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In Silico Screening of *Salvia officinalis* L. Secondary Metabolites Using Swiss ADME

Mr. Santosh A. Chavan[1], Dr. Suresh G. Killedar[2], Mr. Prakash P. Mali[3]

[1,3]Student, Dept. of Pharmacology, Anandi Pharmacy College, Kalambe Tarf Kale, Kolhapur, India.
[2]Professor, Dept. of Pharmacology, Anandi Pharmacy College, Kalambe Tarf Kale, Kolhapur, India.

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ABSTRACT

Salvia officinalis L. (sage), a medicinal herb traditionally used for inflammatory and cognitive disorders, contains diverse bioactive compounds with therapeutic potential. Despite its known pharmacological activities, systematic computational evaluation of its phytoconstituents' pharmacokinetic and drug-likeness properties is limited. This study aimed to evaluate the ADME (absorption, distribution, metabolism, and excretion) profiles and drug-likeness of 20 major secondary metabolites of *S. officinalis* using the SwissADME web tool. The analysis provided detailed insights into physicochemical parameters, lipophilicity, solubility, pharmacokinetic behaviour, and medicinal chemistry properties. Results indicated that compounds such as apigenin, kaempferol, and carnosol exhibited favourable ADME profiles and high drug-likeness scores, suggesting their potential as lead candidates for drug development. This in silico approach supports future experimental and clinical validation of *S. officinalis* constituents.

Keywords: *Salvia officinalis* L., pharmacological properties, secondary metabolites, Swiss ADME, drug-likeness, pharmacokinetic.

1. INTRODUCTION:

Salvia officinalis L. (family Lamiaceae), commonly known as sage, is a perennial aromatic herb native to the Mediterranean region and widely cultivated across the world. It has a long history of use in traditional medicine for treating various ailments, including inflammation, oxidative stress, and cognitive impairment. [1] The therapeutic potential of *S. officinalis* is attributed to its rich phytochemical profile, which includes terpenoids such as thujone, borneol, and camphor, along with phenolic acids like rosmarinic and caffeic acids, and flavonoids such as apigenin and luteolin. These compounds are known for their diverse pharmacological actions, including antioxidant, anti-inflammatory, antimicrobial, and neuroprotective effects. [2,3] Recent literature highlights the increasing scientific interest in *S. officinalis* due to its wide spectrum of biological activities. Several studies have emphasized its potential applications in developing novel therapeutic agents derived from natural products. [4,5] Despite this, the pharmacokinetic and drug-likeness characteristics of its major secondary metabolites have not been systematically explored. Modern drug discovery relies heavily on *in silico* prediction tools to assess key pharmacokinetic properties during the early stages of development. Computational ADME (Absorption, Distribution, Metabolism, and Excretion) evaluation helps in predicting molecular behaviour within biological systems, reducing time, cost, and experimental effort. Among these tools, **SwissADME**, developed by the Swiss Institute of Bioinformatics, is a widely used web platform for evaluating physicochemical descriptors, pharmacokinetic profiles, drug-likeness, and medicinal chemistry properties of small molecules. [6] Given the therapeutic relevance of *S. officinalis* and the lack of detailed computational studies, the present work aims to perform an *in-silico* analysis of twenty selected secondary metabolites from *Salvia officinalis* L. using the SwissADME tool. This study focuses on evaluating their physicochemical characteristics, ADME parameters, and drug-likeness properties to identify promising lead compounds for further pharmacological and formulation development.

2. MATERIALS AND METHODS:

2.1 Description of plant:

Commonly referred to as common sage or garden sage, *Salvia officinalis* L. is a perennial aromatic herb that is a member of the Lamiaceae family. In the western world, it is acknowledged as a culinary herb that is used to flavour meat, sausages, fish, and chicken stuffing. The herb is grown for its essential oils, which are found in its leaves and stem and are utilized in medicines, cosmetics, and perfumes. In addition to being used as an antibacterial, the herb is used medicinally to treat neurological disorders, depression, cerebral ischemia, pharyngitis, high blood pressure, high levels of sweating, and memory impairment. With over 50

known polyphenols, including a variety of phenolic acids and flavonoids, *S. officinalis* leaves are a rich source of polyphenolic chemicals. [7]

Fig. 1: Arial parts of *Salvia officinalis L.*

2.2 Computational Tools:

Tool	Source	Function
SwissADME	Swiss Institute of Bioinformatics	Predicts physicochemical, pharmacokinetic, and drug-likeness properties
pkCSM	University of Melbourne	Assesses ADME and toxicity profiles

