SAGE EXTRACT: EFFECT OF PARTICLE SIZE ON *TPC* AND ANTIOXIDANT ACTIVITY. BIOINFORMATIC APPROACHES

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Abstract. Over the years, experimental studies have shown that secondary metabolites have promising therapeutic potential in a variety of pathologies, but unfortunately, they are usually found in fairly small amounts, and their recovery in the highest possible concentration is a challenge. In view of this, the present project aimed to evaluate the effect of particle size on polyphenol extraction and antioxidant activity of the medicinal species *Salvia officinalis* L., determination of the pharmacokinetic properties and bioactivity score of two compounds (pinocembrin, luteolin) frequently encountered in sage extract, as well as the *in silico* prediction of their biotargets. The data showed that the highest amount of polyphenolic compounds extracted from sage was obtained after maceration of the powder with the smallest particle size, in the range 63–90 μm: 32.47±0.24 milligrams of gallic acid equivalents (*GAE*) per 1 g dried weight (*DW*) of sample, in a system of binary solvents (pharmaceutical ethyl alcohol: distilled water). There was a high correlation between the total polyphenol content (*TPC*) values of the evaluated extracts and their antioxidant activities, the sample with the highest antioxidant activity expressed as Trolox equivalent antioxidant capacity (*TEAC* = 2.90 μg/mL) being also the one with the highest amount of polyphenols. Bioinformatics analyzes performed on the two compounds showed that both possess molecular properties similar to synthetic drugs: can act as enzyme inhibitors, ligands of nuclear receptors, also having an absolute probability score with a large number of biotargets.

Key words: *Salvia officinalis* L., polyphenols, particle size, antioxidant activity, *in silico* approaches.

INTRODUCTION

Salvia officinalis L. is a medicinal species with pharmacological properties due to its secondary metabolites (polyphenols, alkaloids, triterpenes, sterols, etc.). In recent years, a multitude of experimental studies have been reported attesting to the therapeutic potential of this species, which can be successfully used as an anti-inflammatory [21], antioxidant [6], anticancer [25], antiseptic [17], neuroprotective [14], antiviral agent [13].

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In addition, bioinformatics approaches used to anticipate the physicochemical, biological and environmental properties of natural compounds, knowing their chemical structure [2, 3, 4, 5, 22] have become widespread.

For example, in 2018, Monteiro *et al.* [24] demonstrated through a molecular docking study, that two compounds of the flavonoid class, present in sage, namely pinocembrin and luteolin, can inhibit the enzyme beta-secretase 1, responsible for the accumulation of beta amyloid in Alzheimer's neurodegenerative pathology.

In addition to their neuroprotective properties, these phytocompounds also have significant antiviral potential. Thus, the *in silico* study conducted by Babaeekhou *et al.* in 2021 [8], aimed to test the inhibitory activity of biochemical compounds in methanolic extracts of *S. officinalis* L., and *A. dracunculus* L. against SARS-CoV-2 virus. For this molecular docking study, Schrodinger software was used to establish binding energy and biochemical ligand interactions against target viral proteins COV-2-SP and M^{pro}. Initially, the Protein Data Bank database [44] was used to take over the structure of the viral target, and the chemical structures of the biochemical ligands, identified in the 2 extracts, were made using ChemDraw Professional 15.0, and later optimized with LigPrep modules in Maestro. Positive controls were lopinavir and nelfinavir. The results of this study showed that in the case of compounds present in sage and tested, the highest affinity for COV-2-SP and M^{pro} had kaempferol 3-O-rutinoside (docking score: −10,575, −9,705 kcal/mol). Lower binding affinities were recorded for the following compounds: rosmarinic acid (−6,049 kcal/mol), luteolin (−6,039 kcal/mol), apigenin (−5,712 kcal/mol), caffeic (−5,376 kcal/mol), being similar to those of positive controls. This demonstrates the antiviral potential of this species. Also, using the AutoDock 4.2.6 software, Udrea *et al.* [33], showed that compounds such as thioridazine, sulforidazine and mesoridazine, which belong to the category of antipsychotics and antihistamines, can interact with the M^{pro} receptor, and can be considered as a potential drug regimen against COVID-19.

