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Review

Potential Herb–Drug Interactions in the Management of Age-Related Cognitive Dysfunction

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Abstract: Late-life mild cognitive impairment and dementia represent a significant burden on healthcare systems and a unique challenge to medicine due to the currently limited treatment options. Plant phytochemicals have been considered in alternative, or complementary, prevention and treatment strategies. Herbals are consumed as such, or as food supplements, whose consumption has recently increased. However, these products are not exempt from adverse effects and pharmacological interactions, presenting a special risk in aged, polymedicated individuals. Understanding pharmacokinetic and pharmacodynamic interactions is warranted to avoid undesirable adverse drug reactions, which may result in unwanted side-effects or therapeutic failure. The present study reviews the potential interactions between selected bioactive compounds (170) used by seniors for cognitive enhancement and representative drugs of 10 pharmacotherapeutic classes commonly prescribed to the middle-aged adults, often multimorbid and polymedicated, to anticipate and prevent risks arising from their co-administration. A literature review was conducted to identify mutual targets affected (inhibition/induction/substrate), the frequency of which was taken as a measure of potential interaction. Although a limited number of drugs were studied, from this work, interaction with other drugs affecting the same targets may be anticipated and prevented, constituting a valuable tool for healthcare professionals in clinical practice.

Keywords: herb–drug interactions; botanicals; food supplements; nootropics; phytochemicals; nutraceuticals; pharmacokinetics; cognitive dysfunction

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1. Introduction

The aging population and the increased life expectancy have unveiled the need for effectively managing associated cognitive decline to maintain functional capacity and quality of life. Senile dementia is a clinical syndrome observed in the elderly, which includes a range of progressive neurological disorders characterized by a number of cognitive deficits, such perception, logical thought, memory, orientation, and alertness [1]. Dementia and cognitive deficit prevalence is increasing considerably, mostly because old age is the main risk factor [1,2]. In 2015, 47 million people were estimated to be affected by dementia, and the predictions for 2050 amount to 131 million people worldwide [3]. Of note is also that the onset of dementia is occurring increasingly earlier in life [4] and, besides old age, chronic conditions such as diabetes, depression, hypertension, and various forms of vascular disease are also risk factors [2].

Age-related brain disorders, such as dementia and its most prevalent form Alzheimer's disease, are a burden with limited pharmacological therapies available [5]. Multiple mechanisms have been proposed to underlie the causes of dementia, and therefore there are a

variety of potentially valid treatment strategies from the broad concepts of improving angiogenesis and cerebral blood flow [6] or the antioxidant and neuroprotective effect against oxidative stress [7], to more specific targets such as modulating the brain glutamatergic and cholinergic neurotransmission [8] or improving the hippocampal brain-derived neurotrophic factor mRNA levels [9,10]. At present, licensed drugs include cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and a glutamate NMDA (*N*-methyl-D-aspartate) receptor antagonist (memantine) [4,11]; a range of other nonspecific drugs often prescribed include tranquilizers, antipsychotics, antidepressants, and hypnotics.

The burden of the disease may be reduced by identifying new prevention and treatment strategies [1]. In addition to pharmacological intervention, the aged are resorting to complementary and alternative approaches to delay decline and enhance cognitive function. On one hand, the role of diet in late-life cognition has also been postulated and neuroprotective food supplements considered to delay onset of such disorders [6]. On the other, traditional medicine is considered particularly attractive in treating poor-resources populations [12,13], and the World Health Organization has recognized its important role in primary healthcare in such contexts [14].

Natural products and, in particular, botanicals play a central role in healthcare and management, not only because of their widespread use as food supplements, but also as source of new drugs per se, or as lead compounds [15,16]. Precedents for the continuing search for plants and phytochemicals, which can prevent or treat cognitive impairment, are natural compounds such as galantamine from Amaryllidaceae (e.g., *Galanthus* or *Narcissus*) species [4,17]. Although clinical evidence of efficacy is at times rather inconsistent and scarce, many promising plants (as such or concentrated in the form of extracts) have been identified and extensively reviewed [4,5,18–21]. Many of these contain bioactive compounds, belonging to different chemical classes, with good to excellent anticholinesterase activity [5,19,20,22,23], or antioxidant and anti-inflammatory effects, among others [19,21].

Additionally, access to online information has dramatically broadened the scope of treatment options, and the elderly are sometimes making their own health decisions, without consulting a physician. As a result, use of herbal food supplements (also called nutraceuticals, highlighting the link between food and health), touted for benefits such as improved memory and concentration (often called nootropics), is on the rise. Though usually considered by consumers as safe and exempt from side effects due to their natural origin, the potential for interaction with drugs is well documented [24–26] affecting both efficacy and safety (varying from mild to life-threatening episodes) of drugs.

