frontiers in Drug Discovery

TYPE Original Research
PUBLISHED 31 August 2026
DOI 10.3389/fddsv.2026.1939611

OPEN ACCESS

EDITED BY
Conrad Veranso Simoben,
University of Buea, Cameroon

REVIEWED BY
Fidele Ntie-Kang,
University of Buea, Cameroon
Łukasz Szeleszczuk,
Medical University of Warsaw, Poland
Fan Zhang,
Liaoning University of Traditional Chinese Medicine, China

*CORRESPONDENCE
Cláudia Nunes dos Santos,
claudia.nunes.santos@unl.pt

RECEIVED 17 July 2026
REVISED 04 August 2026
ACCEPTED 12 August 2026
PUBLISHED 31 August 2026

CITATION
Carregosa D, Moreira I, Rasteiro D, Vanneschi L and Nunes dos Santos C (2026) *In silico* prediction of the permeability of phytochemicals across the blood-brain barrier.
Front. Drug Discov. 6:1939611.
doi: 10.3389/fddsv.2026.1939611

In silico prediction of the permeability of phytochemicals across the blood-brain barrier

Diogo Carregosa[1,2,3], Iris Moreira[4], Diogo Rasteiro[4], Leonardo Vanneschi[4] and Cláudia Nunes dos Santos[1,2,3,5]*

[1]iNOVA4Health, NOVA Medical School, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Oeiras, Portugal, [2]NOVA Institute for Medical Systems Biology (NIMSB), Universidade Nova de Lisboa, Lisboa, Portugal, [3]iNOVA4Health, Programme in Translational Medicine, Oeiras, Portugal, [4]NOVA Information Management School (NOVA IMS), Universidade Nova de Lisboa, Lisboa, Portugal, [5]iBET, Instituto de Biologia Experimental e Tecnológica, Oeiras, Portugal

Introduction: The role of phytochemicals like xanthines, and (poly)phenols in neurodegenerative diseases has been highly established and explored. However, the mechanism of these molecules to cross the membranes reaching the blood and the brain has largely been understudied.
Methods: In this work, we used in silico methods to predict the permeability of more than 800 molecules across the membranes and specifically the blood-brain barrier. Our dataset included phytochemicals, like xanthine, phenolic terpenes, (poly)phenols and metabolites, including phase II conjugates, while some endogenous molecules and commercial drugs were used as positive/negative controls. We used QikProp to generate 42 computed physicochemical properties to predict the blood absorption, distribution to the brain, metabolism, and elimination of these molecules.
Results: According to Qikprop 555 of 800 molecules were inside the range of 95% of known drugs for all computed properties, while through passive di[usion, 78 molecules may reach the blood and 52 may reach the brain parenchyma. Furthermore, using data from natural molecules present in human CSF samples, we used machine learning to build a model that was capable to predict 171 novel molecules with the potential to reach the brain environment.
Conclusion: Overall, in this work we predicted the natural molecules with the potential to reach the brain, highlighting those that may do so by passive mechanisms. Our study creates an opportunity to track novel molecules in theblood and the brain and highlighting the most drug-promising natural molecules for brain drug development in the treatment and prevention of brain diseases.

KEYWORDS
ADME, BBB, dietary sources, natural molecules, passive diffusion, predictions, QikProp

Introduction

The potential of phytochemicals and other natural molecules has been vastly investigated, namely, regarding protection against neuroinflammation and neurodegenerative diseases (Schaffer and Halliwell, 2012; Arias-Sánchez et al., 2023). Such potential has been revealed in a huge number of publications, across different models from yeast to rodents and humans (Schaffer and Halliwell, 2012; Hussain et al., 2016; Carregosa et al., 2019; 2021; Tayab et al., 2022; Arias-Sánchez et al., 2023). Such small molecules show a particularly great interest since they are often present in dietary products,

showing no side effects. Unfortunately, despite the widespread number of studies using such small molecules, one key question is always overlooked: their capability and the mechanisms responsible for effectively reaching the brain (Carecho et al., 2021). In recent years, some studies have demonstrated the capability of (poly)phenol metabolites and xanthines to reach the brain, mainly in rodent or pig models, but this data has been limited to a small set (<20) of molecules (Gasperotti et al., 2015; Angelino et al., 2019; Carecho et al., 2024) Recent studies in humans, using cerebrospinal fluid (CSF), have also shown the presence of these molecules in the human environment and corroborated the data of animal models (Grabska-Kobylecka et al., 2020; Le Sayec et al., 2023). Yet the list of searched and identified molecules remains small in comparison with the predicted hundreds of phytochemicals metabolites present in human blood and that may reach the brain after dietary intake (Rothwell et al., 2013; da Silva et al., 2016). Noteworthy, the mechanism of transport has only been studied for some molecules, highlighting the role of organic anion transporters (Mori et al., 2003; Wang and Sweet, 2012). Nonetheless, for most molecules, the mechanism of action is still largely speculated.

Many drugs targeting the brain often fail to reach the desired effects in clinical trials, resulting either from fast metabolism and excretion, or poor to almost no permeability across the blood-brain barrier (BBB) (Sun et al., 2022). The consideration of pharmacokinetics and pharmacodynamics when evaluating the potential of a new drug has been an industry standard and computer-based methods are now very capable and straightforward methods to predict the absorption, distribution, metabolism, and toxicity *in vivo*.

In this paper, we investigated the absorption, distribution, and metabolism of an in-house generated database of phytochemicals, including phenolic terpenes, (poly)phenols, and xanthines, present in food products or generated by gut microbiota. Additionally, we evaluate the capability of these natural molecules to reach the brain by passive diffusion using QikProp. Meanwhile, we used a machine learning-based model generated from previously identified natural molecules in the human brain to expand beyond QikProp predictions on passive diffusion. Our work predicts BBB permeable molecules with excellent pharmacokinetic properties that may be potentially used as backbone structures for drug design. Overall, we aim to broader our knowledge on the small natural molecules capable of reaching the brain, and their possible relevance as brain bioactive structures that can be explored in the future.

Results

Overall compliance of the dataset tested on membrane permeability parameters to reach human blood

A total of 42 molecular descriptors (Supplementary Table S1) were generated for 855 molecules (Supplementary Table S2; Figure 1) to evaluate the potential of these molecules to reach the blood and cross the BBB and reach the brain by passive diffusion.

This database includes commercial drugs as controls (known to reach the brain) together with several phytochemicals like (poly) phenols, xanthine, phenolic terpenes and circulating metabolites, endogenous molecules (amino acids, neurotransmitters, xanthine, tryptophan metabolites, and others), already found or expected to circulate in humans and reach the brain, shown in Figure 1. A total of 51 hydroxybenzenes (phenolics), 19 benzaldehydes, 60 benzoic acids, 49 2-(phenyl)acetic acids, 11 2-(phenyl)propanoic acids, 15 2-hydroxy-3-(phenyl)propanoic acids, 48 3-(phenyl)propanoic acids, 48 mandelic acids, 46 cinnamic acids, 46 4-hydroxy-5-(phenyl) valeric acids, 47 5-(phenyl)valeric acids, 46 5-(phenyl)-γ-valerolactones, 36 glycine conjugates, 9 quinic acids, 6 phenyllactic acid, 59 stilbenes, 37 ellagic acids and urolithin metabolites, 17 lignans, 15 xanthines, 15 (phenyl)ethanols, 9 phenolic terpenes, 107 flavonoids, 11 coumarins, 30 endogenous molecules, 12 commercially available drugs and 6 other phenols including phenylacetophenones and benzoic esters were evaluated (Figure 1). This list included several natural plant conjugates like glucosides and galactosides, and human phase II conjugates, namely, sulfate, glucuronide and glutathione. The 12 commercially available drugs (alprazolam, atenolol, chlorpromazine, cimetidine, ibuprofen, imipramine, mannitol, nordazepam, promazine, salbutamol, salicylate, and theophylline) have been used based on positive (brain permeable) and negative (non-permeable) controls already described by free-energy simulations (Carpenter et al., 2014).

Generally, molecules capable of crossing the BBB by passive diffusion have low molecular weight, below 500 $g.mol^{-1}$. QikProp defines the threshold for this parameter between 130 and 750 $g.mol^{-1}$ (Supplementary Table S1). From the list of 855 molecules evaluated, only procyanidin C1 had a molecular weight above 750 $g.mol^{-1}$ and thus was out of the range of molecules with possible brain passive permeability (Figure 2A; Supplementary Table S2).

Another commonly and extensively used parameter for passive BBB permeability is the octanol/water partition coefficient (Carpenter et al., 2014). From our dataset of 855 molecules, only 25 showed a value below the QikProp recommended value of −2, while none were above the upper threshold of 6.5 (Figure 2B; Supplementary Table S2). A total of 300 molecules had values below 0 indicating a poor capability to cross the BBB by passive permeability. The large majority were sulfate, glucuronides, and all glutathione, glucoside, and galactoside conjugates (Figure 2B). This is expected since these conjugates are highly hydrophilic, decreasing the overall lipophilicity of these molecules. From the list of known drugs tested only mannitol showed a value below −2 (value of −3.1). This is expected since mannitol is known not to cross the BBB and has low permeability in the gut (Noorani et al., 2020). From the list of known drugs tested apart from mannitol, no other drug showed a value below 0. Drugs known to cross the BBB showed octanol/water ratio far above 2 (chlorpromazine: 5.1, promazine: 4.5, imipramine: 4.4, alprazolam: 4.1, ibuprofen: 3.5, nordazepam: 2.9).

