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Comprehensive phytochemical and antioxidant evaluation of *Salvia officinalis* via *in vitro* and *in silico* analyses, ADME prediction

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Currently, there is considerable interest in traditional medicine and herbal treatments. *Salvia officinalis* L., commonly known as sage, is a Mediterranean plant and classified under the family Lamiaceae. It is an important medicinal plant utilized for diverse therapeutic applications. The aim of this work was to investigate the phenolic profile and to evaluate the antioxidant activity of aqueous and methanolic extracts of *S. officinalis*. Phytochemical screening revealed the presence of tannins, terpenoids, alkaloids, coumarins, and saponosides in both solvent extracts. The phenolic content was determined by using the Folin–Ciocalteu phenol reagent, and the flavonoid content was determined by the aluminum chloride colorimetric method. The outcome showed that the aqueous extract had a higher total phenol content (55.06 ± 0.03 mg GAE/g extract) compared to the methanol extract (46.51 ± 0.02 mg GAE/g extract). On the other hand, the methanol extract had a higher flavonoid content (20.70 ± 0.13 mg QAE/g extract) compared to the aqueous extract (12.12 ± 0.01 mg QAE/g extract). Furthermore, the methanol extract also exhibited significantly higher antioxidant activity (12.31 ± 0.58 µg/mL) compared to the aqueous extract (23.48 ± 2.52 µg/mL). Therefore, the obtained results indicate that *S. officinalis* represents a valuable source of natural antioxidants. The molecular docking analysis showed that the phenolic compounds of *Salvia officinalis* interact differently with the main antioxidant enzymes: catalase (2CAG), glutathione peroxidase (2P31), and superoxide dismutase (1CB4). Salvianolic acid exhibited the highest affinity toward catalase (ΔG = –10.9 kcal/mol), followed by cirsimaritin and kaempferol (ΔG = –10.2 kcal/mol). Rosmarinic acid and salvianolic acid effectively bind to glutathione peroxidase, while quercetin showed the strongest affinity for superoxide dismutase SOD.

Keywords: *Salvia officinalis*; phenolics; antioxidant activity; phytochemical; molecular docking.

Introduction

Since ancient times, humans have relied on medicinal plants as a natural source of therapeutic agents to treat a wide range of diseases. *Salvia officinalis* L., commonly known as sage, is a well-known medicinal and aromatic herb originating from the Mediterranean region and belonging to the Lamiaceae family. It has a long history of traditional use for the treatment of oral, respiratory, and gastrointestinal disorders and has been extensively investigated in pharmacological and clinical studies (Khaldi et al., 2024). In particular, *S. officinalis* exhibits significant antibacterial, anti-inflammatory, and wound-healing properties (Direito et al., 2025).

Beyond its ethnomedicinal value, *S. officinalis* has attracted great industrial and pharmaceutical interest due to its diverse biological activities and potential therapeutic applications in food preservation, cosmetics, and pharmaceuticals (Nandhakumar & Indumathi, 2013). The pharmacological effects of sage are largely attributed to its complex mixture of bioactive metabolites, mainly phenolic compounds such as rosmarinic acid, caffeic acid, and salvianolic acids, which are responsible for its strong antioxidant activity (Ben Akacha et al., 2024). In addition, terpenoids, alkaloids, and sulfur-containing compounds contribute to its broad spectrum of biological actions.

According to recent research, essential oils and extracts from *S. officinalis* have powerful anti-inflammatory and neuroprotective properties, as well as a strong antioxidant capacity and antibacterial activity against both Gram-positive and Gram-negative bacteria (Boukhatem et al., 2023). Additionally, it has been observed that *Salvia* polyphenols have cytotoxic and anticancer activities against a variety of tumor cell lines, as well as antidiabetic potential through the inhibition of digestive enzymes such α-amylase, α-glucosidase, and lipase (Pereira et al., 2018). According to additional research, some diterpenoids and phenolic constituents may have a neuroprotective function by inhibiting important enzymes associated with neurodegenerative diseases, such as monoamine oxidese (MAO), butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) (Topçu et al., 2020).

Consequently, *S. officinalis* is a prospective source of pharmacologically active compounds and natural antioxidants. Investigating the phytochemical composition and phenolic profile of *S. officinalis* aqueous and methanolic extracts, assessing their antioxidant activity, and using molecular docking and ADMET analyses to clarify the possible mechanisms underlying their antioxidant effects were the goals of the current study.