2.3 Swiss ADME:

The ADME prediction servers utilized are pkCSM (http://biosig.unimelb.edu.au/pkcsm/) from the Biosig Lab University of Melbourne and Swiss ADME (http://swissadme.ch/) from the Swiss Institute of Bioinformatics. A free online tool called Swiss ADME can be used to assess the physicochemical characteristics, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of *Salvia officinalis* L. compounds. Its ease of use in determining the drug likeness profile of compounds through the integration of Lipinski's rule—which looked at orally active chemicals to define physicochemical ranges for high probability of becoming an oral drug, *Salvia officinalis* L. makes it popular. Using SMILES Translator Online Help, the examined compounds were converted into the standard SMILES (simplified molecular-input line-entry system) format. They were then sent to Swiss ADME and pkCSM for ADME analysis, physicochemical parameter prediction, and drug-likeness assessment using the Lipinski rule of five. Lipinski's so-called Rule-of-five outlined the connection between parameters and pharmacokinetics. [8]

2.4 Structure and bioavailability radar:

A quick evaluation of drug likeness was conducted using bioavailability radar, which considered six physicochemical characteristics: lipophilicity (LIPO), size (SIZE), polarity (POLAR), insolubility (INSOLU), unsaturation (INSATU), and flexibility (FLEX). The ideal range for each property was represented by a pink area on each axis representing a physicochemical range, where the molecule's radar plot must completely fall to be deemed drug-like. [9] Size: 150–500 g/mol, polarity: topological polar surface area (TPSA) between 20 and 130 Å2, solubility: log S not greater than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, flexibility: no more than 9 rotatable bonds, lipophilicity: XLOGP3 between -0.7 and +5.0. [10]

2.5 Physicochemical properties:

This section compiles basic molecular and physicochemical parameters such as polar surface area (PSA), molecular weight (MW), molecular refractivity (MR), and the number of distinct atom types. Open Babel version 2.3.0 is used to calculate the values. A complex canonicalization technique that works with molecules or molecular fragments is implemented by Open Babel. Topological polar surface area (TPSA), a fragmental approach, is used to determine the PSA. [11,10]

2.6 Lipophilicity:

Lipophilicity is one of the most crucial elements influencing a drug's bioavailability, according Lipinski's rule of five. As a result, the reference criterion for forecasting the biological activity of possible medications is lipophilicity. [12] The partition coefficient is typically used to express lipophilicity (IogP). While the distribution coefficient (IogD) may be measured, logP refers to the neutral species. The ratio of the total concentrations of ionized and unionized species in both phases is known as the distribution coefficient; a positive logP value indicates a preference for the lipid phase, while a negative value indicates a relative affinity for water. In each of the two phases, log D reflects the ratio of the overall concentrations of all forms of the molecule (a pH-dependent mixture of ionized and un-ionized forms). [13] Greater lipophilicity is correlated with larger log P values. [14] Swiss ADME provides access to five openly accessible prediction models, such as XLOGP3, an atomistic approach which includes knowledge-based frameworks and adjustment variables. [15] Our own version of a totally atomistic technique, WLOGP, is based on Wildman and Crippen's fragmental concept. [16] MLOGP is a topological approach that uses 13 molecular descriptors and is based on the linear relationship. [17,18] SILICOS-IT is a hybrid system that uses seven topological descriptors and 27 segments. When compared to six acknowledged predictors, iLOGP performed on level with or better than two drug-like external sets. The arithmetic mean of the values anticipated by the five mentioned approaches has been identified as the consensus log Po/w. [10]

2.7 Water Solubility:

The molecule's solubility makes many therapeutic research duties easier, including formulation and usability. Water solubility is an essential feature that influences absorption if the medication is to be administered orally. In Swiss ADME, water solubility has been measured using three distinct methodologies. The ESOL model is implemented in the first one, is modified in the second, and SILICOS-IT developed the third predictor. There are three separate categories for water solubility: class, solubility (mol/L), and solubility (mg/mL). [19] When a drug's maximum dose strength dissolves in 250 mL of aqueous media with a pH range of 1 to 7.5, it is said to be extremely soluble. The ESOL model is the first of two topological methods used in Swiss ADME to forecast water solubility. (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<-2 very<0<-10 poorly<-6, moderately<-4 soluble< 2very<0<-10 poorly<-6, moderately<-4 soluble<-2 very<0<highly) and the second one is (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble< 2very<0<-10 poorly<-6, moderately<-4 soluble<-2 very<0<highly). Both differ from the fundamental general solubility equation since they avoid the melting point parameter but the linear correlation between predicted and experimental values were strong (R2=0.69 and 0.81 respectively). The third predictor of Swiss ADME was developed by SILICOS-IT (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<-2 very<0. All predicted values are presented as the decimal logarithm of molar water solubility (log S).