Another *in silico* study aimed to determine the interaction and binding energy of 8 polyphenols, including pinocembrin from sage, to the conversion enzyme angiotensin 2 and protein Spike 1 (SARS-CoV-2), using the molecular docking program AutoDock 4.2.6. Briefly, the results of the experiment showed that in the case of the SARS-CoV-2 receptor, the lowest binding energy (which means hight affinity) was manifested by the pinocembrin ligand, with a value of −7.54 kcal/mol, interacting with the following AA residues: Asn448, Tyr449, Tyr451, Tyr495, Lys444, Phe497, and for the ACE-2 receptor, the binding affinity value was better −8.58 kcal/mol, the ligand interacting with the following amino acids of the receptor: Asn210, Leu9, Pro565, Ser563, Leu91, Val212, Val209. In addition, based on the ADME behavior of pinocembrin, the authors concluded that this compound has effective antiviral potential [15]. Another studies showed that biochemical compounds as rutin, quercetin and myricetin had also strong binding affinities to ACE-2 receptors [9, 10,16].

The process of extracting the secondary metabolites (polyphenols, alkaloids, triterpenes) of natural products, in the highest concentration, is a real challenge. As shown by Hernandez *et al.* [18], but also Zhu *et al.* [39], it depends on a number of factors such as extraction method, extraction time, solvent used, temperature and last but not least the particle size.

Maceration is part of the category of classical, conventional extraction methods, being widely used since ancient times. This method of extraction is usually performed at room temperature, and involves immersing the plant material in a liquid for a certain period of time, in order to recover the compounds with therapeutic properties [7].

In brief, the extraction of bioactive compounds occurs as follows: the solvent (liquid) enters the solid matrix; the solute dissolves in it; then follows the stage of diffusion of the solute out of the matrix, followed by the last stage more precisely the collection of the solute which will contain the metabolites of interest [37]. The main advantages of this technique: low cost, it does not require special equipment and a qualified operator, environmentally friendly characteristics [23].

In the literature there are a number of studies that show that reducing the size of particles by grinding not only increases the diffusion of bioactive compounds, but also determines the lysis of cell walls, which is beneficial in obtaining a high yield of secondary metabolites [11, 29, 31, 36].

Thus, starting from the above, the objectives of our research aimed to: investigating the effect of particle size in the extraction of polyphenols from *S. officinalis* L., using a conventional method (maceration) and a binary solvent system, testing antioxidant activity of extracts, determination of the pharmacokinetic properties and bioactivity score of two compounds (pinocembrin, luteolin) frequently encountered in sage extract, as well as the *in silico* prediction of their biotargets.

MATERIALS AND METHODS

MATERIALS

Equipment

For this experimental study we used the following equipment: Hettich EBA 200 centrifuge, Thermal balance KERN MLB 50-3N, Analytical balance KERN ABS 220-4N, METTLER Toledo MT5 microbalance, Retsch Grindomix GM 200 laboratory mill, Rocker VF6 vacuum filtration system, Mini Rotator Bio RS-24, OCEAN VIEW HR 2000+ spectrophotometer.

Chemicals

Pharmaceutical ethyl alcohol (96.9 %) was purchased from SC.COMAN PRODUCT S.A. Distilled water, Folin Ciocâlteu reagent, Na_2CO_3, and gallic acid, 2,2-Diphenyl-1-picrilhydrazyl (DPPH), Na_2CO_3 powder, trolox were purchased from CARLO ERBA Reagents S.A.S.

METHODS

Primary processing of plant material

The dried leaves of sage (*Salvia officinalis* L.), purchased from a local manufacturer, were ground using the laboratory mill, in impulses for 3 minutes at 4000 rpm and continuously for 30 seconds at 10000 rpm. Moisture content (*MC*) was determined by drying about 1 g plant powder in a Thermobalance Kern at 118 °C. The value of *MC* was 7.67 %, which represents the weight loss (*WL*) from startweight (*SW*) of the sample.

The grounded powder was passed through several sieves with decreasing mesh sizes: 125 µm, 106 µm, 90 µm, 63 µm and the material retained on each site (Fig. 1) was used for the extraction process. The sieving process was performed in pulses for 5 minutes, 60 % amplitude, using a Sieve shaker Retsch with vertical vibration.