Materials and methods

In February 2019 we collected the aerial portion of sage (leaves and stem) in the northeastern Algerian region of Bordj Bou Arreridj. The area has what is known as a semi-arid climate. 351 mm of rain falls on average each year, and the average temperature is 14.3 °C. The morphological characteristic of the plant were used to identify it (Fig. 1). After being washed and allowed to dry for ten days at room temperature (between 25 and 28 °C), the plant material was ground in an electric micronizer and then placed in airtight containers to keep out moisture and light until it was needed again.

Two solvents, methanol and distilled water, were employed to extract bioactive chemicals from the aerial section of sage. 250 milliliters of each solvent were used to soak 50 grams of powdered material (leaves and stem bark) separately for 24 hours while being constantly stirred. The extract was subsequently passed through Whatman filter paper. A rotary evaporator was then used to concentrate the filtrate. Before being used, the extracted materials were kept at 4 °C in the dark.

Fig. 1. General morphology of the plant

The existence of different classes of bioactive chemicals was detected by qualitative phytochemical screening of the sage aqueous and methanol extracts. Trease and Evans' standard protocols were used to screen the extracts for phytochemicals (Aksoy et al., 2013). The qualitative findings are shown as (+) when phytochemicals are present and (-) when they are not. Three separate aqueous and methanolic extracts of *S. officinalis* were subjected to qualitative phytochemical screening.

The Folin–Ciocalteu technique was used to calculate the total phenolic compounds (Aksoy et al., 2013). One milliliter of diluted Folin–Ciocalteu reagent (1:10:1) was added to two hundred microliters. After three minutes of stabilization, 800 µL of saturated sodium carbonate (Na_2CO_3, 7.5%) was added. It was left to incubate at ambient temperature for two hours. The resulting solution was then allowed to sit at room temperature for two hours, and the absorbance at 765 nm was measured. The standard was gallic acid. Gallic acid was used for the plotting of the standard calibration curve. Micrograms of gallic acid equivalents (GAE) per milligram of extract were used to express the findings.

The colorimetric method of aluminum chloride was used to determine the total flavonoid content (Kaisoon et al., 2012). The calibration curve was created using quercetin. One milliliter of the aluminum trichloride solution (2% in methanol) was combined with one milliliter of extracts or standard. For ten minutes, the mixture was incubated at room temperature. At 430 nm, the absorbance of every reference and sample was determined. Micrograms of quercetin equivalents/mg extract (µg/mg) were used to express the data.

The radical scavenging activity of *S. officinalis* extracts against the DPPH radical was determined according to Brand-Williams et al. (1995). 0.025 mL of extract (concentration series of 0.5–20 µg/mL) or standard antioxidant (ascorbic acid) was mixed with 0.975 mL of 1,1-diphenyl-2-picrylhydrazyl (DPPH) solution. After 30 min incubation in the dark room, absorbance decrease of the mixture was monitored at 517 nm.

The percentage of DPPH radical scavenging activity was calculated using the following formula:

$$\text{DPPH Scavenging Activity (\%)} = (A_0 - A_1 / A_0) \times 100,$$

where A_0 is the absorbance of the control and A_1 is the absorbance of the sample.

The results of the experimental section for the *in vitro* and *in vivo* activities were complemented and confirmed by the analysis of molecular docking of the organic molecules that made up this plant using the AutoDock Vina program. Superoxide Dismutase (PDB ID: 1CB4), catalase compound II (PDB ID: 2CAG), and human glutathione peroxidase 7 (PDBID: 2P31) are the proteins that were employed to mimic this function (Rana et al., 2019). A box with dimensions of 40 × 40 × 40 Å 3 delineates the protein's active site (Rana et al., 2019). The ligands (nine molecules: ascorbic acid, rosmarinic acid, caffeic acid, ferulic acid, cirsimaritin, catechin, acetin, kaempferol, and quercetin) and ascorbic acid were utilized as reference molecules to guarantee a successful simulation (Boufadi et al., 2021). All ligands were initially prepared by optimizing them using the Chem3D program to achieve a stable geometry with minimum energy. Next, the receptors (proteins) were prepared using Discovery Studio. This involved removing water molecules and heteroatoms, and adding polar hydrogen atoms and Kollman charges. Docking free energies (ΔG) were converted into inhibition constants using $Ki = \exp(\Delta G/RT)$ (R is the gas constant (1.985×10^{-3} kcal/mol K) and T is temperature in kelvins = 298.15 K) (Benyahlou et al., 2023). Afterwards, molecular docking simulations were conducted using the AutoDock Vina program.