2.8 Pharmacokinetics:

On a plot of two calculated descriptors, the delineation is located in an area with favourable characteristics for GI absorption; PSA versus ALOGP, respectively. In order to evaluate the predictive power of the model for GI passive absorption and prediction for brain access by passive diffusion, the BOILED-Egg (Brain or Intestinal Estimate D permeation predictive model) is laid out using the Egan egg, an elliptical region that is most populated by well-absorbed molecules. A quick, spontaneous, effective, and chaotic way to predict passive GI absorption that is useful for drug development and discovery is produced by the BOILED-Egg model. The yellow portion (yolk) has the best chance of permeating the brain, whereas the white part contains chemicals that are more likely to be consumed by the GI tract. [20] P-glycoprotein (P-gp) is a kind of membrane transporter that moves substances across the intestinal lumen, either extracellularly or intracellularly, and then excretes them. Furthermore, P- glycoprotein inhibits the uptake of a wide range of structurally and functionally varied drugs, including the majority of cancer treatments, resulting in multidrug resistance. P-glycoprotein is also overproduced in cancer cells, which makes chemotherapy inefficient and creates a significant treatment obstacle by promoting drug efflux. In drug biotransformation, cytochrome P450 (CYP) enzymes are the fundamental enzymes. The most significant inhibitors in biotransformation are those that inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. Cellular metabolism, homeostasis, and xenobiotic detoxification are all impacted by CYP isoenzymes. medication toxicity and a decrease in pharmacological activity can thus be caused by medication interactions, which are largely determined by drug metabolism through CYP isoenzymes. [21] Understanding how chemicals interact with cytochromes P450 (CYP) is also crucial. Through metabolic biotransformation, this superfamily of isoenzymes plays a crucial role in drug clearance. [22] Swiss ADME makes it possible to determine whether a substance is an inhibitor of the most significant CYP isoenzymes or a substrate of P-gp. The support vector machine algorithm (SVM) was utilized. [23] In order to categorize datasets with known substrates/non-substrates or inhibitors/non-inhibitors for binary categorization, Swiss ADME uses the support vector machine algorithm (SVM). A "Yes" or "No" classification will be given to the resultant molecule based on whether it is anticipated to be a substrate for both CYP and P-gp, respectively. With an area under the curve (AUC) of 0.77 and a 10-fold cross-validation accuracy of 0.72, the SVM model for the P-gp substrate was built using 1033 molecules for training and evaluated on 415 molecules for testing. The AUC and external accuracy were both 0.94. Several training and test datasets were used to create the Support Vector Machine (SVM) models for the inhibition of Cytochrome P-450 1A2, 2C19, 3A4, 2C9, 2C19, 2D6, 2E1, and molecules. The SVM model was tested on a dataset of 3000 compounds and trained on a dataset of 9145 molecules for the Cytochrome P-450 1A2 inhibitor molecule. The accuracy (ACC) and area under the curve (AUC) of the 10-fold cross-validation

were 0.83 and 0.90, respectively. The results of the external validation showed an AUC of 0.91 and an ACC of 0.84. The SVM model was constructed using a training set of 9272 molecules and evaluated on 3000 molecules for the Cytochrome P-450 2C19 inhibitor compound. An accuracy of 0.80 and an area under the curve of 0.86 were shown by the 10-fold cross validation. The model obtained an accuracy of 0.80 and an area under the curve of 0.87 when tested on an external dataset. A support vector machine model was developed for the Cytochrome P-450 2C9 inhibitor molecule using a training set of 5940 molecules, and it was then evaluated on a collection of 2075 molecules. An accuracy of 78% and an area under the curve of 85% were obtained using a 10-fold cross-validation process. The model's accuracy and area under the curve were 71% and 81%, respectively, after external validation. A support vector machine model was created for the Cytochrome P-450 2D6 inhibitor molecule using a training set of 3664 molecules, and it was evaluated on a collection of 1068 molecules. The accuracy and area under the curve (AUC) were 79% and 85%, respectively, according to the 10-fold cross-validation process. The model had an accuracy of 81% and an AUC of 87% when tested on an external dataset. The SVM model was created using a training set of 7518 molecules in the particular instance of the Cytochrome P-450 3A4 inhibitor molecule, and it was then evaluated on a collection of 2579 molecules. The accuracy and AUC of the 10-fold cross-validation analysis was 77% and 85%, respectively. Additionally, an AUC of 80 and an accuracy of 78% were obtained through external validation. [24]

