination of liquiritigenin and isoliquiritigenin in *Glycyrrhiza uralensis* and its medicinal preparations by capillary electrophoresis with electrochemical detection. J Chromatogr A. 2004;1042:203-9. doi:10.1016/j.chroma.2004.05.04
26. Ramadan M, Kamel M, Ohtani K, Kasai R, Yamasaki K. Minor phenolics from *Crinum bulbispermum* bulbs. Phytochemistry. 2000;54:891-6. doi:10.1016/S0031-9422(00)00184-9
27. Pan X, Kong L, Zhang Y, Cheng C, Tan R. In vitro inhibition of rat monoamine oxidase by liquiritigenin and isoliquiritigenin isolated from *Sinofranchetia chinensis*. Acta Pharmacol Sin. 2000;21:949-53.
28. Kong L, Zhang Y, Pan X, Tan R, Cheng C. Inhibition of xanthine oxidase by liquiritigenin and isoliquiritigenin isolated from *Sinofranchetia chinensis*. Cell Mol Life Sci. 2000;57:500-5. doi:10.1007/PL00000710
29. Hulka BS, Moorman PG. Breast cancer: hormones and other risk factors. Maturitas. 2001;38(1):103-13. doi:10.1016/S0378-5122(00)00196-1
30. Adlercreutz H. Phyto-oestrogens and cancer. Lancet Oncol. 2002;3(6):364-73. doi:10.1016/S1470-2045(02)00777-5
31. Keinan-Boker L, van der Schouw YT, Grobbee DE, Peeters PHM. Dietary phyto-estrogens and breast cancer risk. Am J Clin Nutr. 2004;79(2):282-8. doi:10.1016/S0002-9165(22)03825-4
32. Qiu S, Dong S, Fan J, Wu C, Qi X. Effect of high mobility group box 1 pathway inhibition on gene expression in the prefrontal cortex of mice exposed to alcohol. Alcohol. 2025;127:47-53. doi:10.1016/j.alcohol.2024.10.047
33. Matuzok TM, Prikhodko VA, Napalkova SM, Buyuklinskaya OV, Okovityi SV. Effects of glycyrrhizinic acid on neuromotor function in leptin-resistant mice. Drug Dev Regist. 2025;14(3):2030. doi:10.33380/2305-2066-2025-14-3-2030
34. Nazari S, Rameshrad M, Hosseinzadeh H. Toxicological effects of *Glycyrrhiza glabra* (licorice): a review. Phytother Res. 2017;31(11):1635-51. doi:10.1002/ptr.589
35. Iafrati MD, Karas RH, Aronovitz M, Kim S, Sullivan TR Jr, Lubahn DB, O'Donnell TF Jr, Korach KS, Mendelsohn ME. Estrogen inhibits the vascular injury response in estrogen receptor alpha-deficient mice. Nat Med. 1997;3:545-8.
36. Korach KS. Insights from the study of animals lacking functional estrogen receptor. Science. 1994;266:1524-7.
37. Phillips DM, Balducci L. Current management of breast cancer. Am Fam Physician. 1996;53:657-65.
38. Broeders MJ, Verbeek AL. Breast cancer epidemiology and risk factors. Q J Nucl Med. 1997;41:179-88.
39. Harris RJ, Lippman ME, Veronesi U, Willett W. Medical progress: breast cancer. N Engl J Med. 1992;327:319-28.
40. Dong S, et al. Activation of rapid signaling pathways and the subsequent transcriptional regulation for the proliferation of breast cancer MCF-7 cells by the treatment with an extract of *Glycyrrhiza glabra* root.Food Chem Toxicol.2007;45(12):24707.
41. Gumpricht E, et al. Licorice compounds glycyrrhizin and 18beta-glycyrrhetinic acid are potent modulators of bile acid-induced cytotoxicity in rat hepatocytes. J Biol Chem. 2005;280(11):10556-63.
42. Jung JI, et al. Isoliquiritigenin induces apoptosis by depolarizing mitochondrial membranes in prostate cancer cells. J Nutr Biochem. 2006;17(10):689-95.