Regarding skin permeability, 26 molecules showed values outside the recommended range of −8 to −1 (Figure 2C; Supplementary Table S2). Five of the 26 molecules had values above −1 (reflecting high lipophilicity): sesamin, sesamolin, dimethoxyresorcinol, dimethoxycatechol and trimethoxyphloroglucinol, (Figure 2C; Supplementary Table S2). The remaining molecules with values below −8 reflecting highly polar molecules with phase II conjugates (glutathione, sulfate, or glucuronide conjugates), or procyanidin C1 with a large molecular weight.

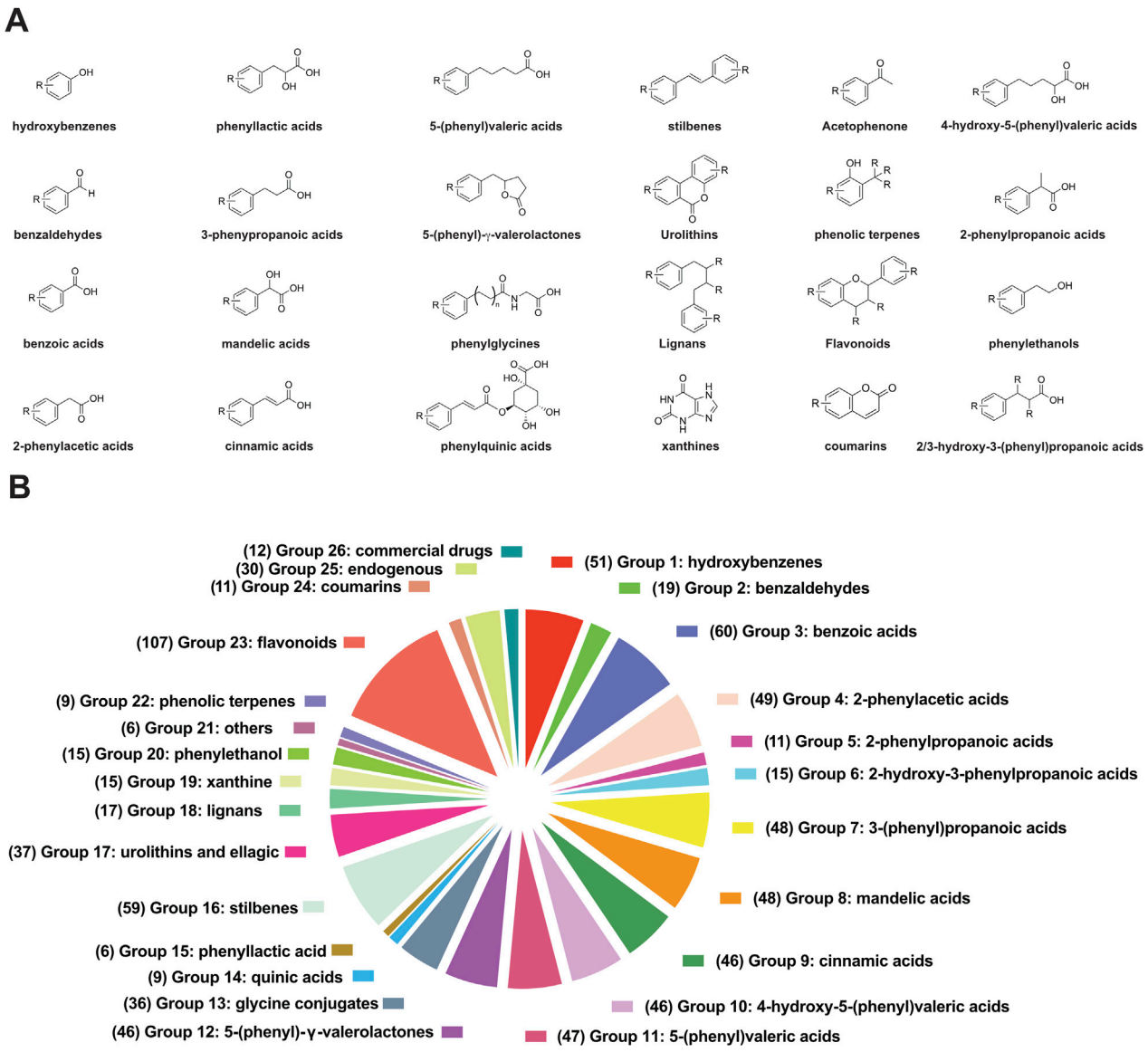

FIGURE 1
A total of 855 molecules were evaluated across several molecular groups. **(A)** Representative chemical structures of the 26 groups of phytochemicals tested. **(B)** Overall number of groups evaluated and number of molecules per group (in parenthesis), including endogenous and commercial drugs.

Based upon a quantitative multiple linear regression, QikProp can predict the percentage of human oral absorption for the molecules evaluated (Schrödinger, 2015). Overall, molecules with a percentage above 85% are considered highly absorbed (Supplementary Table S1). From our set of molecules evaluated, 78 molecules (including 1 endogenous and 6 commercial drugs), were above this threshold (Figure 2D; Supplementary Table S4). Interestingly 31 molecules had 100% predicted human oral absorption (Figure 2D; Supplementary Table S2). Based on the chemical groups and features, QikProp can predict the number of possible metabolites that can be originated from each molecule. Increased number of metabolic reactions per molecule reduces its theoretical concentration and thus the possibility of reaching the blood and several organs. QikProp defines this limit as 8 metabolites (Supplementary Table S1) (Schrödinger, 2015). In our dataset, 110 molecules were above this threshold (Figure 2E; Supplementary Table S2.). Unfortunately, QikProp does not specify the type of metabolic reaction predicted for each molecule. Upon reaching the blood, molecules can be captured by serum albumin reducing blood concentration and the capability to spread across the different organs. For this reason, binding to human albumin is also an important parameter that was predicted (Figure 2F). All molecules tested showed low binding to human serum albumin indicated by the predicted logarithm of retention factor on human serum albumin (log Khsa<1). From the list of molecules tested, only 15 molecules were outside the defined lower range (Figure 2F; Supplementary Table S2), indicating the low probability or inability to bind to human serum albumin.

Key pharmacological safety predictions were also performed to analyze interactions with drug efflux (P-glycoprotein, P-gp) and

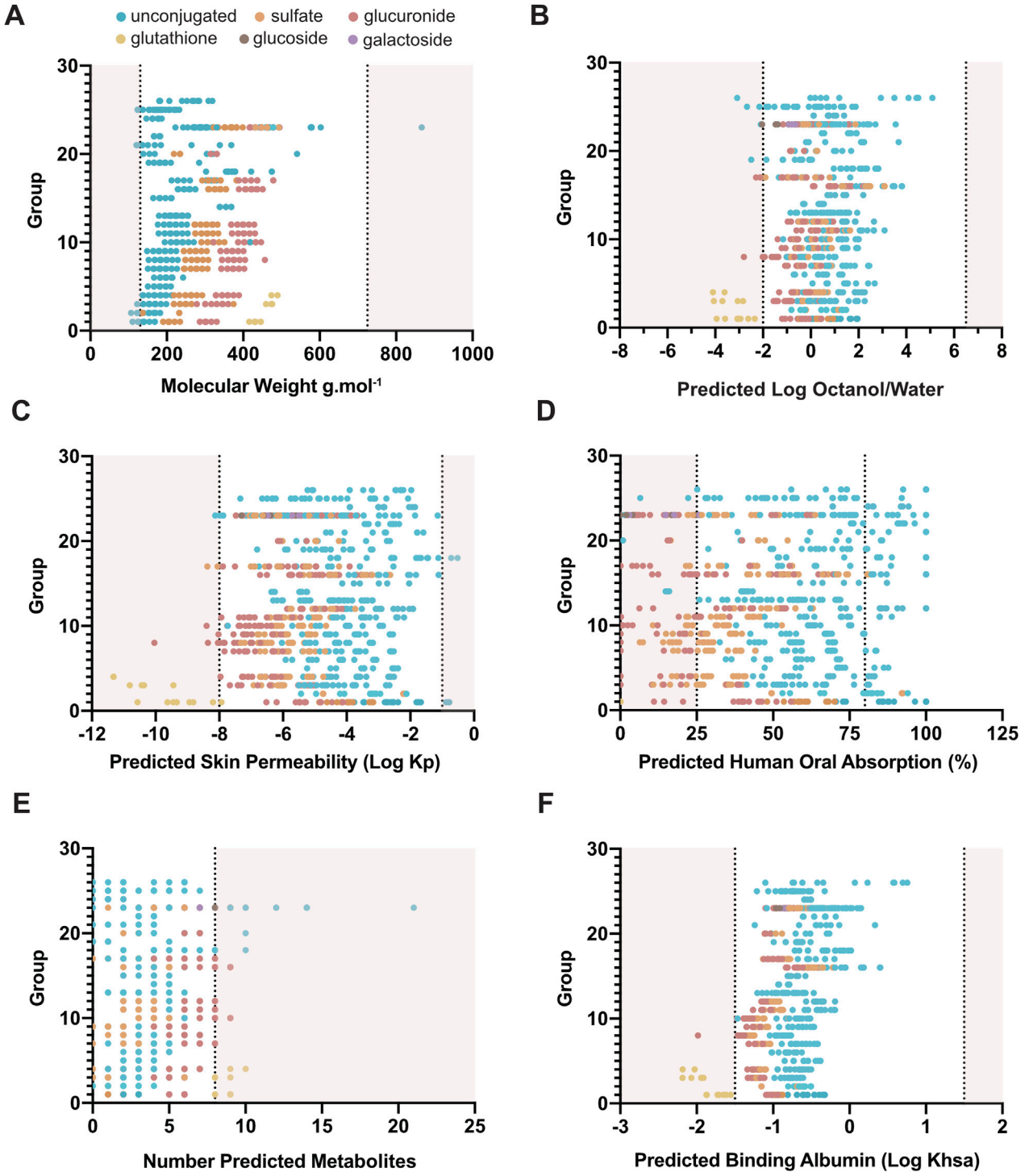

FIGURE 2
QikProp predictions of the relevant parameters for membrane permeability and blood presence. **(A)** Molecular weight of the molecules tested. Each dot represents one molecule. Each dot color reflects the type of conjugation. Red areas represent values outside the range defined by QikProp (Supplementary Table S1). **(B)** Predicted logarithm octanol/water. **(C)** Predicted skin permeability. **(D)** Predicted human oral absorption. **(E)** Predicted number of biotransformed metabolites. **(F)** Predicted binding coefficient to human albumin.