2.9 Medicinal Chemistry:

Swiss ADME was used in this study to examine the physicochemical, pharmacokinetic, and drug-like properties of both natural and synthesized substances. The lipophilicity of the compounds varied significantly; greater values indicated improved membrane permeability and possibly increased non-specific binding. [25] This section's goal is to support medicinal chemists in their continuous efforts to create new medications. Chemicals referred to as PAINS (Pan Assay Interference Compounds, frequent hits, or promiscuous compounds) provide strong assay findings regardless of the protein targets. These substances are intriguing candidates for further research because it has been confirmed that they show activity in a variety of assays. If such moieties are found in the molecule being evaluated, SwissADME advises caution. [26] In an alternative approach, Brenk stresses smaller and less hydrophobic molecules, breaking with the strict limitations of "Lipinski's rule of 5," in order to increase the potential for therapeutic development. Compounds with potentially hazardous, chemically reactive, or undesired groups—such as nitro groups, sulfates, phosphates, 2halopyridines, and thiols—are excluded using this method. The values of ClogP/ClogD are restricted to a range of 0 to 4 by the Brenk model. Additionally, the model requires that there be less than four hydrogen bond donors and fewer than seven hydrogen bond acceptors. The model stipulates that compounds must have between 10 and 28 heavy atoms in order to be considered molecularly large. [27] Compounds must have a simple structure, with less than eight rotatable bonds, fewer than five ring systems, and no ring systems with more than two fused rings, in order to be categorized as medicinal. [28] In high-throughput screening (HTS), the idea of lead likeness is to offer starting points with high affinity so that further interactions can be investigated during the lead optimization stage. Chemical changes in leads tend to make them less hydrophobic than drug-like compounds by decreasing their size and increasing their lipophilicity. A rule-based technique is frequently used for lead optimization, where molecules with a molecular weight between 100 and 350 Da and a ClogP between 1 and 3.0 are regarded as superior to drug-like compounds and therefore more lead-like. [29,30]

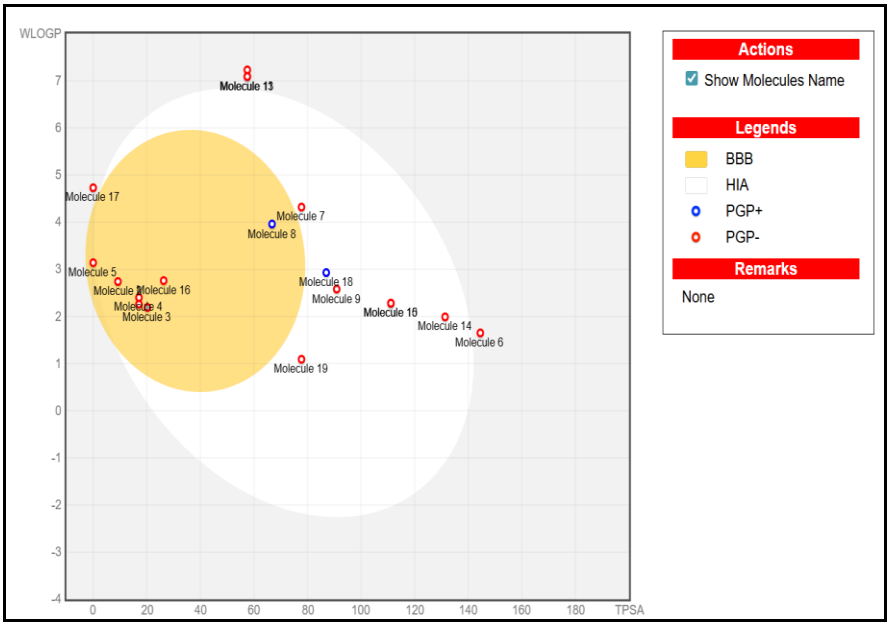

Fig.2: Boiled Egg Model of the Phytoconstituents of *Salvia officinalis* L.

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3. Results:

Table 1: General Characteristics of Phytoconstituents of *Salvia officinalis* L.