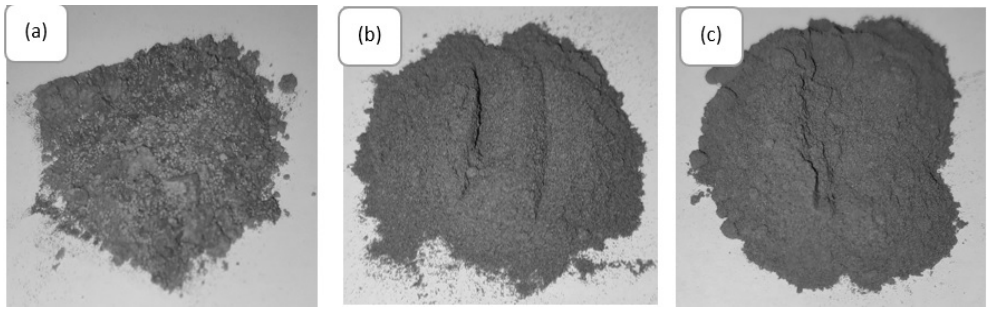


Fig. 1. *Salvia officinalis* L. leaves grounded to different particle size: (a) 106–125 µm; (b) 90–106 µm; (c) 63–90 µm.

Preparation of hydroethanolic extracts of sage

1 g of each powder was immersed in 10 mL of solvent (Pharmaceutical EtOH: distilled water, ratio 50:50 v/v and 70:30 v/v). The extraction process, more precisely the maceration was performed at room temperature, protected from sunlight, for 7 days; the first 4 days with continuous stirring for 6 hours at 30 rpm at Mini-rotator Bio RS-24 and another 3 days without stirring. The samples were then centrifuged twice for 10 minutes at 6.000 rpm and filtered

under vacuum through filter paper. The extracts were stored in glass vials at a temperature of −18 °C until analysis of the total polyphenol content (*TPC*) and antioxidant activity.

Determination of total polyphenols content of *Salvia officinalis* L. extracts

The total content of polyphenolic compounds of the sage extracts was determined using the Folin-Ciocâlteu reagent following the method of Singleton *et al.* [30] with some modifications. From each experimental variant 500 µL diluted extract was taken, over which 2.5 mL of Folin-Ciocâlteu reagent were added. After 5 minutes 2 mL of Na_2CO_3 were added. The samples were kept in the dark at room temperature for 1 hour and then analyzed at the spectrophotometer at a wavelength of 765 nm against blank (hydroethanolic solvent). A calibration curve (R^2 = 0.9995) was prepared using standard solutions of gallic acid (10, 20, 30, 40, 50, 60, 70 µg/mL). The results were expressed in milligrams equivalent gallic acid per gram of dried plant.

Determination of the free radical scavenging activity of samples

After the *TPC* analysis, performed in order to establish the total polyphenol content, the samples were subjected to DPPH analysis in order to identify their antioxidant activity [40]. All 6 extracts, resulted based on the variation of the particle size, were diluted in order to obtain 3 concentrations (500–5000 µg/mL). From each sample of different concentration, 250 µL extract was taken over which 1750 µL DPPH (80 µM) was added. The samples were kept in the dark at room temperature for 30 minutes and then analyzed at a wavelength of 517 nm. The percentage of DPPH free radical inhibition was calculated based on the following equation:

$$I\% = \frac{A0 - A1}{A0} * 100 \quad (1)$$

where $A0$ is the absorbance of the control sample (hydroethanolic solvent) and $A1$ is absorbance of the sample (extract).

The half maximal inhibitory concentration (IC_{50}) of each extract was then identified, and the DPPH radical scavenging activity of each sample was expressed as TROLOX equivalent antioxidant capacity (*TEAC*), representing the ratio between Trolox IC_{50} (µg/mL) and sample IC_{50} (µg/mL).

Bioinformatic approaches. *In silico* pharmacokinetic and bioactivity studies. Prediction of molecular targets of pinocembrin and luteolin

The pharmacokinetic properties of pinocembrin and luteolin were calculated using computational program Molinspiration Cheminformatics [41], following

Lipinski's rule of five. According to this rule a molecule shows a good permeability if it meets the following parameters: molecular weight ≤ 500 Daltons, log P ≤ 5, number of hydrogen bond donors ≤5, and number of hydrogen bond acceptors ≤ 10. Also, the molecular volume of the 2 natural compounds was identified, which can provide us with information about the following characteristics: the penetration capacity of the blood-brain barrier, intestinal absorption. In addition, determining the number of rotary bonds indicates the ability of a molecule to bind to ion channels or receptors.