drug metabolism (Cytochrome P450, CYP) using SwissADME (Daina et al., 2017). In circulation P-gp (also known as ABCB1) is responsible for drug efflux and excretion of xenobiotics. In our dataset 139 molecules were identified as predicted P-gp substrates, mostly flavonoids (group 23) and stilbenes (group 16) (Figures 3A,B). Meanwhile, we evaluated the capability of the natural molecules in our dataset to interact with CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 that are important enzymes

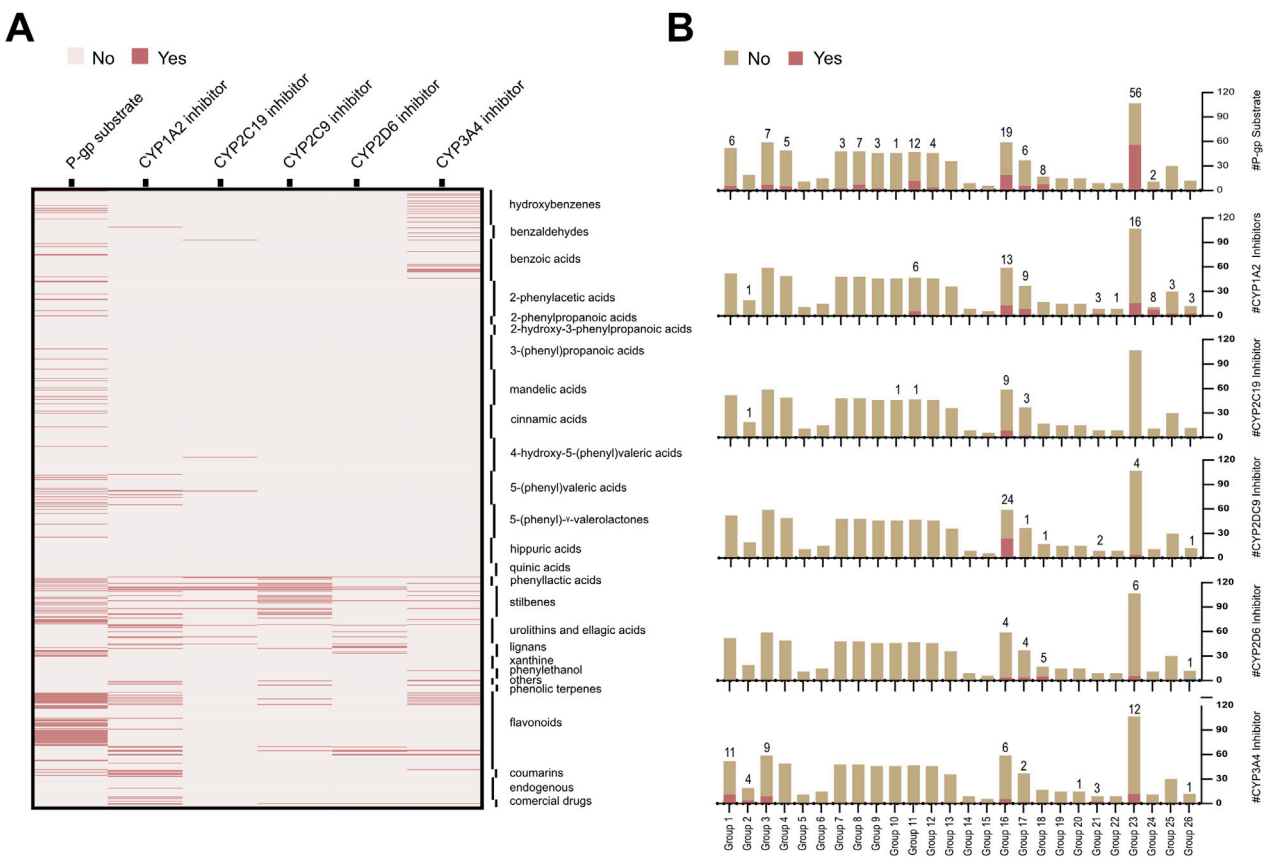

FIGURE 3
SwissADME predictions of interaction with drug efflux transporter P-gp and CYP enzymes. **(A)** Heatmap representing the overall distribution of the interaction of the dataset with P-glycoprotein (P-gp) and Cytochrome P450 (CYP) variants CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. **(B)** Number of interacting molecules, per molecular group.

associated with detoxification and drug metabolism (Daina et al., 2017; Zhao et al., 2021). Overall, most phenolic acids (group 1–15), apart from 5-(phenyl)valeric acids (group 11–12) did not shown inhibitory activity on CYP1A2, CYP2C19, and CYP2D6. By contrast several hydroxybenzenes, benzaldehydes and benzoic acids (groups 1–3) showed interaction with CYP3A4 (Figures 3A,B). Yet, the most active groups predicted to have CYP inhibition were stilbenes (group 16), urolithins and ellagic acids (group 17), and flavonoids (group 23, Figures 3A,B).

Overall compliance of the dataset across all scores and the #star score

Upon generating the molecular descriptors for the molecules of the dataset, QikProp selects 24 molecular descriptors that are considered relevant to define a molecule as drug-like (#star score, Supplementary Table S1). Qikprop calculates if a molecule is outside the range of 95% of known drugs for each of these 24 molecular descriptors. The #star score is given by the number of parameters outside the range, meaning a higher #star score reflects a molecule with lesser drug-like properties. A total of 300 of the 855 molecules tested had at least 1 #star, while the other 555 molecules tested were inside the range of 95% of known drugs for all 24 molecular descriptors (Supplementary Table S2). From the list of 300 molecules with at least one #star, the large majority were glucuronide, glutathione, glucosides and galactoside conjugates.

For the overall list of all 42 descriptors generated and evaluated 63 molecules were inside the QikProp defined range for all parameters (Supplementary Table S4). These included several endogenous molecules (group 26), hydroxycoumarins (group 24), flavonoids (group 23) like equol and daidzein, myricetin, kaempferol, luteolin, eriodictyol, catechin, and epicatechin, phenolic terpenes (group 22), tyrosol and hydroxytyrosol (group 20), several methyluric metabolites (group 19), urolithin A, B, C and D and dimethyl ellagic acid (group 17), several phenyl-γ-valerolactones aglycones (group 12), benzaldehydes like vanillin and isovanillin (group 2) and the hydroxybenzene methylpyrogallol (group 1).

Compliance of the dataset with passive diffusion BBB permeability scores and selection of the molecules that may reach the brain by passive diffusion

Two main parameters relevant for BBB permeability were initially analyzed: brain/blood partition coefficient and MDCK (Madin-Darby canine kidney cell) permeability. Brain/blood partition coefficient is an important measure to understand a molecule preference between brain and blood and their