We used Lipinski's rule to evaluate the medicinal capacity of phytocompounds, characterized by five parameters:no more than 5 hydrogen bond donors (-OH and -NH groups), must not exceed 10 hydrogen bond acceptors (O and N atoms), a molecular mass less than 500 Da, an octanol-water partition coefficient (milogP) ≤ 5, no more than one rule may be violated (Lipinski, 2004).

For the best ligands (the highest scores), the ADMET (Absorption, Distribution, Metabolism,Excretion and Toxicity) profile was used: online software (Swiss ADME website) for the prediction of physicochemical and pharmacokinetic parameters (Daina et al., 2017). Pro-tox 3.0 was used for the evolution of toxicity risks.

All the methods were carried out in triplicate. The results were expressed as mean ± standard deviation (SD). The significance of the difference was tested by the one-way ANOVA using GraphPad Prism 5.01. Difference between the means is considered statistically significant at the 5% level ($P < 0.05$).

Results and discussion

The extraction yield assesses a solvent's ability to extract particular desirable elements from plant material. The different solvent extracts' % yields from the sage aerial portion are displayed in Table 1. Methanol produced the highest percentage yield (28.8%) for the total weight of *S. officinalis* in the maceration extraction procedure, as opposed to the aqueous extract (19.5%). Choosing the right solvent is crucial to getting a high extraction yield.

Table 1
Percent for the total weight of the *Salvia officinalis* in maceration extraction

Extract	Yield, I.
Methanolic	28.80
Aqueous	19.57

Table 2 reports the findings of the phytochemical screening. One important technique for identifying the primary classes of secondary metabolites in the examined plant extracts is phytochemical screening (Khiya et al., 2019). Alkaloids, triterpenoids, coumarins, tannins, and saponosides were detected via phytochimical screening. Nonetheless,

the findings indicate that anthocyanins are absent, which is consistent with the findings of Khiya et al. (2019). This plant has historically been used to treat a variety of illnesses, which may be due to the presence of many kinds of secondary metabolites.

Table 2
Preliminary phytochemical screening of methanolic and aqueous extracts of *S. officinalis*

Bioactive compounds	Methanolic extract	Aqueous extract
Tannins	+	+
Alkaloids	+	+
Anthocyanins	–	–
Coumarins	+	+
Triterpenoids	+	+
Saponosides	+	+

Note: + – presence; "–" – absence.

Plants are mostly composed of polyphenols and flavonoids, which are significant antioxidants. These substances are organic and are essential to human well-being. This study examined the total phenolic and flavonoid content of methanol and aqueous extracts of the sage aerial portion (Table 3). The results demonstrated that the methanol extract (46.51 ± 0.015 mg GAE/g extract) had a lower level of total phenol than the aqueous extract (55.06 ± 0.029 mg GAE/g extract).

Table 3
Total phenolic content and total flavonoid content of *S. officinalis* extracts

Extract	Total phenol, µg/GAE/mg	Total flavonoids, µg/EQE/mg
Aqueous	55.06 ± 0.029	12.12 ± 0.011
Methanol	46.51 ± 0.015	20.70 ± 0.132

Martins et al. (2015) demonstrated that the aqueous extract had a higher concentration of phenolic chemicals than the methanolic extract. This outcome supports our conclusions. In comparison to the water extract (12.12 ± 0.011 mg QAE/g extract), the methanol extract showed a greater flavonoid concentration (20.70 ± 0.132 mg QAE/g extract). Our results showed that in both extracts, the total flavonoid content was lower than the total phenolic content. Prior research on extracts from *Salvia officinalis* has shown that the solvent employed and the plant's location have an impact on the total phenolic and flavonoid contents (Duletić-Laušević et al., 2019).

One stable free radical is DPPH. The ability of an antioxidant agent to release electrons to a free radical and hence reduce reactive radical structure is the fundamental idea behind free radical scavenging action. A compound's IC_{50}, or the concentration at which 50% of the molecule is inhibited, indicates its DPPH free radical scavenging activity (Abdelkader et al., 2014). As antioxidants scavenged radicals by donating hydrogen to form the stable DPPH molecule, the absorbance dropped and the color changed from purple to yellow. Higher antioxidant activity is indicated by a lower IC_{50}. The outcomes of the aqueous and methanol extracts' DPPH• radical scavenging activity in comparison to the reference standards ascorbic acid (Vit C) are shown in Table 4.