Based on the canonical SMILES of the 2 compounds, taken from the PubChem database [43] and using Molinspiration property engine v2018.10, we calculated the bioactivity scores of the 2 phytocompounds.

Regarding the identification of drug targets of pinocembrin and luteolin, we used SwissTragetPrediction [42] as a prediction tool. The SMILES sequence of each compound was loaded into the software and the 2-D structure was automatically modeled. In the results window, the relevant information generated for each target was highlighted in tabular form (Fig. 2).

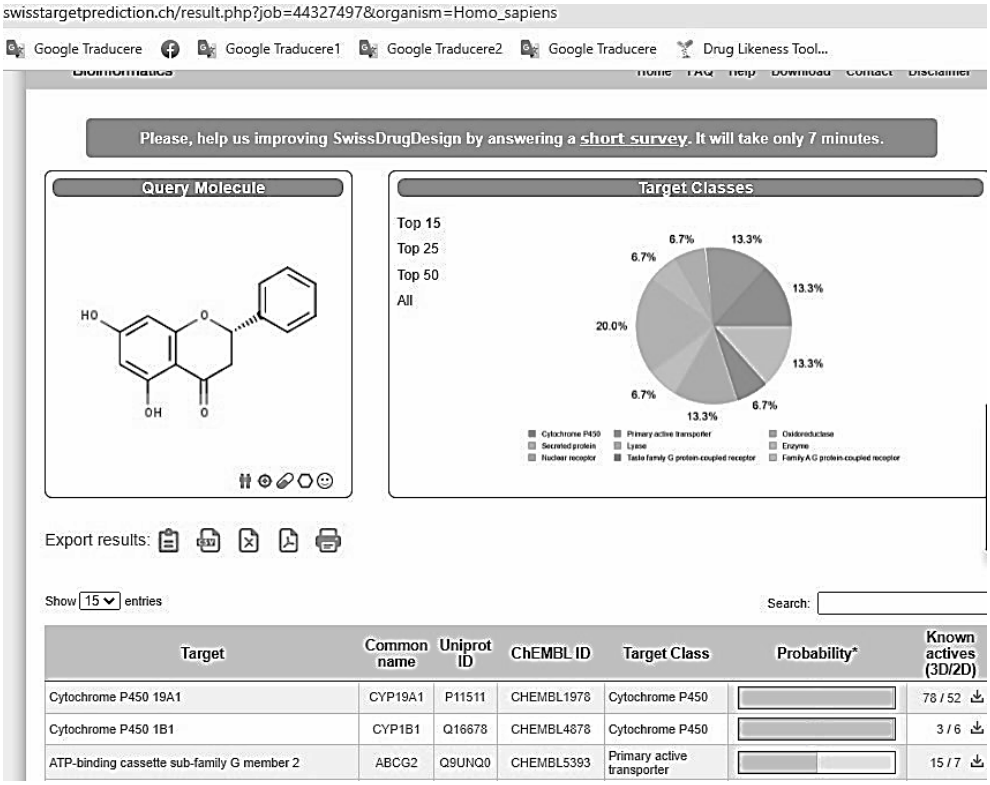


Fig. 2. Screenshoot depicts the SwissTargetPrediction tool [42].

RESULTS AND DISCUSSION

AMOUNT OF *TPC*

The results in Table 1 highlighted that the sage extracts in which the size of the solid particles was between 63 and 90 μm, had the highest total content of polyphenols, respectively 32.47±0.24 mg/g *GAE* and 31.96±0.63 mg/g *GAE*, followed by those with a size between 90 and 106 μm (31.18±0.04 mg/g *GAE*; 29.32±0.05 mg/g *GAE*) and by those with a larger size (106−125 μm) (28.60±0.26 mg/g *GAE*; 25.79±0.3 mg/g *GAE*).

Table 1

The mass fraction of *TPC* extracted from sage by maceration under different conditions using different particle size and solvents

Sample code	Particle size (μm)	Ratio EtOH: distilled water (v/v)	*TPC* (mg/g *GAE*)
S1	63–90	70:30	32.47 ± 0.24
S2	90–106	70:30	31.18 ± 0.04
S3	106–125	70:30	28.60 ± 0.26
S4	63–90	50:50	31.96 ± 0.63
S5	90–106	50:50	29.32 ± 0.05
S6	106–125	50:50	25.79 ± 0.3

Data expressed as mean of 3 replicates ± SD (standard deviation).