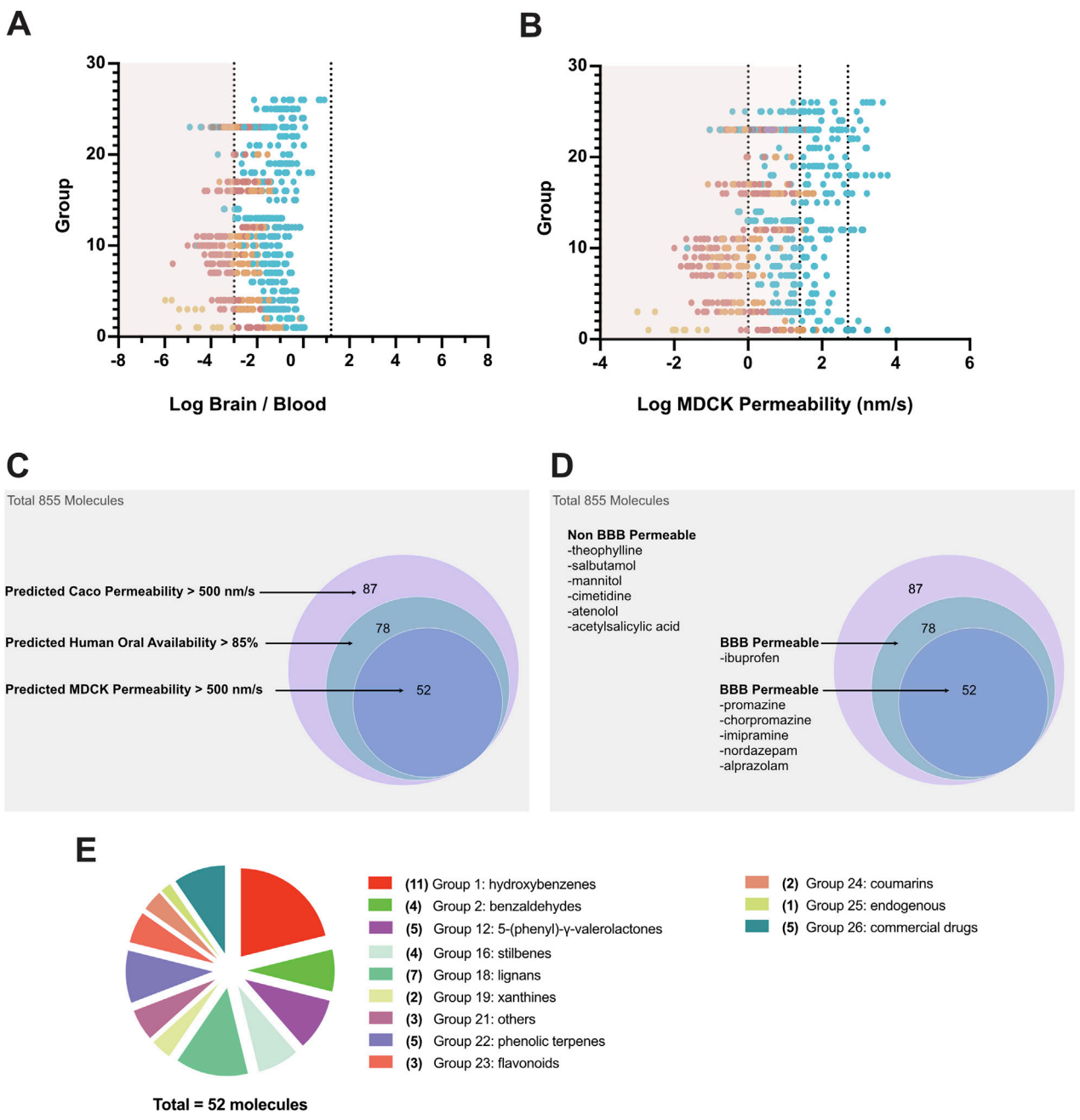

FIGURE 4
QikProp prediction for blood-brain barrier permeability by passive diffusion. **(A)** Brain/blood permeability partition coefficient. Each dot represents one molecule. Each dot color reflects the type of conjugation according to previous figures. Red areas represent values outside the range defined by Qikprop (Supplementary Table S1). **(B)** Predicted permeability across the MDCK cell line model. **(C)** Venn diagram depicting the strategy for the selection of the predicted brain permeable molecules by passive diffusion according to QikProp, relying on QikProp predicted human oral absorption, QPCACO and importantly MDCK transport (nm/s) above 500 nm/s. **(D)** This strategy grouped all 5 BBB permeable drugs that may cross the BBB by passive diffusion, excluding drugs that cannot reach the brain by passive diffusion. **(E)** The 52 molecules compatible with the potential to reach the brain by passive diffusion ranged across multiple structural groups, mainly smaller phenolics, which are listed in Table 1.

distribution across the two environments (Schrödinger, 2015). From the molecules tested, 673 molecules were inside the range of recommended values according to QikProp (−3 to 1.2, Figure 4A; Supplementary Table S2). Interestingly, most molecules, apart for 14 (Supplementary Table S2), showed a value below 0 meaning most molecules preferred the blood environment. Amongst these 14 molecules were methoxylated compounds like guaiacol, veratrole, and methoxyresorcinol (group 1), both 4,8-Dihydroxysesamin isomers (group 18), methyl benzoate and 4-vinyl phenol (group 21), coumarin (group 24), and the drugs promazine, imipramine, chlorpromazine and alprazolam (group 26).

MDCK cell model is considered a good mimic for blood-brain barrier permeability by non-active transport (Wang et al., 2005;

10.3389/fddsv.2026.1939611

TABLE 1 List of predicted BBB permeable molecules by passive diffusion.

Common names	IUPAC Names
Group 1: hydroxybenzenes	
catechol	benzene-1,2-diol
guaiacol	2-methoxyphenol
veratrole	1,2-dimethoxybenzene
1-methylpyrogallol	3-methoxybenzene-1,2-diol
2-methylpyrogallol	2-methoxybenzene-1,3-diol
trimethoxyphloroglucinol	1,3,5-trimethoxybenzene
4-methylcatechol	4-methylbenzene-1,2-diol
3-methylcatechol	3-methylbenzene-1,2-diol
methoxyresorcinol	3-methoxyphenol
dimethoxyresorcinol	1,3-dimethoxybenzene
1,3-dimethoxypyrogallol	2,6-dimethoxyphenol
Group 2: benzaldehydes	
benzaldehyde-4-sulfate	4-formylphenyl hydrogen sulfate
benzaldehyde-3-sulfate	3-formylphenyl hydrogen sulfate
benzaldehyde-2-sulfate	2-formylphenyl hydrogen sulfate
benzaldehyde	benzaldehyde
Group 12: 5-(phenyl)- γ -valerolactone	
5-(phenyl)- γ -valerolactone	5-[(phenyl)methyl]oxolan-2-one
5-(2′-hydroxyphenyl)-γ-valerolactone	5-[(2-hydroxyphenyl) methyl]oxolan-2-one
5-(3′-methoxyphenyl)-γ-valerolactone	5-[(3-methoxyoxyphenyl) methyl]oxolan-2-one
5-(4′-methoxyphenyl)-γ-valerolactone	5-[(4-methoxyphenyl) methyl]oxolan-2-one
5-(3′-hydroxy-4-methoxyphenyl)-γ-valerolactone	5-[(3-hydroxy-4-methoxyphenyl) methyl]oxolan-2-one
Group 16: stilbenes	
3,4-dimethoxyresveratrol	(E)-4-(3,4-dimethoxystyryl)phenol
3,5-dimethoxyresveratrol	(E)-4-(3,5-dimethoxystyryl)phenol
3-hydroxy-3,5-dimethoxyresveratrol	(E)-4-(3,5-dimethoxystyryl)benzene-1,2-diol
2-hydroxy-3,5-dimethoxyresveratrol	(E)-4-(3,5-dimethoxystyryl)benzene-1,3-diol
Group 18: lignans	
matairesinol	(3R,4R)-3,4-bis[(4-hydroxy-3-methoxyphenyl)methyl]oxolan-2-one
pinoresinol	4-[(3S,3aR,6S,6aR)-6-(4-hydroxy-3-methoxyphenyl)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]furan-3-yl]-2-methoxyphenol
laricriresinol	4-[(2S,3R,4R)-4-[(4-hydroxy-3-methoxyphenyl)methyl]-3-(hydroxymethyl)oxolan-2-yl]-2-methoxyphenol
syringaresinol	(7α,7′α,8α,8′α)-3,3′,5,5′-Tetramethoxy-7,9′:7′,9-diepoxylignane-4,4′-diol
4,8-dihydroxysesamin	(3,6-Bis(benzo[d][1,3]dioxol-5-yl)tetrahydro-1H,3H-furo[3,4-c]furan-1,4-diol)
sesamin	5-[(3S,3aR,6S,6aR)-3-(1,3-benzodioxol-5-yl)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]furan-6-yl]-1,3-benzodioxole
sesamolin	5-[[(3S,3aR,6R,6aR)-3-(1,3-benzodioxol-5-yl)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]furan-6-yl]oxy]-1,3-benzodioxole

(*Continued*)

TABLE 1 Continued

Common names	IUPAC Names
Group 19: xanthines	
caffeine	1,3,7-trimethylpurine-2,6-dione
isocaffeine or 1,3,9-trimethylxanthine	1,3,9-trimethylpurine-2,6-dione
Group 21: others	
methyl benzoate	methyl benzoate
4-ethylphenol	4-ethylphenol
4-vinyl phenol	4-ethenyl phenol
Group 22: phenolic terpenes	
p-cymene-2,9-diol or 2-(-3-Hydroxy-4-methylphenyl)propan-1-ol	2-(-3-Hydroxy-4-methylphenyl)propan-1-ol
p-cymene-2,8-diol or 2-(-3-Hydroxy-4-methylphenyl) propan-2-ol	2-(-3-Hydroxy-4-methylphenyl)propan-2-ol
p-cymene-3,9-diol or 2-(-2-Hydroxy-4-methylphenyl) propan-1-ol	2-(-2-Hydroxy-4-methylphenyl)propan-1-ol
p-cymene-3,7-diol or 2-hydroxymethyl-5-(1-methylethyl) phenol	2-hydroxymethyl-5-(1-methylethyl)phenol
p-cymene-2,7-diol or 5-hydroxymethyl-2-(1-methylethyl) phenol	5-hydroxymethyl-2-(1-methylethyl)phenol
Group 23: flavonoids	
methyldaidzein or formononetin	7-hydroxy-3-(4-methoxyphenyl)chromen-4-one
psoralen	furo[3,2-g]chromen-7-one
flavone	2-phenylchromen-4-one
Group 24: coumarins	
7-methoxycoumarin	7-methoxychromen-2-one
coumarin	chromen-2-one
Group 25: endogenous	
melatonine	N-[2-(5-methoxy-1H-indol-3-yl)ethyl]acetamide
Group 26: commercial drugs	
promazine	N,N-dimethyl-3-phenothiazin-10-ylpropan-1-amine
nordazepam	7-chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one
imipramine	3-(5,6-dihydrobenzo[b][1]benzazepin-11-yl)-N,N-dimethylpropan-1-amine
chlorpromazine	3-(2-chlorophenothiazin-10-yl)-N,N-dimethylpropan-1-amine
alprazolam	8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

Schrödinger, 2015). QikProp predicts the transport in nm/s and values above 500 nm/s are considered great and a strong indication of passive permeation, while values below 25 nm/s are indicative of poor to no permeability by passive diffusion (Supplementary Table S1) (Schrödinger, 2015). From the total number of molecules tested, 268 showed values above 25 nm/s (Figure 4B; Supplementary Table S2). This included mainly hydroxybenzenes (group 1), benzaldehydes (group 2), 4-hydroxy-5-(phenyl)valeric acids (group 10), 4-hydroxy-5-(phenyl)valeric acids (group 11), phenolic terpenes (group 22), flavonoids (group 23), some endogenous molecules like N-acetyl-5-hydroxytryptamine and melatonin (group 25), and almost all drugs (group 26) apart from mannitol.