Table 4
DPPH free radical scavenging activities of methanol and aqueous extracts of *Salvia officinalis*

Extract	IC_{50}, µg/mL
Aqueux	23.48 ± 2.52
Methanol	12.31 ± 0.58
Ascorbic acid	3.57 ± 0.12

The current study's findings showed that the methanol extract of *S. officinalis* had a lower IC_{50} (12.31 ± 0.58 µg/mL) than the aqueous extract, which had an IC_{50} of 23.48 ± 2.52 µg/ml. indicating that, in contrast to the aqueous methanol extract, the methanol extract had high antioxidant activity. Our findings are consistent with those of Lima et al. (2007). Compared to the positive control, the activity of both extracts was lower. The quantitative and qualitative variance of the chemicals present in the extracts is directly related to antioxidant activity. A review of the literature suggests that *S.officinalis* includes flavonoids and other phenolic chemicals, which are regarded responsible for its antioxidant capabilities (Kadhim et al., 2016). The relationship between plant products' antioxidant activity and phenolic chemical content has been assessed in a number of studies (Nandhakumar & Indumathi, 2013). According to Ahmed et al. (2018), flavonoids are strong scavengers of the majority of oxidizing molecules, including singlet oxygen, as well as other free radicals linked to disease. Due to the presence of phenolic chemicals that are not flavonoids, each plant extract had a lower concentration of total flavonoids than total phenolics (Kaisoon et al., 2011). Farhat et al. (2014) state that the majority of the phenolic components in *S. officinalis* are flavonoids. Antioxidant activity and flavonoid content are correlated, according to the results obtained.

The molecular docking analysis revealed distinct binding affinities of the studied phenolic compounds toward the three major antioxidant enzymes: catalase (2CAG), glutathione peroxidase (2P31), and superoxide dismutase (1CB4) (Table 5). The binding energies ranged from –4.7 to –10.9 kcal/mol, indicating variable interaction strengths among the compounds. Among the ligands tested, salvianolic acid showed exceptional affinity toward catalase (2CAG) (ΔG = –10.9 kcal/mol; K_i = 0.01 µM) followed by cirsimaritin and kaempherol (ΔG = –10.2 kcal/mol; K_i = 0.03 µM), highlighting its interest in inhibiting anti oxydants enzymes.

For glutathione peroxidase, rosmarinic acid and salvianolic acid showed the best affinities (ΔG = –6.9 and –6.8 kcal/mol, respectively). Regarding SOD, quercetin (ΔG = –8.0 kcal/mol; K_i = 1.37 µM) and kaempferol (ΔG = –7.9 kcal/mol; K_i = 1.62 µM) were identified as the most potent binders, confirming their well-known radical-scavenging potential and ability to stabilize the SOD active site. In contrast, ascorbic acid showed the weakest affinity.

Table 5
Binding parameters (energy and K_i) of ligands with their targets

Targets	Catalase (2CAG)		Glutathione peroxydase (2P31)		SOD (1CB4)	
Molecules	energy, kcal/mol	K_i, µM	energy, kcal/mol	K_i, µM	energy, kcal/mol	K_i, µM
Caffeic acid	–7.1	6.25	–4.9	256.02	–5.6	78.55
Ferulic acid	–8.8	0.35	–4.7	358.82	–5.6	78.55
Rosmarinic acid	–7.4	3.76	–6.9	8.76	–6.9	8.76
Quercetin	–9.6	0.09	–6.8	10.36	–8.0	1.37
Acacetin	–9.9	0.06	–6.2	28.53	–7.8	1.92
Catechin	–9.2	0.18	–6.2	28.53	–7.8	1.92
Cirsimaritin	–10.2	0.03	–6.6	14.53	–7.3	4.46
Kaempherol	–10.2	0.03	–6.4	20.36	–7.9	1.62
Salvianolic acid	–10.9	0.01	–6.8	10.36	–7.0	7.40
Ascorbic acid	–6.0	39.99	–5.5	93.00	–5.6	78.55

Figures 2–6 provides a summary of the primary interactions that have been established between ligands and the protein active site. Salvianolic acid had the strongest affinity for catalase, indicating a powerful ability to control catalase activity via π–π stacking interactions and numerous hydrogen bonds. Overall, flavonoids with conjugated aromatic systems and numerous hydroxyl groups, which promote strong hydrogen bonding and pi-alkyl, pi-pi stacking, and pi-cation, such as kaempferol, quercetin, cirsimaritin, and acacetin, showed consistent multi-target action. According to these results, polyphenolic compounds with phenolic hydroxylation patterns and prolonged conjugation are attractive building blocks for the creation of multipurpose antioxidant treatments.