Sr. No	Molecules	Pub chem ID	Molecular formula	Canonical SMILES	Molecular weight (in g/mol)
1	Thujone	261491	$C_{10}H_{16}O$	C[C@@H]1[C@H]2C[C@]2(CC1=O)C(C)C	152.23
2	Cineole	2758	$C_{10}H_{18}O$	CC1(C2CCC(O1)(CC2)C)C	154.25
3	Borneol	6552009	$C_{10}H_{18}O$	C[C@@]12CC[C@@H](C1(C)C)C[C@@H]2O	154.25
4	Camphor	2537	$C_{10}H_{16}O$	CC1(C2CCC1(C(=O)C2)C)C	152.23
5	Pinene	15837102	$C_{10}H_{16}$	CC1=C2CC(C2(C)C)CC1	136.23
6	Rosmarinic Acid	5281792	$C_{18}H_{16}O_8$	C1=CC(=C(C=C1C[C@H](C(=O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)O)O	360.3
7	Carnosic Acid	65126	$C_{20}H_{28}O_4$	CC(C)C1=C(C(=C2C(=C1)CC[C@@H]3[C@@]2(CCCC3(C)C)C(=O)O)O)O	332.4
8	Carnosol	442009	$C_{20}H_{26}O_4$	CC(C)C1=C(C(=C2C(=C1)[C@@H]3C[C@@H]4[C@@]2(CCCC4(C)C)C(=O)O3)O)O	330.4
9	Apigenin	5280443	$C_{15}H_{10}O_5$	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O	270.24
10	Luteolin	5280445	$C_{15}H_{10}O_6$	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O	286.24
11	Ursolic Acid	64945	$C_{30}H_{48}O_3$	C[C@@H]1CC[C@@]2(CC[C@@]3(C(=CC[C@H]4[C@]3(CC[C@@H]5[C@@]4(CC[C@@H](C5(C)C)O)C)C)[C@@H]2[C@H]1C)C)C(=O)O	456.7
12	Oleanolic Acid	10494	$C_{30}H_{48}O_3$	C[C@]12CC[C@@H](C([C@@H]1CC[C@@]3([C@@H]2CC=C4[C@]3(CC[C@@]5([C@H]4CC(CC5)(C)C)C(=O)O)C)C)(C)C)O	456.7
13	Betulinic Acid	64971	$C_{30}H_{48}O_3$	CC(=C)[C@@H]1CC[C@]2([C@H]1[C@H]3CC[C@@H]4[C@]5(CC[C@@H](C([C@@H]5CC[C@]4([C@@]3(CC2)C)C)(C)C)O)C)C(=O)O	456.7
14	Quercetin	5280343	$C_{15}H_{10}O_7$	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O	302.23
15	Kaempferol	5280863	$C_{15}H_{10}O_6$	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O	286.24
16	Bornyl Acetate	6448	$C_{12}H_{20}O_2$	CC(=O)OC1CC2CCC1(C2(C)C)C	196.29
17	Caryophyllene	5281515	$C_{15}H_{24}$	C/C/1=C\CCC(=C)[C@H]2CC([C@@H]2CC1)(C)C	204.35
18	Rosmanol	13966122	$C_{20}H_{26}O_5$	CC(C)C1=C(C(=C2C(=C1)[C@@H]([C@@H]3[C@@H]4[C@@]2(CCCC4(C)C)C(=O)O3)O)O)O	346.4
19	Caffeic Acid	689043	$C_9H_8O_4$	C1=CC(=C(C=C1/C=C/C(=O)O)O)O	180.16
20	Ferulic Acid	445858	$C_{10}H_{10}O_4$	COC1=C(C=CC(=C1)/C=C/C(=O)O)O	194.18

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Table 2: Lipophilicity of the Phytoconstituents of *Salvia officinalis* L.

Sr. No	Molecules	Ilogp	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log *P0/w*
1	Thujone	2.28	2.27	2.26	2.30	2.63	2.35
2	Cineole	2.58	2.74	2.74	2.45	2.86	2.67
3	Borneol	2.33	2.72	2.19	2.45	2.27	2.39
4	Camphor	2.12	2.19	2.40	2.30	2.85	2.37
5	Pinene	2.57	2.55	3.14	4.29	3.19	3.15
6	Rosmarinic Acid	1.48	2.36	1.65	0.90	1.50	1.58
7	Carnosic Acid	2.69	4.89	4.32	3.25	3.95	3.82
8	Carnosol	2.93	4.38	3.96	3.25	4.05	3.72
9	Apigenin	1.89	3.02	5.58	0.52	2.52	2.11
10	Luteolin	1.86	2.53	2.28	-0.03	2.03	1.73
11	Ursolic Acid	0.00	7.34	7.09	5.82	5.46	5.14
12	Oleanolic Acid	3.94	7.49	7.23	5.82	5.85	6.07
13	Betulinic Acid	3.83	8.21	7.09	5.82	5.75	6.14
14	Quercetin	1.63	1.54	1.99	-0.56	1.54	1.23
15	Kaempferol	1.70	1.90	2.28	-0.03	2.03	1.58
16	Bornyl Acetate	2.50	4.30	2.76	2.76	2.66	3.00
17	Caryophyllene	3.25	4.38	4.73	4.63	4.19	4.24
18	Rosmanol	2.52	3.41	2.93	2.42	3.16	2.89
19	Caffeic Acid	0.97	1.15	1.09	0.70	0.75	0.93
20	Ferulic Acid	1.62	1.51	1.39	1.00	1.26	1.36

Table 3: Water solubility of the phytoconstituents of *Salvia officinalis* L.