Considering that dementia's peak incidence, in developing countries, is among those aged 80–89 years [2,3] and also that polypharmacy often occurs in the geriatric population with pre-existing comorbidities [27], the risk of interactions is increased manifold. A thorough evaluation by the doctor is thus needed to select an intervention with a favorable risk–benefit and prevent the common problems of drug–drug or herbal–drug interactions (HDI) [28]. Understanding pharmacokinetic and pharmacodynamic interactions is warranted to avoid undesirable adverse drug reactions, which result in unwanted side-effects or therapeutic failure.

The aim of this narrative review of the literature is to evaluate potential risks of HDI between purported botanical cognitive enhancers often taken by the elderly and ten representative drugs of different pharmacotherapeutic classes commonly prescribed to this age group. The work is limited to phytochemicals with reported benefits in cognition, disregarding the effect of other constituents of the plants considered.

The ability of mutual (bioactive-drug) target (enzymes, transporters and receptors) modulation (substrates, inhibitors and inducers) was taken as a measure of the interaction potential. This work not only identifies the bioactives with the highest HDI potential, but can also be further utilized as a suitable database for physicians and healthcare professionals to improve clinical outcomes and prevent adverse effects.

2. Methodology

The workflow used to retrieve information is represented in Figure 1 using a color code to distinguish between paths taken regarding plants (blue), drugs (red), and exclusions (green). In short, several online electronic databases (e.g., Scopus, Google Scholar, ScienceDirect, Medline, Medline Plus, and Pubmed) were used to search for relevant literature on the use of plants for cognition related ailments. Keywords, such as nootropics, memory, cognitive enhancement, herbs, food supplements, and nutraceuticals, were used. A total of 685 papers was selected based on title and abstract and thorough checking of reference lists for additional papers. Previous reviews on the use of herbs as cognitive enhancers were also investigated for further relevant information, double checked by another investigator.

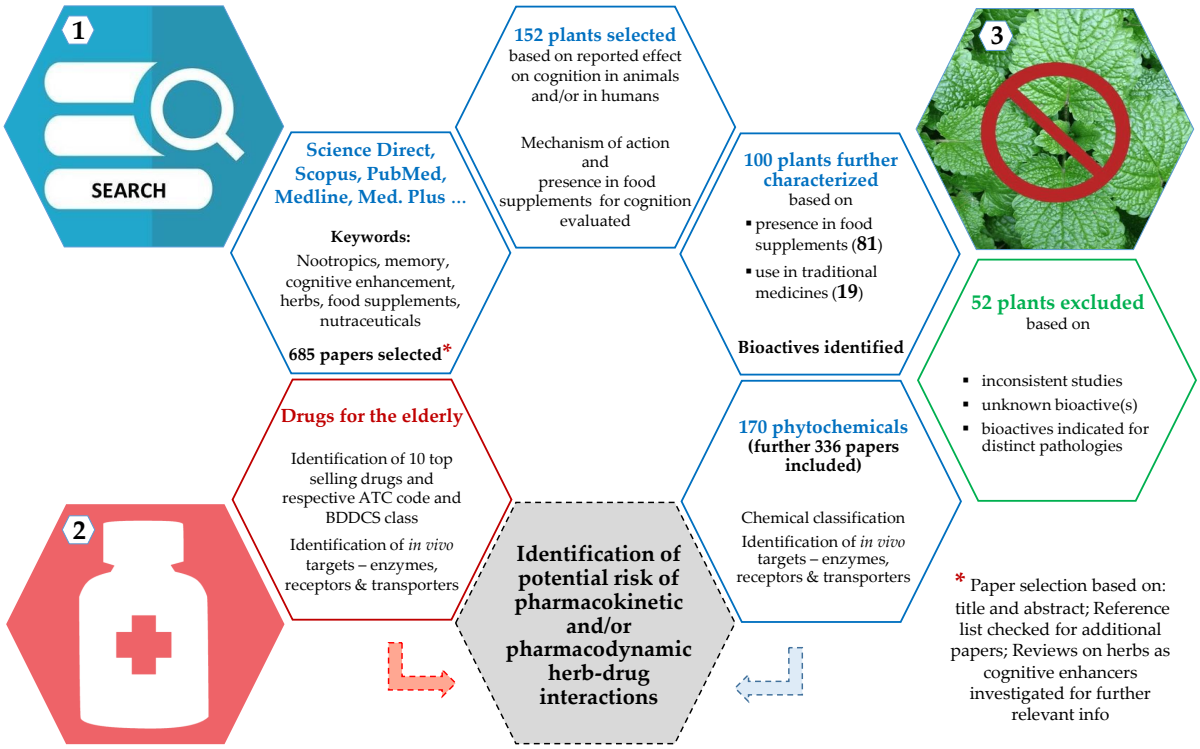


Figure 1. Workflow used to retrieve information to identify potential risk of HDI in aged food supplements' consumers. Herbals are represented in blue (**1**), drugs in red (**2**), and exclusions in green (**3**). The number of publications used, botanicals characterized, and bioactives identified and studied, is highlighted in bold.