The antioxidant potential of *S. officinalis* has been extensively validated through both *in vitro* and *in silico* approaches, revealing its remarkable capacity to modulate oxidative stress pathways at the molecular level. The plant's bioactivity is mainly attributed to its high content of phenolic acids and flavonoids, notably rosmarinic acid, caffeic acid, salvianolic acid, and quercetin, which collectively exhibit strong antioxidant activity.

Recent computational studies have provided mechanistic insights into these effects. *In silico* docking analyses demonstrate that major phenolic constituents of *S. officinalis* interact efficiently with key antioxidant enzymes such as catalase (2CAG), superoxide dismutase (1CB4), and glutathione peroxidase (2P31).

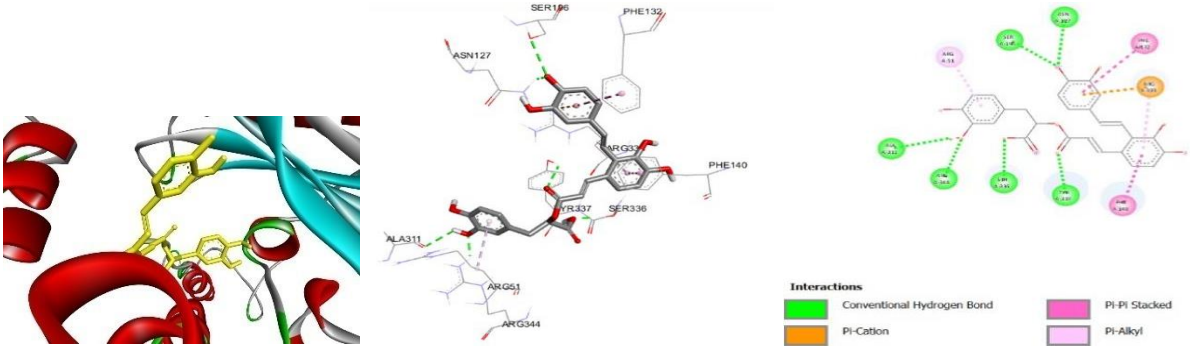

Fig. 2. Visualization of 2D and 3D binding sites of salvianolic acid with catalase (2CAG)

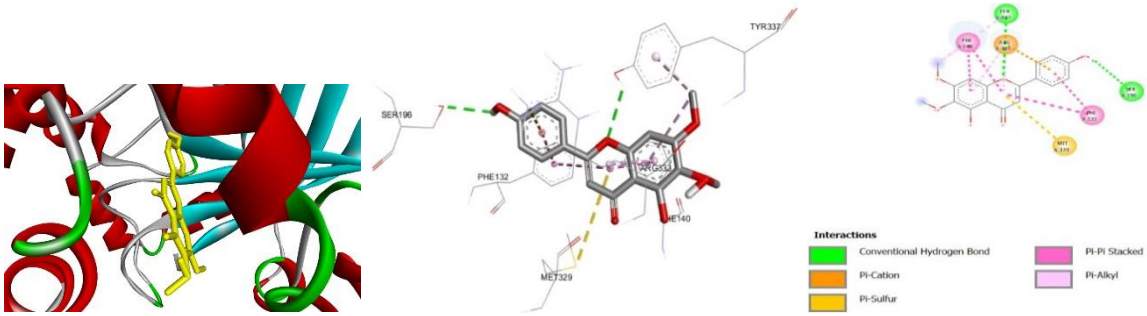

Fig. 3. Visualization of 2D and 3D binding sites of cirsimaritin with catalase (2CAG)

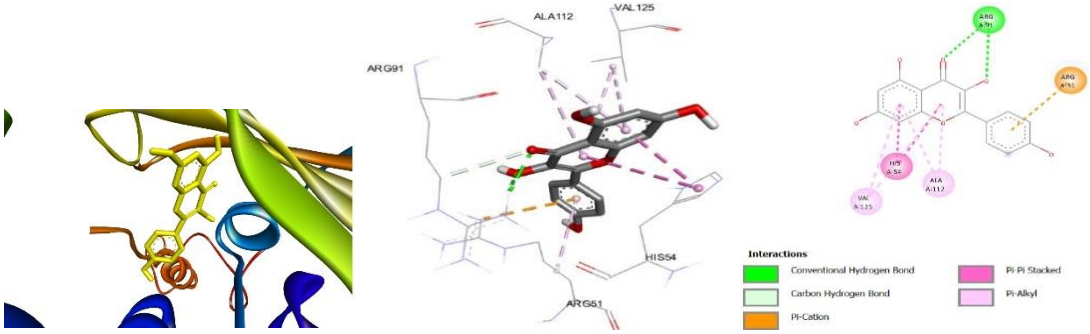

Fig. 4. Visualization of 2D and 3D binding sites of kaempherol with catalase (2CAG)