To determine the molecules with the potential to cross the BBB by passive diffusion, we overlapped the information gathered from human oral absorption, QPPCACO and QPPMDCK models

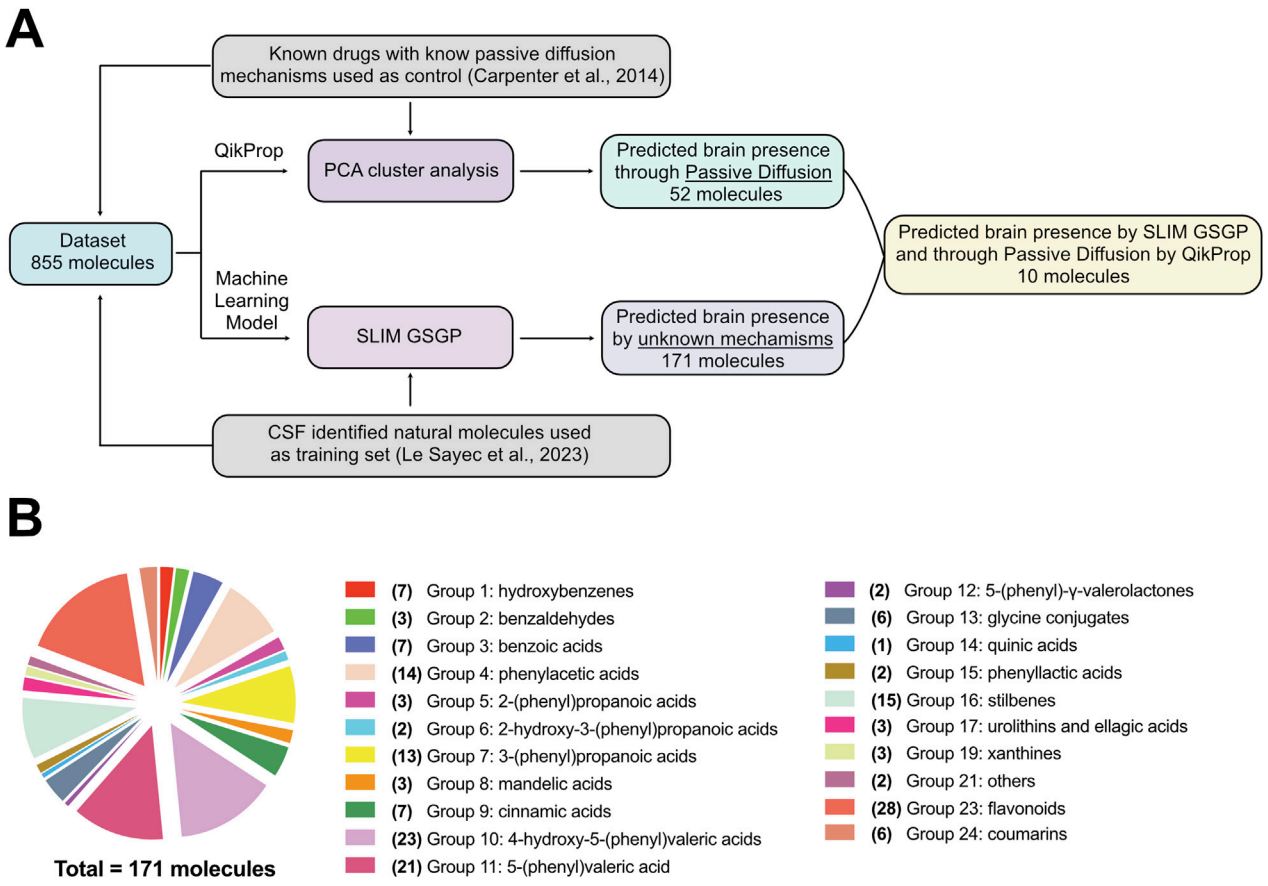

FIGURE 5
Phytochemicals predicted to reach the brain by QikProp and SLIM GSGP and overall number of phytochemicals that may reach the brain. **(A)** Framework used to identify novel phytochemicals in the human brain. QikProp was used to predict the molecules capable of reaching the brain by passive diffusion. Meanwhile, a dataset of previously identified natural molecules (Le Sayec et al., 2023) was used to train a machine learning model (SLIM GSGP), identifying 171 new phytochemicals that may reach the brain, 10 of which were identified as predicted to cross the BBB by passive diffusion mechanisms by QikProp (Table 1). **(B)** Distribution of SLIM GSGP predicted BBB permeable molecules across the molecular groups.

(Figure 4C). The diagram depicts the number of molecules with human oral absorption>85%, predicted CACO permeability >500 nm/s and predicted MDCK permeability >500 nm/s (Figure 4C). Interestingly, the cluster containing all molecules with MDCK permeability >500 nm/s contained the five brain-permeable commercial drugs (promazine, chlorpromazine, imipramine, nordazepam, and alprazolam), while only one BBB permeable drug was absent, ibuprofen, which was found to have MDCK permeability of 189 nm/s below the 500 nm/s threshold (Figure 4D). This was explained by the fact that ibuprofen was suggested to cross the BBB in a saturable way being dependent on cell transporters (Parepally et al., 2006). All the remaining 6 non-BBB permeable drugs tested showed permeabilities bellow 25 nm/s and below the 85% human oral threshold (Figure 4D). Altogether, we used this combined classification (human oral availability, CACO permeability, and mainly MDCK permeability) to classify the tested molecules according to their potential to cross the BBB by passive diffusion (Figure 4D). In total, the cluster contained 52 molecules of several classes (Figure 4E), the names of these molecules are shown in Table 1.

Predicting molecules that may reach the human brain using a machine learning model fed with detected phytochemicals in the human brain

A predictive framework to identify previously unreported phytochemicals in the human brain was developed (Figure 5A). Building on the fact that our dataset contained a subset of experimentally detected compounds in human CSF samples (Le Sayec et al., 2023), a proxy for the human brain parenchyma, we used these molecules as ground truth, for training and validating multiple machine learning models integrating in the silico–derived molecular descriptors generated by QikProp. This approach enabled the systematic prediction of CSF/brain-penetrant phytochemicals beyond those previously identified using QikProp only relying on passive diffusion (Table 1), expanding the known chemical landscape of diet-derived metabolites in the brain beyond what is present in the literature.

The final model chosen was Semantic Learning algorithm based on Inflate and deflate Mutation in Geometric Semantic Genetic Programming (SLIM GSGP), which displayed a final median root

mean square error of 0.31 across 15 runs of Monte Carlo cross validations. Leveraging this model, we predicted 171 previously unreported phytochemicals with the potential to reach the human brain/CSF (Figure 5A). A comparison between the list of molecules predicted to reach the brain by passive diffusion through QikProp and the list of 171 phytochemicals reported by SLIM GSGP showed an overlap of 10 molecules. The 10 molecules were: 4-methylcatechol, 1,3-dimethylpyrogallol, methoxyresorcinol, guaiacol, 5-(3-methoxyphenyl)-γ-valerolactone, 3-hydroxy-3,5-dimethoxyresveratrol, caffeine, methyldaidzein, coumarin, and psoralen (Table 1). Although our machine learning model is driven by structural similarity and cannot predict mechanism of transport we hypothesize, by exclusion, that the remaining 161 molecules that may reach the brain according to the SLIM GSGP model (but outside QikProp passive diffusion predictions) may not be able to do so by passive diffusion (Supplementary Table S5; Figure 5A). This would leave a big range of other possible mechanisms of transport like carrier-mediated transport, receptor-mediator transport, adsorptive-mediated transport, active transporters and/or pumps, which would require other type of predictions and validations.

Most molecules predicted to reach the brain/CSF environment by the SLIM GSGP model (Figure 5B) were flavonoids (group 23), stilbenes (group 16), 4-hydroxy-5-(phenyl)valeric acids (group 10), and 5-(phenyl)valeric acids (group 11), alongside multiple structural isomers of molecules already observed in the human brain (Le Sayec et al., 2023). This compositional convergence with experimentally validated metabolites (Le Sayec et al., 2023) reinforces the biological plausibility of our predictions.

Overall, these findings extend prior experimental evidence on the molecules present in the brain. We predicted a total of 213 novel phytochemicals that may reach the brain/CSF, either by passive mechanisms (52 phytochemicals according to QikProp) and possibly through other non-defined mechanisms by SLIM GSGP (171 phytochemicals, 10 in common with QikProp). These molecules will add to previous data on experimentally identified compounds used in our training set (Le Sayec et al., 2023), providing a prioritized set of candidate molecules for targeted metabolomics validation. By expanding the landscape of putative brain-accessible phytochemicals, this work advances the discovery of bioavailable, diet-derived compounds with potential neurobiological relevance.