	ESOL				Ali				SILICOS-IT			
Molecules	Log S (ESOL)	Solubility		Class	Log S	Solubility		Class	Log S	Solubility		Class
		mg/mL	mol/L			mg/mL	mol/L			mg/mL	mol/L	
Thujone	-2.15	1.08e+00	7.11e-03	Soluble	-2.27	8.27e-01	5.43e-03	Soluble	-2.15	1.08e+00	7.10e-03	Soluble
Cineole	-2.52	4.63e-01	3.00e-03	Soluble	-2.59	3.98e-01	2.58e-03	Soluble	-2.45	5.45e-01	3.53e-03	Soluble
Borneol	-2.51	4.77e-01	3.09e-03	Soluble	-2.80	2.45e-01	1.59e-03	Soluble	-1.91	1.92e+00	1.24e-02	Soluble
Camphor	-2.16	1.04e+00	6.86e-03	Soluble	-2.18	1.00e+00	6.57e-03	Soluble	-2.60	3.83e-01	2.52e-03	Soluble
Pinene	-2.29	6.97e-01	5.12e-03	Soluble	-2.20	8.65e-01	6.35e-03	Soluble	-2.68	2.86e-01	2.10e-03	Soluble
Rosmarinic Acid	-3.44	1.31e-01	3.63e-04	Soluble	-5.04	3.32e-03	9.22e-06	Moderately soluble	-2.17	2.41e+00	6.70e-03	Soluble
Carnosic Acid	-5.03	3.07e-03	9.23e-06	Moderately soluble	-6.26	1.83e-04	5.51e-07	Poorly soluble	-4.16	2.33e-02	7.00e-05	Moderately soluble
Carnosol	-4.77	5.65e-03	1.71e-05	Moderately soluble	-5.50	1.05e-03	3.17e-06	Moderately soluble	-4.45	1.16e-02	3.52e-05	Moderately soluble
Apigenin	-3.94	3.07e-02	1.14e-04	Soluble	-4.59	6.88e-03	2.55e-05	Moderately soluble	-4.40	1.07e-02	3.94e-05	Moderately soluble
Luteolin	-3.71	5.63e-02	1.97e-04	Soluble	-4.51	8.84e-03	3.09e-05	Moderately soluble	-3.82	4.29e-02	1.50e-04v	Soluble
Ursolic Acid	-7.23	2.69e-05	5.89e-08	Poorly soluble	-8.38	1.92e-06	4.21e-09	Poorly soluble	-5.67	9.72e-04	2.13e-06	Moderately soluble
Oleanolic	-7.32	2.16e-05	4.74e-08	Poorly	-8.53	1.34e-	2.94e-09	Poorly	-6.12	3.45e-	7.55e-	Poorly

Acid				soluble		06		soluble		04	07	soluble
Betulinic Acid	-7.71	8.87e-06	1.94e-08	Poorly soluble	-9.28	2.40e-07	5.26e-10	Poorly soluble	-5.70	9.09e-04	1.99e-06	Moderately soluble
Quercetin	-3.16	2.11e-01	6.98e-04	Soluble	-3.91	3.74e-02	1.24e-04	Soluble	-3.24	1.73e-01	5.73e-04v	Soluble
Kaempferol	-3.31	1.40e-01	4.90e-04	Soluble	-3.86	3.98e-02	1.39e-04	Soluble	-3.82	4.29e-02	1.50e-04	Soluble
Bornyl Acetate	-3.63	4.56e-02	2.32e-04	Soluble	-4.57	5.34e-03	2.72e-05	Moderately soluble	-2.58	5.20e-01	2.65e-03	Soluble
Caryophyllene	-3.87	2.78e-02	1.36e-04	Soluble	-4.10	1.64e-02	8.01e-05	Moderately soluble	-3.77	3.49e-02	1.71e-04	Soluble
Rosmanol	-4.25	1.96e-02	5.65e-05	Moderately soluble	-4.92	4.20e-03	1.21e-05	Moderately solublev	-3.64	7.97e-02	2.30e-04	Soluble
Caffeic Acid	-1.89	2.32e+00	1.29e-02	Very soluble	-2.38	7.55e-01	4.19e-03	Soluble	-0.71	3.51e+01	1.95e-01	Soluble
Ferulic Acid	-2.11	1.49e+00	7.68e-03	Soluble	-2.52	5.86e-01	3.02e-03	Soluble	-1.42	7.43e+00	3.83e-02	Soluble

Table 4: Pharmacokinetic Parameters of the Phytoconstituents of *Salvia officinalis* L.

Molecules	**GI absorption**	**BBB permeant**	**P-Gp substrate**	**CYP1A2 inhibitor**	**CYP2C19 inhibitor**	**CYP2C9 inhibitor**	**CYP2D6 inhibitor**	**CYP3A4 inhibitor**	**Log Kp (cm/s)**
Thujone	High	Yes	No	No	No	No	No	No	-5.62 cm/s
Cineole	High	Yes	No	No	No	No	No	No	-5.30 cm/s
Borneol	High	Yes	No	No	No	No	No	No	-5.31 cm/s
Camphor	High	Yes	No	No	No	No	No	No	-5.67 cm/s
Pinene	Low	Yes	No	No	No	No	No	No	-5.32 cm/s
Rosmarinic Acid	Low	No	No	No	No	No	No	No	-6.82 cm/s
Carnosic Acid	High	No	No	No	No	Yes	No	No	-4.86 cm/s
Carnosol	High	Yes	Yes	No	No	Yes	No	No	-5.21 cm/s
Apigenin	High	No	No	Yes	No	No	Yes	Yes	5.80 cm/s
Luteolin	High	No	No	Yes	No	No	Yes	Yes	-6.25 cm/s
Ursolic Acid	Low	No	Yes	No	No	No	No	No	-3.87 cm/s
Oleanolic Acid	Low	No	No	No	No	No	No	No	-3.77 cm/s
Betulinic Acid	Low	No	No	No	No	Yes	No	No	-3.26 cm/s
Quercetin	High	No	No	Yes	No	No	Yes	Yes	-7.05 cm/s