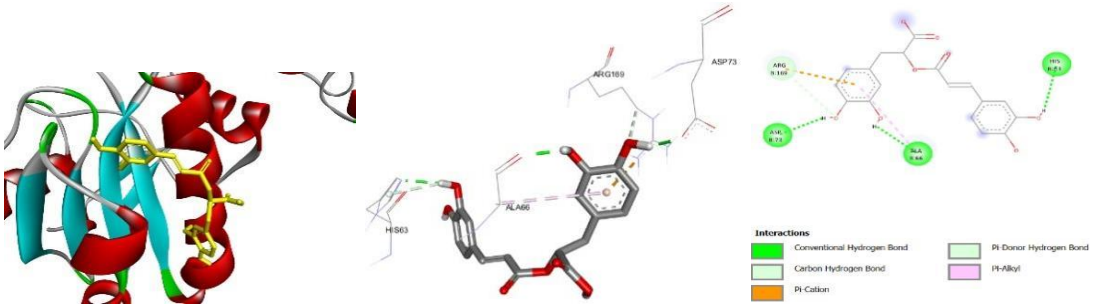

Fig. 5. Visualization of 2D and 3D binding sites of rosmarinic acid with gluthatione peroxydase (2P31)

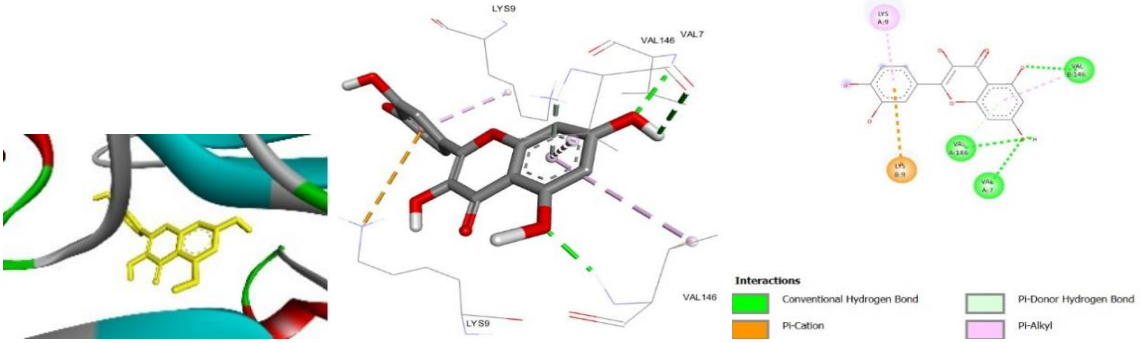

Fig. 6. Visualization of 2D and 3D binding sites of quercetin with SOD (1CB4)

Compounds such as salvianolic acid (ΔG ≈ –10.9 kcal/mol) and rosmarinic acid (ΔG ≈ –6.9 kcal/mol) form multiple hydrogen-bond and π–π stacking interactions with catalytically active residues, suggesting a stabilizing effect that could enhance enzymatic protection against reactive oxygen species (ROS). Similarly, flavonoids like quercetin and kaempferol exhibit high affinity for the metal centers of SOD, supporting their role in maintaining redox balance through both direct radical scavenging and enzyme modulation. These findings align with *in vitro* assays showing high DPPH and FRAP activities for *S. officinalis* extracts (Duletić-Laušević et al., 2016; Maache et al., 2023).

The substantial lowering ability anticipated by calculation was confirmed by Espinoza-Culupú et al. (2023), who also showed that hydroethanolic extracts of *S. officinalis* obtained 87.7% DPPH scavenging activity at 0.5 mg/mL. Rosmarinic acid was found to be the most abundant phenolic compound by HPLC analysis, confirming its significant role in the antioxidant response. Furthermore, according to Otmanine et al. (2024), rosmarinic acid binds well to acetylcholinesterase (ΔG = –8.4 kcal/mol) according to in silico docking, indicating an additional neuroprotective component of its antioxidant capacity through the suppression of enzymatic pathways linked to oxidative stress.