Discussion

Several studies have highlighted the importance and beneficial effects of phytochemicals including xanthines and (poly)phenols and metabolites in brain function, highlighting their role in several hallmarks of neurodegenerative conditions like neuroinflammation, oxidative stress, BBB protection and protein aggregation (Arts and Hollman, 2005; Vauzour, 2012; Kennedy, 2014; Hussain et al., 2016; Carregosa et al., 2019; 2021; Tayab et al., 2022; Arias-Sánchez et al., 2023; Carecho et al., 2024). Although many of these molecules can exert beneficial effects without even reaching the brain (Schaffer and Halliwell, 2012), the large majority will be required to cross the blood-brain barrier reaching target proteins and receptors to exert their function. However, our knowledge on the mechanism of transport of these molecules has been largely underexplored to a restricted selection of molecules while for others it has only been hypothesized and not fully explored (Carecho et al., 2021). In this study, we explored a dataset of more than 800 molecules regarding their capability to reach the brain and their potential mechanism. We used *in silico* tools predicting the capability of 78 molecules to reach the blood by passive diffusion, while only 52 show properties that indicate their potential to reach the brain by passive diffusion. Meanwhile, an in house constructed computational model based on previous evidence of natural molecules in human CSF, showed that 171 molecules may be capable of reaching the brain.

We have compiled a list of phytochemicals, like phenolic terpenes, xanthine, and (poly)phenols and metabolites that have been identified in blood/urine of dietary interventions (Scalbert and Williamson, 2000; Williamson and Manach, 2005; Vitale et al., 2013; Del Rio et al., 2013; Rodriguez-Mateos et al., 2014; Hostetler et al., 2017; Williamson et al., 2018; Mena et al., 2019; Carregosa et al., 2022; García-Villalba et al., 2022). In this dataset, several additional molecules that were not identified in blood and/or the brain but predicted, based on structural isomers, or possible phase I metabolism or phase II conjugation, were also included to anticipate their future experimental identification by metabolomics. Notably, our computational framework predicts that 78 molecules (71 novel molecules) may reach the blood via passive diffusion. These findings go beyond highlighting a gap in current knowledge: they provide a prioritized, hypothesis-driven roadmap for targeted metabolomic validation, refine candidate selection for brain bioavailability, and demonstrate the predictive power of our model to uncover previously unrecognized metabolite pools with potential biological relevance. It is, however, important to note that we have been conservative in our analysis, as we only considered molecules with a human oral intake percentage above 85%. A less conservative analysis like 75% oral absorption would suggest 144 different molecules would reach the blood. Our 85% threshold was set as suggested in (Schrödinger, 2015) and aimed to reduce false positives.

The capability of some xanthine, and (poly)phenols and metabolites to reach the brain have been demonstrated (Gasperotti et al., 2015; Angelino et al., 2019; Le Sayec et al., 2023; Carecho et al., 2024). In the past, we have successfully used *in silico* models to predict brain permeability by passive diffusion (Figueira et al., 2017; Angelino et al., 2019; Le Sayec et al., 2023). However, these studies highlighted the presence of many molecules in the brain uncapable of theoretically reaching the brain by passive diffusion, while other studies confirmed the necessity of cell transporter like organic acid transporter (OAT)1 and OAT3 (Wang and Sweet, 2012; Wang et al., 2013). From our dataset, only 52 molecules could potentially reach the brain by passive diffusion. Their presence and quantification in the brain will still depend on external factors like the concentration in the food and consequently in the blood and the degree of *in vivo* metabolism imposed to each molecule.

Several of the previously performed metabolomic studies have identified sulfate conjugates in the brain (Angelino et al., 2019; Le Sayec et al., 2023). From all the molecules predicted in our model only benzaldehydes with sulfate conjugation could reach the brain by passive diffusion. It is possible that most sulfate conjugates may be transported by non-passive mechanisms like protein transporters, however unlike for unconjugated phenolic transporters like OAT1 and OAT3, no data exists yet on the

transport of conjugated molecules. Another option is that conjugation happens across the endothelial barrier or inside the brain, yet the presence of unconjugated molecules should in theory also be observed, which have not been always observed (Le Sayec et at., 2023; Angelino et al., 2019; Carecho et al., 2021; Gasperotti et al., 2015). One reason may be that the low concentrations expected to be present in the brain may obscure the detection of such unconjugated molecules with the current metabolomics approaches.

From the 52 molecules predicted to cross the BBB by passive diffusion by QikProp, there is no core chemical structure shared across the predicted molecules. Most of the phenolic molecules have only one hydroxyl group, or one hydroxyl group with one or more methyl/methoxylated groups, but this is not the case for some classes of molecules like caffeine, flavonoids, and commercial drugs. Interestingly, all these molecules, apart from caffeine or commercial drugs, have not been identified in the animal brain and human CSF. Such molecules have low abundance in dietary sources or are only generated through gut-hepatic metabolism, meaning low circulating concentrations lead to lower, probably undetectable brain concentrations. It is also important to mention that targeted metabolomics analysis may not have considered for these molecules, or that as most methoxylated phenolics high ionization energies make them difficult to detected and quantify.

The low number of molecules identified through QikProp as capable of reaching the brain by passive diffusion compared to the higher number of xanthine and (poly)phenols and metabolites in the brain (Angelino et al., 2019; Le Sayec et al., 2023) suggests that other forms of molecular transport may be responsible for the presence of natural molecules in the brain, like the previously mentioned OAT1 and OAT3 (Wang and Sweet, 2012; Wang et al., 2013) For that reason, we have generated a machine learning model feeding with information about molecules present in CSF. Our SLIM GSGP model predicted 171 phytochemicals that may reach the brain/CSF environment. The SLIM GSGP model showed an overlap of 10 molecules with QikProp results, meaning 10 of the 171 phytochemicals predicted by SLIM GSGP were predicted to reach the brain by passive diffusion while the remaining 161 molecules are hypothesized, by exclusion, to do so by non-passive mechanisms predicted by QikProp (although our SLIM GSGP model cannot investigate transport mechanisms). This discrepancy of molecules predicted by QikProp but not predicted from SLIM GSGP result from the overall design of both models. While QikProp rely on physiochemical features to predict lipophilicity and passive diffusion, SLIM GSGP were fed with a smaller set of molecules present in the brain/CSF, feeding structural features and not limited by passive diffusion mechanisms. Most molecules predicted to reach the brain by SLIM GSGP were phase I or phase II modifications of previously identified molecules in the brain. This information may be useful to potentiate the identification of novel molecules in the CSF and possibly the brain in future metabolomic studies.

Several limitations are inherent to *in silico* tools and specifically our study. Most obviously, *in silico* tools reflect mostly predictive tools generated from training sets, thus the training sets can highly condition the results obtained. This is mostly true for our SLIM GSGP, as the data generated from QikProp is highly empiric and based on chemical properties (although also predictive, based on linear regressions). For SLIM GSGP, we have used a dataset of molecules identified and quantified in human CSF. Molecules in CSF were used as proxy of molecules in the brain parenchyma, although the CSF may not necessarily reflect the totality of molecules in the brain tissue, but no data was found on human phytochemicals in human brain tissue samples. Another major limitation of our study is the lack of an *in vitro* and *in vivo* validation system of the mechanism of transport. This will be a future opportunity to perform *In vitro* studies exploring the expression of cell transporters (Wang and Sweet, 2012; Carecho et al., 2024), using transport inhibitors (Figueira et al., 2017) or knock down specific transporters may be a solution to explore and find the mechanism responsible for transport. Importantly, despite our prediction on brain permeability, many factors limit brain exposure which cannot be accounted for: dietary exposure, metabolism, protein binding, and pharmacokinetic parameters and blood clearance. Importantly, bioenhancers (Pyrak et al., 2024) and nano formulations (Sonawane et al., 2025) could be alternatives to improve the brain permeability for several of tested molecules.

In summary, we highlighted a set of natural molecules predicted to reach blood circulation and the brain, thus positioning them as candidates to be further validated in the brain, and explored for their functions and drug potential. Additionally, this work just briefly covered one of the mechanisms of brain permeability (passive diffusion), making clear that molecules present in the brain outside this mechanism will require the study of other mechanisms of transport and specific molecular transporters. Exploring such mechanisms and receptors may help us understand several concepts like intra-individual variability, saturation and the uptake across the brain. Overall, in this study we offer a prediction on the brain permeability of many molecules with interesting bioactive potential in oxidative stress, neuroinflammation, protein aggregation, and other hallmarks of neurodegenerative diseases, which may now be exploited by our knowledge on their brain permeability.

Methods

Generation of the library of chemical structures

A database containing the structures of 855 molecules including xanthines, phenolic terpenes, (poly)phenols and their circulating metabolites, endogenous molecules and commercial drugs found or expected to circulate in humans was created based upon existing databases like phytohub (da Silva et al., 2016) and phenol-explorer (Neveu et al., 2010), or predicted metabolites (Supplementary Table S2).

The 3D structures were created in Chem3D Pro (v.20.0, PerkinElmer, Waltham, MA, USA). Each structure was hand drawn to ensure the right spatial conformation. Molecules were drawn in their free form (without salts or non-mentioned conjugates). All isomers were treated as different molecules. Automatic name generation was performed to cross-validate structure and naming with the beforementioned databases. At the end, the structures and names of the molecules were validated by two independent users. Initially, these structures were imported as mol2 files into Maestro software package (version 2022–1, Schrödinger, New York, NY, USA). The structures were then treated with LigPrep (version 2022–1, Schrödinger) using OPLS4 forcefield. We defined pH 7.4 ± 2.0 as biological relevant target pH, using Epik (version 2022–1, Schrödinger). If multiple

energy states were reported for a single molecule, the lowest energy state was chosen, including lowest protonation state. All isomers were treated as different molecules. All molecular modeling was carried out on a macOS (Ventura) computer with M1 processor.