Also, recently the experimental study conducted by Prasedya et *al.* [27] showed that the phytochemical composition of the ethanolic extract of *Sargassum cristaefolium*, popularly known as brown seaweed, had higher content of polyphenols in the case of samples with smaller particles. Thus, at the size of 45 μm *TPC* it was 43.27 mg *GAE*/g extract, and at the one of 4000 μm the value of *TPC* was approximately 3 times smaller, 14.19 mg *GAE*/g extract.

However, there are studies in the literature that show that not always reducing the size of particles leads to the extraction of higher concentrations of phytocompounds, but on the contrary there is a decrease [19] or cases where no there was a significant difference in particle size variation [1].

In 2015, Pop and colleagues [26] using a double extraction time compared to the one used by us (7 days) and a binary system of solvents with 80 % EtOH, obtained lower *TPC* values than those in the present study, namely 19.49 mg *GAE*/g dried plant. This may demonstrate that, on the one hand, a prolonged extraction time may not always lead to a higher concentration of phytocompounds, and on the other hand the use of plant material as such without being subjected to

the primary processing stage (grinding and sieving) in order to reduce its size, represents an impediment in obtaining extracts with the highest amounts of phenolic compounds.

As can be seen in the Figure 3, the recovery of polyphenols from sage was somewhat dependent on the type of solvent used, its polarity and the solubility of the phenolic compounds. Thus, the sample with the highest amount of polyphenols was S1 in which the binary solvent with a ratio of pharmaceutical EtOH: distilled water 70:30 was used. Our results are in line with previous reports [34, 35, 38] which demonstrate that the use of a binary solvent system, in our case pharmaceutical ethyl alcohol-distilled water, is more effective in extraction of polyphenols, than a mono-solvent system (pure ethanol or water).

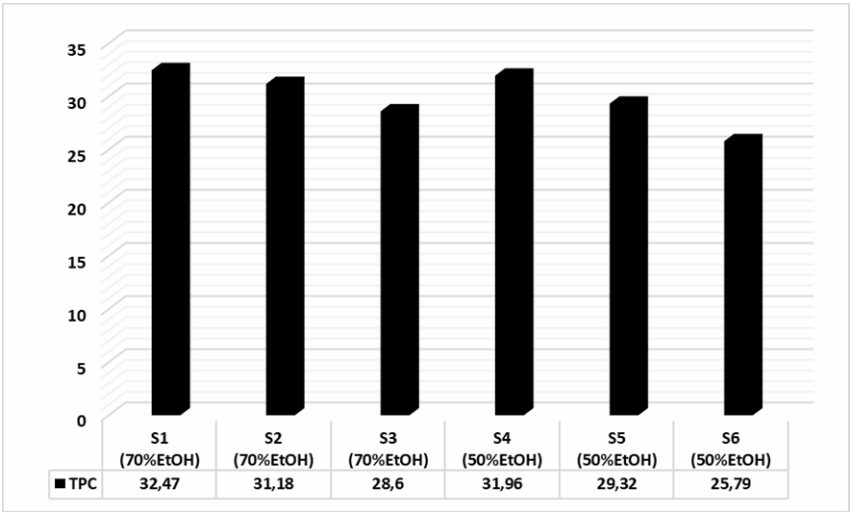


Fig. 3. *TPC* (mg *GAE*/g dried plant) *S. officinalis L.* extracts and percentage of pharmaceutical ethyl alcohol (v/v).

Comparing the *TPC* value of sample S3 with that of sample S6, in which we used the same particle size but different solvents, we can see a significant difference between the two *TPC* values. In the case of samples S1 and S4, the *TPC* values are similar. In contrast, the difference between the *TPC* value of sample S1 (32.47 ± 0.24 mg/g *GAE*) and that of sample S6 (25.79 ± 0.3 mg/g *GAE*) is a notable one, the results of our study highlighting the existence of a close dependencies between the particle size of plant material and the solvent used.

DPPH RADICAL SCAVENGING ACTIVITY

It is well known that plant extracts have the ability to reduce the negative effects of oxidative stress in the human body, which is installed as a result of

excessive growth of reactive oxygen species, eventually leading to the installation of cellular apoptosis [32]. Moreover, these extracts may have antioxidant activities comparable or even superior to those of synthetic antioxidants [12]. Thus, among the objectives of this study is the determination of the antioxidant capacity of the extracts obtained.