A number of phytochemicals from *S. officinalis* have also been shown to interact with lipoxygenase and xanthine oxidase, two enzymes implicated in the production of lipid and purine-derived free radicals, according to complementary *in silico* studies conducted by Bendaas et al. (2025). The antioxidant, antibacterial, and antifungal qualities of the plant extracts that have been demonstrated experimentally are molecularly supported by our computational results. These results support *S. officinalis* as a potential source of bioactive chemicals for use in pharmaceutical and nutraceutical products, especially in the creation of antioxidant treatments and functional meals. To assess their pharmacokinetic and toxicity profiles, as well as their physicochemical and pharmacokinetic properties, the compounds exhibiting the highest binding energies were examined (Daina et al., 2017).

It was determined that cirsimaritin, quercetin, kaempherol, and rosmarinic acid meet Lipinski's rule of five (Lipenski, 2004) based on Table 6, which lists the computed physicochemical and pharmacokinetic parameters of the docked phytocompounds. As a result, these compounds might make great oral medication candidates. Salvianolic acid, on the other hand, defies Lipinski's rule regarding the quantity of hydrogen bond donors. Cirsimaritin, quercetin, and kaempferol showed molecular weights below 500 g/mol, miLogP values under 5, and fewer than five hydrogen-bond donors, suggesting good oral absorption potential. Conversely, rosmarinic and salvianolic acids displayed high topological polar surface areas (TPSA > 140 Å²) and hydrogen-bonding capacity (nOHNH > 5), predicting lower membrane permeability and possible limitations in gastrointestinal absorption. All compounds were highly water-soluble and non-substrates of P-glycoprotein with negative Log K_p values indicating limited transdermal diffusion (Daina et al., 2017).

With LD_{50} values ranging from 159 to 5000 mg/kg and no discernible signs of hepatotoxicity, neurotoxicity, or mutagenicity, toxicity projections showed a good safety profile. Some flavonoids only showed little respiratory toxicity, most likely as a result of structural warnings. All flavonoid compounds were anticipated to have a moderate risk of nephrotoxicity.

All things considered, these findings demonstrate that the flavonoids of *S. officinalis*, in particular cirsimaritin, quercetin, and kaempferol, have a substantial antioxidant capacity together with appropriate pharmacokinetic behavior and low toxicity, extending their potential as safe natural antioxidants or nutraceutical options.

Table 6
Calculated physicochemical and pharmacokinetic parameters of the docked phytocompounds

Molecules	Cirsimaritin	Quercetin	Kaempherol	Rosmarinic acid	Salvianolic acid
Physicochemical and pharmacokinetic parameters (Molinspiration Cheminformatics)					
miLogP < 5	0.47	-0,56	-0,03	0.90	1.34
TPSA (oA) <500	89.13	131.36	111.13	144.52	184.98
MW < 500 (g/mol)	314.29	302.24	286.24	360.31	495.45
nON < 10	6	7	6	8	10
nOHNH < 5	2	5	4	5	7
Lipinski's violation	Yes	yes	yes	yes	No (NHorOH>5
Solubility and pharmacokinetics properties (SwissADME)					
Water solubility	Yes	Yes	Yes	Yes	yes
BBB permeant	No	No	No	No	No
Gastrointestinal absorption	Hight	Hight	Hight	Low	Low
Log *K*p : Skin permeation: cm/s	-5.86	-7.05	-6.70	-6.82	-6.53
P-gp substrate	No	No	No	No	No
Toxicity risks					
DL_{50} (mg/kg)	4000	159	3919	5000	5000
Hepatotoxicity	No	No	No	No	No
Neurotoxicity	No	No	No	No	No
Nephrotoxicity	MR	MR	MR	MR	MR
Respiratory toxicity	Yes	Yes	Yes	No	No
Cardiotoxicity	No	No	No	No	No
Carcinogenicity	No	MR	No	No	No
Mutagenicity	No	MR	No	No	No

Cirsimaritin, kaempferol, and quercetin are found inside the white ellipse, which indicates good gastrointestinal absorption, according to the data. Salvianolic acid, on the other hand, is entirely outside of both the white and yellow portions of the HIA zone, although rosmarinic acid is located close to its margin. Their strong hydrogen-bonding ability and high polarity (TPSA > 150 Å²) restrict passive diffusion across biological membranes, as evidenced by their placement. Because of their hydrophilic nature, these chemicals are expected to have limited intestinal absorption and no BBB penetration.

None of the tested compounds are located within the yellow region, confirming that none are expected to cross the BBB, which is advantageous for avoiding central nervous system side effects. Furthermore, their PGP-status (non-substrates of P-glycoprotein) suggests low efflux susceptibility, potentially improving systemic retention and metabolic stability.