Kaempferol	High	No	NO	Yes	No	No	Yes	Yes	-6.70 cm/s
Bornyl Acetate	High	Yes	No	No	No	Yes	No	No	-4.44 cm/s
Caryophyllene	Low	No	No	No	Yes	Yes	No	No	-4.44 cm/s
Rosmanol	High	No	Yes	No	No	No	Yes	NO	-5.99 cm/s
Caffeic Acid	High	No	No	No	No	No	No	No	-6.58 cm/s
Ferulic Acid	High	Yes	No	No	No	No	No	No	-6.41 cm/s

Table 5: Drug likeness of the Phytoconstituents of *Salvia officinalis* L.

Sr. No	Molecules	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
1	Thujone	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
2	Cineole	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
3	Borneol	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 1 violation: MW<160	0.55
4	Camphor	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
5	Pinene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
6	Rosmarinic Acid	Yes; 0 violation	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	Yes	0.56
7	Carnosic Acid	Yes; 0 violation	Yes	Yes	Yes	Yes	0.56
8	Carnosol	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
9	Apigenin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
10	Luteolin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
11	Ursolic Acid	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.85
12	Oleanolic Acid	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.85
13	Betulinic Acid	Yes; 1 violation: MLOGP>4.15	No; 3 violations: WLOGP>5.6, MR>130,	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.85

			#atoms>70				
14	Quercetin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
15	Kaempferol	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
16	Bornyl Acetate	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.55
17	Caryophyllene	Yes; 1 violation: MLOGP>4.15	Yes	Yes	Yes	No; 1 violation: Heteroatoms<2	0.55
18	Rosmanol	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
19	Caffeic Acid	Yes; 0 violation	Yes	Yes	Yes	Yes	0.56
20	Ferulic Acid	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.85

Table 6: Medicinal Chemistry Properties of Phytoconstituents of *Salvia officinalis* L.

Sr. No	Molecules	Pains	Brenk	Leadlikeness	Synthetic accessibility
1	Thujone	0 alert	0 alert	No; 1violation: MW<250	2.79
2	Cineole	0 alert	0 alert	No; 1violation: MW<250	3.65
3	Borneol	0 alert	0 alert	No; 1violation: MW<250	3.43
4	Camphor	0 alert	0 alert	No; 1violation: MW<250	3.22
5	Pinene	0 alert	1 alert: isolated_alkene	No; 1violation: MW<250	4.18
6	Rosmarinic Acid	1 alert: catechol_A	2 alerts: catechol, michael_acceptor_1	No; 1violation: MW>350	3.38
7	Carnosic Acid	1 alert: catechol_A	1 alert: catechol	No; 1violation: XLOGP3>3.5	3.81
8	Carnosol	1 alert: catechol_A	1 alert: catechol	No; 1violation: XLOGP3>3.5	4.88
9	Apigenin	0 alert	0 alert	Yes	2.96
10	Luteolin	1 alert: catechol_A	1 alert: catechol	Yes	3.02
11	Ursolic Acid	0 alert	1 alert: isolated_alkene	No; 2 violations: MW>350, XLOGP3>3.5	6.21
12	Oleanolic Acid	0 alert	1 alert: isolated_alkene	No; 2 violations: MW>350, XLOGP3>3.5	6.08
13	Betulinic Acid	0 alert	1 alert: isolated_alkene	No; 2 violations: MW>350, XLOGP3>3.5	5.63
14	Quercetin	1 alert: catechol_A	1 alert: catechol	Yes	3.23
15	Kaempferol	0 alert	0 alert	Yes	3.14
16	Bornyl Acetate	0 alert	0 alert	No; 2 violations: MW<250, XLOGP3>3.5	3.64
17	Caryophyllene	0 alert	1 alert: isolated alkene	No; 2 violations:	4.51

				MW<250, XLOGP3>3.5	
18	Rosmanol	1 alert: catechol A	1 alert: catechol	Yes	5.07
19	Caffeic Acid	1 alert: catechol A	2 alerts: catechol, michael_acceptor_1	No; 1 violation: MW<250	1.81
20	Ferulic Acid	0 alert	1 alert: michael_acceptor_1	No; 1 violation: MW<250	1.93

4. DISCUSSION:

The use of herbal medicine is currently common in both developed and developing nations because of its natural source and verified side effects. [31] Ayurveda is one of the oldest medical systems, offering extensive leads to discover the effective and therapeutically useful compounds for drug development from herbs. More than 30% of all plant species have been utilized medicinally at some point, according to the World Health Organization. [32] Drug research is in its early stages thanks to the use of computer-based drug design in predicting the medications' ADMET properties. [33,34,35] These *in silico* methods are justified by the fact that they require a comparatively smaller time and cost factor than traditional ADMET profiling. [36,37] QSAR, or quantitative structure-activity relationships, are frequently used in software tools that are now used to predict the ADMET properties of possible drug candidates. [38,39]

The present in silico investigation provides a comprehensive analysis of the pharmacokinetic, physicochemical, and drug-likeness properties of twenty phytoconstituents isolated from *Salvia officinalis* L. using the SwissADME and pkCSM tools. The major findings of this study highlight the compounds with promising pharmacological potential, good oral bioavailability, and compliance with standard drug-likeness filters, underscoring their suitability as potential lead molecules for further drug development.