As can be seen in the Figure 4 all extracts showed strong DPPH free radical scavenging activities. The IC_{50} values of the samples are comparable or even better than that of the standard antioxidant, Trolox (IC_{50} = 43.67 µg/mL), which is a synthetic derivative of vitamin E. Classifying them, from the series of extracts, the best antioxidant activity had the sample S1 (IC_{50} = 15.05 µg/mL), followed by S4 (IC_{50} = 15.68 µg/mL) and S2 (IC_{50} = 18,62 µg/mL).

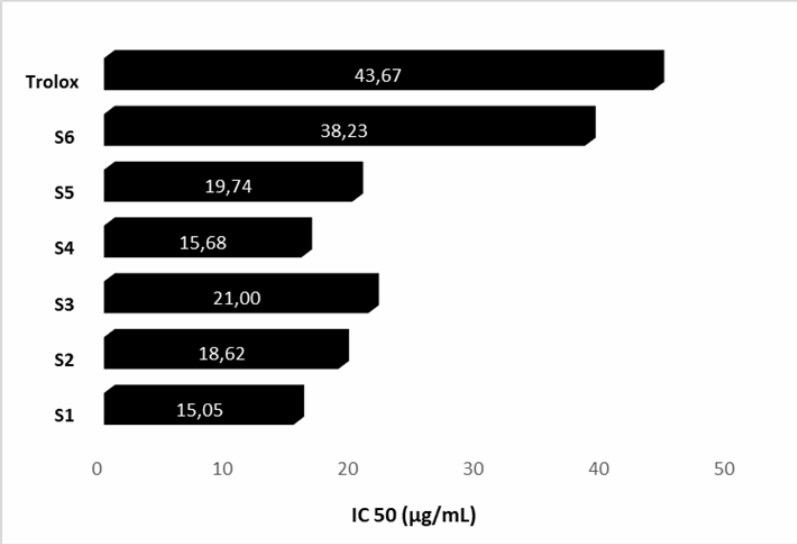


Fig. 4. Sage extracts and Trolox providing 50 % inhibition of DPPH (IC_{50}).

Our results are in harmony with those obtained in previous studies, such as that of Kelen and Tepe [20], which states that extracts from 2 species of sage had IC_{50} values lower than 19 µg/mL, but also that of Rasmy and collaborators [28], which declare IC_{50} values of 10 ± 1.22 and 14 ± 1.46 µg/mL extract of *S. officinalis* L.

Starting from the IC_{50} values of the samples and the standard, we calculated the equivalent Trolox antioxidant capacity of all 6 extracts.

The results in Table 2 show, as mentioned above, the best free radical scavenging activity was performed by the S1 sample, with a maximum *TEAC* value of 2.90 µg/mL. If in the case of IC_{50}, a low value indicates high antioxidant activity, in the *TEAC* test the higher value denotes the high efficiency of the extract in terms of antioxidant potential.

In addition, Figure 5 shows the existence of a high correlation (r^2 = 0.9535) between the *TPC* values of the evaluated extracts and their antioxidant activities. Thus, with the increase of the polyphenol content in the extract, there is an increase in the antioxidant capacity.

Table 2

Trolox equivalent antioxidant capacity of sage extracts

Sample code	*TEAC* (µg/mL)
S1	2.90
S2	2.35
S3	2.08
S4	2.79
S5	2.21
S6	1.14

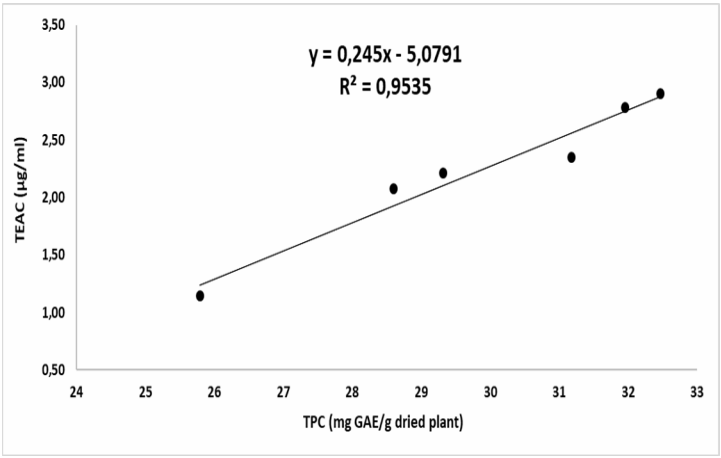


Fig. 5. Linear correlation between the total phenolic compound of sage extracts and their antioxidant activity.