The BOILED-Egg model confirms that cirsimaritin, kaempferol and quercetin possess optimal physicochemical profiles for oral absorption, whereas rosmarinic and salvianolic acids are more suitable for topical or localized antioxidant applications due to their limited permeability but excellent aqueous solubility (Fig. 7).

Conclusion

According to the study's findings, *Salvia officinalis* crude extracts made using two solvents, methanol and water, contain bioactive compounds, indicating its potential as a beneficial natural antioxidant source. The results show that this plant has significant antioxidant qualities and is high in flavonoid and total phenolic components. Therefore, a variety of phytochemicals are responsible for this activity.

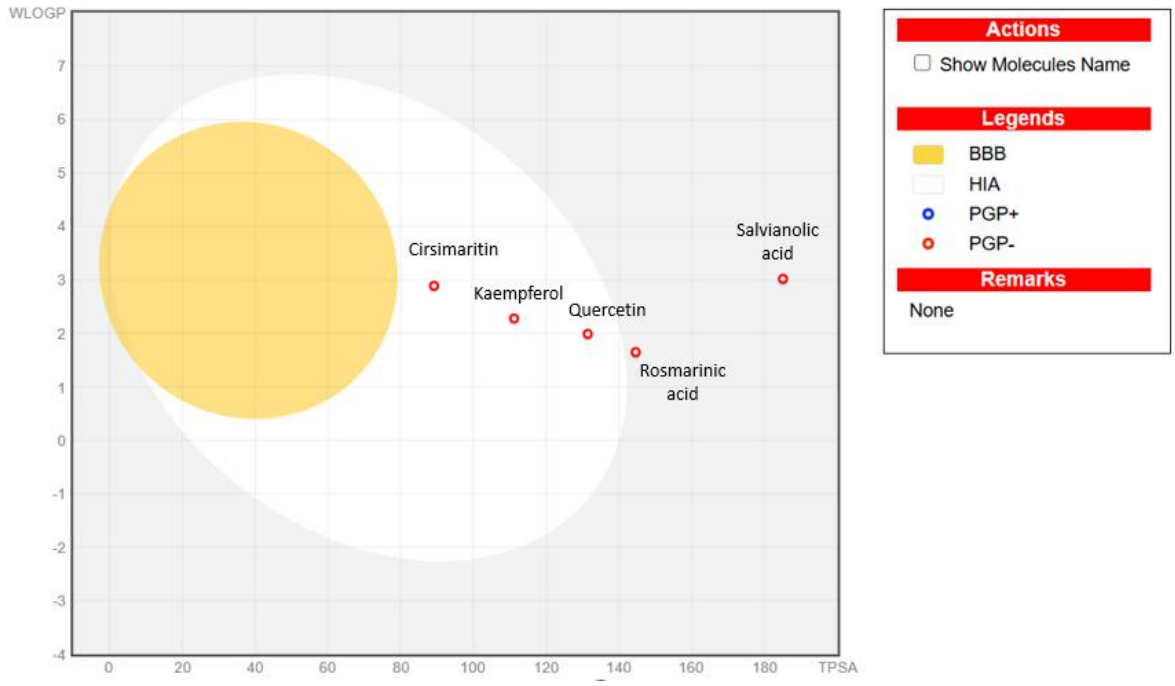

Fig. 7. BOILED-Egg model for the molecules showing the best binding energies

This *in silico* study highlights the significant antioxidant properties of the phenolic chemicals found in *S. officinalis*. Docking findings demonstrated that salvianolic acid, cirsimaritin, and kaempferol exhibit the highest binding affinities toward catalase, glutathione peroxidase, and superoxide dismutase, showing their capacity to influence major antioxidant enzymes through numerous hydrogen bonds and π–π interactions. While rosmarinic and salvianolic acids, because of their high polarity, showed poor membrane permeability, ADME investigation verified that cirsimaritin, quercetin, and kaempferol adhere to Lipinski's guidelines and exhibit good gastrointestinal absorption. According to toxicity evaluation, all compounds had a favorable safety profile, with flavonoids having a moderate risk of nephrotoxicity. The BOILED-Egg model provided additional evidence for their superior intestinal absorption and lack of blood-brain barrier penetration. All things considered, *S. officinalis* flavonoids, in particular quercetin, kaempferol, and cirsimaritin, stand out as safe, bioactive options for the creation of nutraceutical and natural antioxidant compositions.

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