The lipophilicity assessment revealed that most metabolites exhibited consensus LogP values within the optimal range of 1–5, indicating balanced hydrophilic–lipophilic characteristics essential for membrane permeability. Compounds such as apigenin, kaempferol, and carnosol demonstrated ideal LogP and molecular weight values, suggesting strong potential for oral absorption and metabolic stability. Conversely, highly lipophilic triterpenoids such as ursolic acid, oleanolic acid, and betulinic acid showed elevated LogP values (>5), which may limit aqueous solubility and oral bioavailability, but enhance membrane affinity — an advantageous feature for lipophilic tissue targeting, including anti-inflammatory or anticancer effects.

Water solubility predictions indicated that a majority of compounds (e.g., apigenin, kaempferol, ferulic acid) were soluble or moderately soluble, which is beneficial for gastrointestinal absorption. However, triterpenoid compounds such as ursolic, oleanolic, and betulinic acids displayed poor solubility, correlating with their high molecular weights (>450 Da). These findings emphasize that solubility is inversely proportional to lipophilicity in large bioactive molecules, a critical determinant during formulation development.

The pharmacokinetic analysis demonstrated that most of the evaluated compounds had high gastrointestinal (GI) absorption, supporting their potential as orally bioavailable agents. Moreover, carnosol, borneol, and ferulic acid were predicted to cross the blood–brain barrier (BBB), suggesting their potential for central nervous system (CNS)-related therapeutic applications such as neuroprotection and memory enhancement — aligning with the traditional use of *S. officinalis* in cognitive disorders. In contrast, polar compounds like rosmarinic acid showed poor BBB permeability, limiting their CNS bioavailability but supporting peripheral pharmacological roles such as antioxidant or anti-inflammatory actions.

The drug-likeness evaluation further confirmed that the majority of metabolites adhered to Lipinski's rule of five with zero violations, highlighting their favourable physicochemical and pharmacokinetic balance. Compounds such as apigenin, kaempferol, quercetin, and carnosol complied with multiple drug-likeness models (Lipinski, Veber, Egan, and Muegge), while triterpenoids with high molecular weights exhibited one or more violations, consistent with their limited oral absorption. In the medicinal chemistry filter analysis, most compounds displayed zero PAINS alerts, suggesting high assay specificity and reduced risk of false-positive activity. Apigenin and kaempferol were identified as lead-like molecules, possessing moderate lipophilicity, low molecular weight, and excellent synthetic accessibility scores. These attributes make them suitable scaffolds for further optimization in drug design. Furthermore, synthetic accessibility values below 4 for most compounds indicate that these phytoconstituents can be efficiently synthesized or modified in medicinal chemistry workflows. Overall, the results demonstrate that flavonoids (apigenin, kaempferol, quercetin) and diterpenoids (carnosol, carnosic acid) possess the most promising pharmacokinetic and medicinal chemistry profiles. Their balanced lipophilicity, favourable drug-likeness, high bioavailability, and low toxicity risk collectively suggest that these compounds could serve as potential leads for the development of anti-

inflammatory, antioxidant, and neuroprotective agents. These computational insights are consistent with previously reported experimental studies highlighting the pharmacological activities of *Salvia officinalis* constituents.

5. CONCLUSION:

The present in silico study provides valuable insights into the pharmacokinetic, physicochemical, and drug-likeness characteristics of twenty phytoconstituents of *Salvia officinalis* L. using SwissADME and pkCSM tools. Compounds such as **apigenin**, **kaempferol**, **quercetin**, and **carnosol** demonstrated favourable ADME properties, high gastrointestinal absorption, and compliance with major drug-likeness filters, highlighting their potential as lead candidates for drug development. These findings support the pharmacological basis of *S. officinalis* in traditional medicine, particularly for its **anti-inflammatory, antioxidant, and neuroprotective** effects.

This computational profiling not only aids in prioritizing phytoconstituents for **experimental validation and molecular docking studies** but also provides a rational framework for **future formulation and pharmacodynamic investigations**. Overall, the study reinforces the potential of *Salvia officinalis* as a promising natural source for developing novel therapeutic agents and emphasizes the importance of integrating **in silico approaches** in early-stage drug discovery from medicinal plants.

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Conflict of Interest Statement:
The authors have no conflicts of interest to declare.