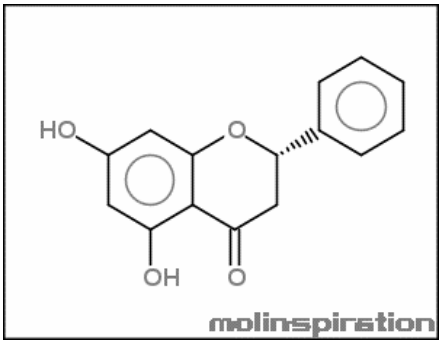
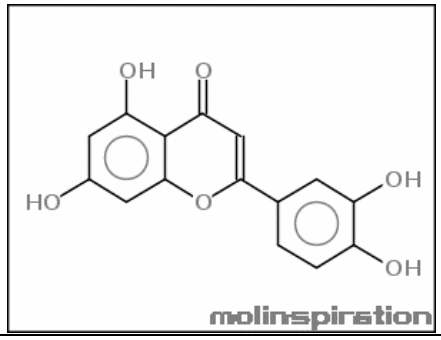
IN SILICO PHARMACOKINETIC

In recent years, the design of new forms of drugs with the help of computer tools has taken a large scale, becoming even indispensable in the pharmaceutical industry. As mentioned, using bioinformatics methods, one of the objectives of our paper aimed to estimate the molecular properties, bioactivity score and interaction with different targets, of two flavonoids (pinocembrin, luteolin), which are usually found in sage extract. The data presented in Table 3 show that: the miLogP values

of pinocembrin and luteolin are in the acceptable range according to Lipinski's rule; molecular weights are <500 Daltons, suggesting that these compounds can be easily absorbed, diffused and transported. In addition, the number of rotatable bonds being ≤10, denotes a good score of oral bioavailability.

Table 3

Pharmacokinetic properties of pinocembrin and luteolin

Compound/ 2-D Structure	**Molecular descriptors**	
Pinocembrin 	miLogP[a]	2.60
	TPSA[b]	66.76 Å^2
	Natoms	19
	MW[c]	256.26 g/mol
	nON[d]	4
	nOHNH[e]	2
	N violations	0
	N rotb[f]	1
	Volume	222.24 Å^3
Luteolin 	miLogP[a]	1.97
	TPSA[b]	111.12 Å^2
	Natoms	21
	MW[c]	286.24 g/mol
	nON[d]	6
	nOHNH[e]	4
	N violations	0
	N rotb[f]	1
	Volume	232.07 Å^3

[a]Logarithm of partition coefficient between n-octanol and water (miLogP); [b]topological polar surface area (*TPSA*); [c]molecular weigh (MW); [d]number of hydrogen bond acceptors (nON); [e]number of hydrogen bond donors (nOHNH); [f]number of rotatable bonds (N rotb).

According to Avram *et al.* [4], a molecule is biologically inactive if the value of the bioactivity score is less than −0.5, and has good biological activity if this score is greater than 0. Thus, regarding the bioactivity of the 2 compounds evaluated in this study, the *in silico* results (Table 4) indicate that both pinocembrin and luteolin have high activities as ligands to the nuclear receptor and as enzyme inhibitors, luteolin being also a good kinase inhibitor.

Table 4
Bioactivity score of pinocembrin and luteolin

Compound	*GPCR* ligand[a]	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Pinocembrin	–0.00	–0.20	–0.32	0.37	–0.17	0.21
Luteolin	–0.02	–0.07	0.26	0.39	–0.22	0.28

[a]G protein-coupled receptor (*GPCR*).

Regarding the target prediction, for the studied flavonoids, as we mentioned in the chapter materials and methods, we used the bioinformatics tool SwissTargetPrediction. Figure 6 shows the top 10 targets with the best probability scores for pinocembrine. As can be seen the most likely targets of this ligand are: Cytochrome P450 19A1, Cytochrome P450 1B1, ATP-binding cassette sub-family G member 2, Monoamine oxidase B, Multidrug resistance-associated protein 1, Testis-specific androgen-binding protein, Carbonic anhydrase VII, Carbonic anhydrase XII, Estradiol 17-beta-dehydrogenase 1, Carbonic anhydrase IV.