Calculation of molecular descriptors and passive diffusion parameters

For each molecule, a total of 42 descriptors were calculated (Supplementary Table S1) using QikProp in normal mode (version 2024–1, Schrödinger, 2015).These molecular descriptors are relevant to predict drug-like molecules and the ones with higher capability to permeate cellular barriers. Concerning the drug-like feature, QikProp calculates a non-compliance score (#stars score) in agreement with previous works (Ntie-Kang et al., 2013; Ntie-Kang, 2013; Angelino et al., 2019; Le Sayec et al., 2023). The #stars parameter is calculated for each molecule tested and indicates the number of molecular descriptors that are out of the range of values defined for 95% of known drugs, according to QikProp (Schrödinger, 2015). The #stars parameter is calculated based upon the following paraments: MW, dipole, IP, EA, SASA, FOSA, FISA, PISA, WPSA, PSA, volume, #rotor, donorHB, accptHB, glob, QPpolrz, QPlogPC16, QPlogPoct, QPlogPw, QPlogPo/w, logS, QPLogKhsa, QPlogBB, #metabol, detailed in Supplementary Table S1. Twelve commercial drugs were tested of which six are known to cross the BBB. Drugs with BBB permeability were: promazine, chlorpromazine, imipramine, nordazepam, alprazolam and ibuprofen; while the drugs with very low to no BBB permeability were theophylline, atenolol, salbutamol, salicylate, cimetidine and mannitol (Carpenter et al., 2014).

Predicting CYP and P-gp interactions

To predict the capability of the molecules in our dataset to inhibit CYP450 or work as P-gp substrate, the mol2 structures of all compounds were imported into SwissADME platform (Diana et al., 2017). The potential to inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 were included in included in SwissADME and all were evaluated. Data was exported as a binary result (yes/no) into csv files.

Machine learning models to predict non-passive mechanisms of BBB transport

To predict the presence of novel phytochemicals in the human brain we constructed and tested several Machine Learning models feeding information from the presence of some molecules of our dataset (118 from 855 molecules) in the human brain (Le Sayec et al., 2023), and the data generated from the *in silico* generated molecular descriptors. This model does not have in consideration passive transport like QikProp but rather similarities with the fed molecules (training set). The training set was selected based on the evidence on a highest number of dietary molecules in human brain/CSF. Since most of the search molecules (127 molecules), were detected (124 molecules) a negative set definition would be unbalanced and provide skewed results. For that reason, a regression model was fitted aimed at predicting the molecule quantification in the brain. Several models were initially tested without major success, namely, Decision Tree, Neural Network, KNN, SVR, Ridge, LightGBM, XGBoost, DNN.

The final model chosen was a Semantic Learning algorithm based on Inflate and deflate Mutations (SLIM GSGP). Data preprocessing was minimal since all features were present for all compounds in the dataset. The test set represents 8% out of all the molecules present in the brain/CSF (Le Sayec et al., 2023). The model displayed a root mean square error of 0.19 for the training set and 0.35 for the test set, averaging a RMSE of 0.31 across 15 runs of Monte Carlo cross validation. Monte Carlo cross-validation was used for its robustness in presence of scarce amounts of data, which was the case, since the information on the availability of these compounds in the brain/CSF is very limited. For each algorithm, a predefined search space of hyperparameters was explored. The optimal configuration was selected based on the best mean RMSE CV score. Hyperparameters search space: slim_version, ms_upper and p_inflate. Grid search values: ms_upper [0.05, 0.1, 0.2, 0.3], slim_version [SLIM*SIG2, SLIM*SIG1], p_inflate [0.6, 0.7, 0.8, 0.9, 1]. To ensure replicability, all random processes (e.g., dataset splitting, cross-validation, model initialization) were controlled using a fixed random seed (seed = 42). In the CV, the random seed for the train-validation split for each run corresponds to the fixed seed plus the run index of the corresponding run (seed = 42 + run_index). Compounds were classified as capable of reaching the brain if they surpassed the highest limit of detection (8.78 nM) used in (Le Sayec et al., 2023).

Graphical and statistical analysis

All graphs have also been generated in Graphpad Prism 10.0 running MacOS Ventura.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

DC: Data curation, Writing – review and editing, Software, Supervision, Writing – original draft, Methodology, Formal Analysis, Conceptualization, Investigation. IM: Conceptualization, Methodology, Formal Analysis, Writing – review and editing, Software, Data curation. DR: Software, Data curation, Writing – review and editing, Methodology, Formal Analysis. LV: Writing – review and editing, Data curation, Software, Conceptualization, Methodology, Funding acquisition, Formal Analysis, Supervision. CN: Supervision, Project administration, Funding acquisition, Conceptualization, Writing – review and editing, Writing – original draft, Investigation, Resources, Validation.

Funding

The author(s) declared that financial support was received for this work and/or its publication. European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program under grant agreement No 804229. NIMSB is funded by

the European Union under Horizon Europe [project 101060346]. However, the views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them. iNOVA4Health Research Unit (LISBOA-01–0145-FEDER-007344), which is co-funded by Fundacão para a Ciência e Tecnologia (FCT)/Ministério da Ciência e do Ensino Superior, through national funds, and by FEDER under the PT2020 Partnership Agreement. FCT for the PhD scholarship of DC (2020.04630.BD). This work was supported by the Research Unit iNOVA4Health (UID/4462/2025) and by the Associated Laboratory LS4FUTURE (LA/P/0087/2020), all financially supported by FCT/Ministério da Educação, Ciência e Inovação. This work was also supported by national funds through FCT, under the project - UID/04152/2025 - Centro de Investigação em Gestão de Informação (MagIC)/NOVA IMS -https://doi.org/10.54499/UID/04152/2025 (2025–01–01/2028–12–31) and UID/PRR/04152/2025 https://doi.org/10.54499/UID/PRR/04152/2025 (2025–01–01/ 2026–06–30).

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fddsv.2026.1939611/full#supplementary-material

References

Angelino, D., Carregosa, D., Domenech-Coca, C., Savi, M., Figueira, I., Brindani, N., et al. (2019). 5-(Hydroxyphenyl)-γ-valerolactone-sulfate, a key microbial metabolite of flavan-3-ols, is able to reach the brain: evidence from different *in silico,*, *in vitro* and *in vivo* experimental models. *Nutrients* 11, 2678. doi: 10.3390/nu11112678

Arias-Sánchez, R. A., Torner, L., and Fenton Navarro, B. (2023). Polyphenols and neurodegenerative diseases: potential effects and mechanisms of neuroprotection. *Molecules* 28, 5415. doi: 10.3390/molecules28145415

Arts, I. C., and Hollman, P. C. (2005). Polyphenols and disease risk in epidemiologic studies. *Am. J. Clin. Nutr.* 81, 317–325. doi: 10.1093/ajcn/81.1.317S

Carecho, R., Carregosa, D., and dos Santos, C. N. (2021). Low molecular weight (poly) phenol metabolites across the blood-brain barrier: the underexplored journey. *Brain Plast.* 6, 193–214. doi: 10.3233/BPL-200099

Carecho, R., Marques, D., Carregosa, D., Masuero, D., Garcia-Aloy, M., Tramer, F., et al. (2024). Circulating low-molecular-weight (poly)phenol metabolites in the brain: unveiling *in vitro* and *in vivo* blood–brain barrier transport. *Food Funct.* 15, 7812–7827. doi: 10.1039/D4FO01396D

Carpenter, T. S., Kirshner, D. A., Lau, E. Y., Wong, S. E., Nilmeier, J. P., and Lightstone, F. C. (2014). A method to predict blood-brain barrier permeability of drug-like compounds using molecular dynamics simulations. *Biophys. J.* 107, 630–641. doi: 10.1016/j.bpj.2014.06.024

Carregosa, D., Carecho, R. M., Figueira, I., and Santos, C. N. (2019). Low molecular weight metabolites from polyphenols as effectors for attenuating neuroinflammation. *J. Agric. Food Chem. Acs.Jafc.* 9b02155, 1790–1807. doi: 10.1021/acs.jafc.9b02155

Carregosa, D., Mota, S., Ferreira, S., Alves-Dias, B., Loncarevic-Vasiljkovic, N., Crespo, C. L., et al. (2021). Overview of beneficial effects of (Poly)phenol metabolites in the context of neurodegenerative diseases on model organisms. *Nutrients* 13, 2940. doi: 10.3390/nu13092940

Carregosa, D., Pinto, C., Ávila-Gálvez, M. Á., Bastos, P., Berry, D., and Santos, C. N. (2022). A look beyond dietary (poly)phenols: the low molecular weight phenolic metabolites and their concentrations in human circulation. *Compr. Rev. Food Sci. Food Saf.* 21, 3931–3962. doi: 10.1111/1541-4337.13006

da Silva, A., Giacomoni, F., and Pavot, B. (2016). "PhytoHub V1. 4: a new release for the online database dedicated to food phytochemicals and their human metabolites," in *Proceedings of the 1st International Conference on Food Bioactivities and Health*, 13–15. Norwich, UK.