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Cytochrome P450 19A1	CYP19A1	P11511	CHEMBL1978	Cytochrome P450	0.99533651238	78 / 52
Cytochrome P450 1B1	CYP1B1	Q16678	CHEMBL4878	Cytochrome P450	0.99533651238	3 / 6
ATP-binding cassette sub-family G member 2	ABCG2	Q9UNQ0	CHEMBL5393	Primary active transporter	0.504893511617	15 / 7
Monoamine oxidase B	MAOB	P27338	CHEMBL2039	Oxidoreductase	0.465623633307	164 / 127
Multidrug resistance-associated protein 1	ABCC1	P33527	CHEMBL3004	Primary active transporter	0.347652208386	0 / 2
Testis-specific androgen-binding protein	SHBG	P04278	CHEMBL3305	Secreted protein	0.347652208386	4 / 3
Carbonic anhydrase VII	CA7	P43166	CHEMBL2326	Lyase	0.339889055769	51 / 7
Carbonic anhydrase XII	CA12	O43570	CHEMBL3242	Lyase	0.339889055769	105 / 6
Estradiol 17-beta-dehydrogenase 1	HSD17B1	P14061	CHEMBL3181	Enzyme	0.332035537736	29 / 1
Carbonic anhydrase IV	CA4	P22748	CHEMBL3729	Lyase	0.332035537736	9 / 7

Fig. 6. Target prediction results for pinocembrin [42].

In the case of predicting biological targets for luteolin, the results of our study attest to the promising potential of this compound. Figure 7 lists the top 10 of the 30 targets with total similarity and an absolute probability score (1.0).

SwissTargetPrediction

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
NADPH oxidase 4	NOX4	Q9NPH5	CHEMBL1250375	Enzyme	1.0	6 / 8
Aldose reductase	AKR1B1	P15121	CHEMBL1900	Enzyme	1.0	17 / 71
Cyclin-dependent kinase 5/CDK5 activator 1	CDK5R1 CDK5	Q15078 Q00535	CHEMBL1907600	Kinase	1.0	6 / 18
Xanthine dehydrogenase	XDH	P47989	CHEMBL1929	Oxidoreductase	1.0	12 / 20
Monoamine oxidase A	MAOA	P21397	CHEMBL1951	Oxidoreductase	1.0	5 / 18
Tyrosine-protein kinase receptor FLT3	FLT3	P36888	CHEMBL1974	Kinase	1.0	5 / 7
Carbonic anhydrase II	CA2	P00918	CHEMBL205	Lyase	1.0	8 / 14
Cyclin-dependent kinase 1/cyclin B	CCNB3 CDK1 CCNB1 CCNB2	Q8WWL7 P06493 P14635 O95067	CHEMBL2094127	Other cytosolic protein	1.0	4 / 11
Arachidonate 5-lipoxygenase	ALOX5	P09917	CHEMBL215	Oxidoreductase	1.0	5 / 47
Adenosine A1 receptor (by	ADORA1	P30542	CHEMBL226	Family A G protein-coupled	1.0	6 / 23

Fig. 7. Target prediction results for luteolin [42].

CONCLUSIONS

The highest amount of polyphenolic compounds extracted from the medicinal species *S. officinalis* L. was obtained after maceration of the powder with the smallest particle size, in the range 63–90 μm (32.47±0.24 mg/g *GAE*). In addition, as the concentration of alcohol in the extraction medium increased, the total polyphenol content increased.

There was a high correlation between the *TPC* values of the evaluated extracts and their antioxidant activities, the sample with the highest antioxidant activity (*TEAC* = 2.90 μg/mL) being also the one with the highest amount of polyphenols. Bioinformatics analyzes performed on the two compounds showed that both possess molecular properties similar to synthetic drugs: can act as enzyme inhibitors, ligands of nuclear receptors, and have a score of absolute probability with a large number of biotargets.

In short, our study comes as a complement to those experimental and *in silico* studies that have shown that phytotherapy based on phenolic compounds offers therapeutic benefits with few side effects at the expense of synthetic drugs.

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