Daina, A., Michielin, O., and Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci. Rep.* 7, 42717. doi: 10.1038/srep42717

Del Rio, D., Rodriguez-Mateos, A., Spencer, J. P. E., Tognolini, M., Borges, G., and Crozier, A. (2013). Dietary (Poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid. Redox Signal* 18, 1818–1892. doi: 10.1089/ars.2012.4581

Figueira, I., Garcia, G., Pimpão, R. C., Terrasso, A. P., Costa, I., Almeida, A. F., et al. (2017). Polyphenols journey through blood-brain barrier towards neuronal protection. *Sci. Rep.* 7, 11456. doi: 10.1038/s41598-017-11512-6

García-Villalba, R., Giménez-Bastida, J. A., Cortés-Martín, A., Ávila-Gálvez, M. Á., Tomás-Barberán, F. A., Selma, M. V., et al. (2022). Urolithins: a comprehensive update on their metabolism, bioactivity, and associated gut microbiota. *Mol. Nutr. Food Res.* 66, 2101019. doi: 10.1002/mnfr.202101019

Gasperotti, M., Passamonti, S., Tramer, F., Masuero, D., Guella, G., Mattivi, F., et al. (2015). Fate of microbial metabolites of dietary polyphenols in rats: is the brain their target destination? *ACS Chem. Neurosci.* 6, 1341–1352. doi: 10.1021/acschemneuro.5b00051

Grabska-Kobylecka, I., Kaczmarek-Bak, J., Figlus, M., Prymont-Przyminska, A., Zwolinska, A., Sarniak, A., et al. (2020). The presence of caffeic acid in cerebrospinal fluid: evidence that dietary polyphenols can cross the blood-brain barrier in humans. *Nutrients* 12, 1531. doi: 10.3390/nu12051531

Hostetler, G. L., Ralston, R. A., and Schwartz, S. J. (2017). Flavones: food sources, bioavailability, metabolism, and bioactivity. *Adv. Nutr. Int. Rev. J.* 8, 423–435. doi: 10.3945/an.116.012948

Hussain, T., Tan, B., Yin, Y., Blachier, F., Tossou, M. C. B., and Rahu, N. (2016). Oxidative stress and inflammation: what polyphenols can Do for us? *Oxid. Med. Cell Longev.* 2016, 1–9. doi: 10.1155/2016/7432797

Kennedy, D. O. (2014). Polyphenols and the human brain: plant "Secondary Metabolite" ecologic roles and endogenous signaling functions drive benefits. *Adv. Nutr.* 5, 515–533. doi: 10.3945/an.114.006320

Le Sayec, M., Carregosa, D., Khalifa, K., de Lucia, C., Aarsland, D., Santos, C. N., et al. (2023). Identification and quantification of (poly)phenol and Methylxanthine metabolites in human cerebrospinal fluid: evidence of their ability to cross the BBB. *Food Funct.* 14, 8893–8902. doi: 10.1039/d3fo01913f

Mena, P., Bresciani, L., Brindani, N., Ludwig, I. A., Pereira-Caro, G., Angelino, D., et al. (2019). Phenyl-γ-valerolactones and phenylvaleric acids, the main colonic metabolites of flavan-3-ols: synthesis, analysis, bioavailability, and bioactivity. *Nat. Prod. Rep.* 36, 714–752. doi: 10.1039/C8NP00062J

Mori, S., Takanaga, H., Ohtsuki, S., Deguchi, T., Kang, Y. S., Hosoya, K. I., et al. (2003). Rat organic anion transporter 3 (rOAT3) is responsible for brain-to-blood efflux of

homovanillic acid at the abluminal membrane of brain capillary endothelial cells. *J. Cereb. Blood Flow and Metabolism* 23, 432–440. doi: 10.1097/01.WCB.0000050062.57184.75

Neveu, V., Perez-Jimenez, J., Vos, F., Crespy, V., du Chaffaut, L., Mennen, L., et al. (2010). Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. *Database* 2010, bap024. doi: 10.1093/database/bap024

Noorani, B., Chowdhury, E. A., Alqahtani, F., Ahn, Y., Patel, D., Al-Ahmad, A., et al. (2020). LC–MS/MS-based *in vitro* and *in vivo* investigation of blood–brain barrier integrity by simultaneous quantitation of mannitol and sucrose. *Fluids Barriers CNS* 17, 61. doi: 10.1186/s12987-020-00224-1

Ntie-Kang, F. (2013). An *in silico* evaluation of the ADMET profile of the StreptomeDB database. *Springerplus* 2, 353. doi: 10.1186/2193-1801-2-353

Ntie-Kang, F., Mbah, J. A., Lifongo, L. L., Owono Owono, L. C., Megnassan, E., Meva'a Mbaze, L., et al. (2013). Assessing the pharmacokinetic profile of the CamMedNP natural products database: an *in silico* approach. *Org. Med. Chem. Lett.* 3, 10. doi: 10.1186/2191-2858-3-10

Parepally, J. M. R., Mandula, H., and Smith, Q. R. (2006). Brain uptake of nonsteroidal anti-inflammatory drugs: Ibuprofen, flurbiprofen, and indomethacin. *Pharm. Res.* 23, 873–881. doi: 10.1007/s11095-006-9905-5

Pyrak, B., Gubica, T., and Rogacka-Pyrak, K. (2024). Cyclodextrin nanosponges as bioenhancers of phytochemicals. *Prospects Pharm. Sci.* 22, 170–177. doi: 10.56782/pps.272

Rodriguez-Mateos, A., Vauzour, D., Krueger, C. G., Shanmuganayagam, D., Reed, J., Calani, L., et al. (2014). Bioavailability, bioactivity and impact on health of dietary flavonoids and related compounds: an update. *Arch. Toxicol.* 88, 1803–1853. doi: 10.1007/s00204-014-1330-7

Rothwell, J. A., Perez-Jimenez, J., Neveu, V., Medina-Remón, A., M'hiri, N., García-Lobato, P., et al. (2013). Phenol-Explorer 3.0: a major update of the phenol-explorer database to incorporate data on the effects of food processing on polyphenol content. *Database* 2013, 2013. doi: 10.1093/database/bat070

Scalbert, A., and Williamson, G. (2000). Dietary intake and bioavailability of polyphenols. *J. Nutr.* 130, 2073S–2085S. doi: 10.1093/jn/130.8.2073S

Schaffer, S., and Halliwell, B. (2012). Do polyphenols enter the brain and does it matter? Some theoretical and practical considerations. *Genes Nutr.* 7, 99–109. doi: 10.1007/s12263-011-0255-5

Schrödinger, L. L. C. (2015). *Qikprop*.

Sonawane, V., Wagh, D. I., Bhamare, S. P., Surana, K. R., Sonawane, D. D., and Mahajan, S. K. (2025). Enhancing water solubility of a BCS class II drug using hydrotropy, mixed solvency, co-solvency, and nanosuspension techniques. *Prospects Pharm. Sci.* 23, 134–141. doi: 10.56782/pps.500

Sun, D., Gao, W., Hu, H., and Zhou, S. (2022). Why 90% of clinical drug development fails and how to improve it? *Acta Pharm. Sin. B* 12, 3049–3062. doi: 10.1016/j.apsb.2022.02.002

Tayab, M. A., Islam, M. N., Chowdhury, K. A. A., and Tasnim, F. M. (2022). Targeting neuroinflammation by polyphenols: a promising therapeutic approach against inflammation-associated depression. *Biomed. and Pharmacother.* 147, 112668. doi: 10.1016/j.biopha.2022.112668

Vauzour, D. (2012). Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. *Oxid. Med. Cell Longev.* 2012, 1–16. doi: 10.1155/2012/914273

Vitale, D. C., Piazza, C., Melilli, B., Drago, F., and Salomone, S. (2013). Isoflavones: estrogenic activity, biological effect and bioavailability. *Eur. J. Drug Metab. Pharmacokinet.* 38, 15–25. doi: 10.1007/s13318-012-0112-y

Wang, L., and Sweet, D. H. (2012). Potential for food–drug interactions by dietary phenolic acids on human organic anion transporters 1 (SLC22A6), 3 (SLC22A8), and 4 (SLC22A11). *Biochem. Pharmacol.* 84, 1088–1095. doi: 10.1016/j.bcp.2012.07.027

Wang, Q., Rager, J. D., Weinstein, K., Kardos, P. S., Dobson, G. L., Li, J., et al. (2005). Evaluation of the MDR-MDCK cell line as a permeability screen for the blood–brain barrier. *Int. J. Pharm.* 288, 349–359. doi: 10.1016/j.ijpharm.2004.10.007

Wang, L., Halquist, M. S., and Sweet, D. H. (2013). Simultaneous determination of gallic acid and gentisic acid in organic anion transporter expressing cells by liquid chromatography–tandem mass spectrometry. *J. Chromatogr. B* 937, 91–96. doi: 10.1016/j.jchromb.2013.08.024

Williamson, G., and Manach, C. (2005). Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. *Am. J. Clin. Nutr.* 81, 243S–255S. doi: 10.1093/ajcn/81.1.243S

Williamson, G., Kay, C. D., and Crozier, A. (2018). The bioavailability, transport, and bioactivity of dietary flavonoids: a review from a historical perspective. *Compr. Rev. Food Sci. Food Saf.* 17, 1054–1112. doi: 10.1111/1541-4337.12351

Zhao, M., Ma, J., Li, M., Zhang, Y., Jiang, B., Zhao, X., et al. (2021). Cytochrome P450 enzymes and drug metabolism in humans. *Int. J. Mol. Sci.* 22, 12808. doi: 10.3390/ijms222312808