A total of 152 plants were retrieved as having an effect in cognition, through a number of different mechanisms. From those, 100 plants were considered for further characterization and checked for inclusion in official compendia—European Pharmacopoeia (Ph. Eur.) [29], United States Pharmacopoeia (USP) [30], The Japanese Pharmacopoeia (JP) [31], Indian Pharmacopeia (IP) [32], Pharmacopoeia of the People's Republic of China (PPRC) [33], World Health Organization (WHO) monographs on selected medicinal plants [34], and the Herbal Medicines Compendium (HMC)-USP [35]. Plants (52) not matching the eligibility criteria were excluded. Exclusions were made when studies were inconsistent, or the plant bioactive(s) unknown, poorly studied or indicated for different pathologies.

The plants selected (100) corresponded to 170 bioactives related to cognition enhancement, whose presence in commercial food supplements was also checked. Bioactives were grouped in chemical families and the relative weight of each class determined. For every bioactive, a thorough pharmacokinetic characterization was made regarding action as substrates, inducers, or inhibitors of target enzymes (e.g., cytochrome P450 (CYP), AMP-activated protein kinase (AMPK), monoamine oxidase (MAO), cyclooxygenase (COX),

and arachidonate 5-lipoxygenase (ALOX5)), transporters (ATP binding cassette (ABC)), such as P-glycoprotein (P-gP) and MRP (multidrug resistance-associated protein), and solute carriers (SCL) and receptors (e.g., *N*-methyl-D-aspartate (NMDA)), identified as being involved in selected drugs' disposition.

Ten representative drugs commonly prescribed to the elderly, belonging to 10 pharmacotherapeutic groups, were selected according to unpublished prescription data (2017–2019) supplied by the National Pharmacies Association. They were classified according to the Anatomical Therapeutic Chemical Classification System (ATC) [36], the Biopharmaceutical Drug Disposition and Classification System (BDDCS) [37–43] and checked for increased risk if an interaction occurs [44]. The pharmacokinetics of each drug was evaluated as described for bioactives.

Finally, the potential risk of pharmacodynamic and/or pharmacokinetic HDI was evaluated by identifying simultaneous action in the same target(s) and the number of mutual targets affected, used as a measure of the probability of interaction occurrence.

3. Botanicals for Cognitive Enhancement

3.1. Identification and Selection of Botanicals (and Respective Bioactives) Implicated in Cognition Enhancement

Botanicals (whole plant or parts of the plant), their extracts, or isolated bioactives, were identified through an online search, as detailed in Section 2. The plants considered for additional study and the main bioactive molecules reported as responsible for enhancing cognition are presented in Table 1. Plants excluded, typically due to lack or inconsistent evidence of efficacy in cognition, unknown bioactive, or toxicity, are shown in the footnote of the same Table. As an example, *Albizia adianthifolia*, despite the antioxidant and acetylcholinesterase (AChE) inhibitory activities shown [45,46] (therefore with potential to manage memory loss and neurodegenerative disorders), has been disregarded. In fact, little is known about the specific function and pharmacokinetic properties of the more than 90 secondary metabolites, isolated from several parts of the plant, including those of a new triterpenoid saponin (adianthifolioside J) recently identified [47]. *Ricinus communis* was also excluded, because the level of evidence for its use in cognitioN-related diseases is poor, despite the fact that its bioactive, ricinine, was considered a central nervous system stimulant [48] and a promising cognitioN-enhancing drug [49].

3.2. Mechanisms of Action in Cognition Enhancement

Herbals in food supplements present substantial variability in composition according to ecotype, culture conditions, harvesting season, extraction method, and other processing operations. Moreover, the high complexity of the plant matrices and the multiplicity of compounds they contain (sometimes with synergic or antagonic action) may also contribute to contradictory and inconsistent findings. It is therefore not uncommon to find literature reports that point in different directions. A thorough description of the multiple mechanisms by which plants can improve cognition is out of the scope of this work and only a simplified overview is provided.

Of the plants studied, 63% are listed in at least one of the official compendia consulted and presented in Table 1. Ph. Eur., for example, lists 37 plants, 10 of which are part of a general chapter dedicated to herbal drugs used in Traditional Chinese Medicine, published for information only.

The main mechanisms identified in these plants, as associated with cognition enhancement, relate either to neuroprotection, neurotransmission, or a combination of both (Table 1 and Figure 2A).

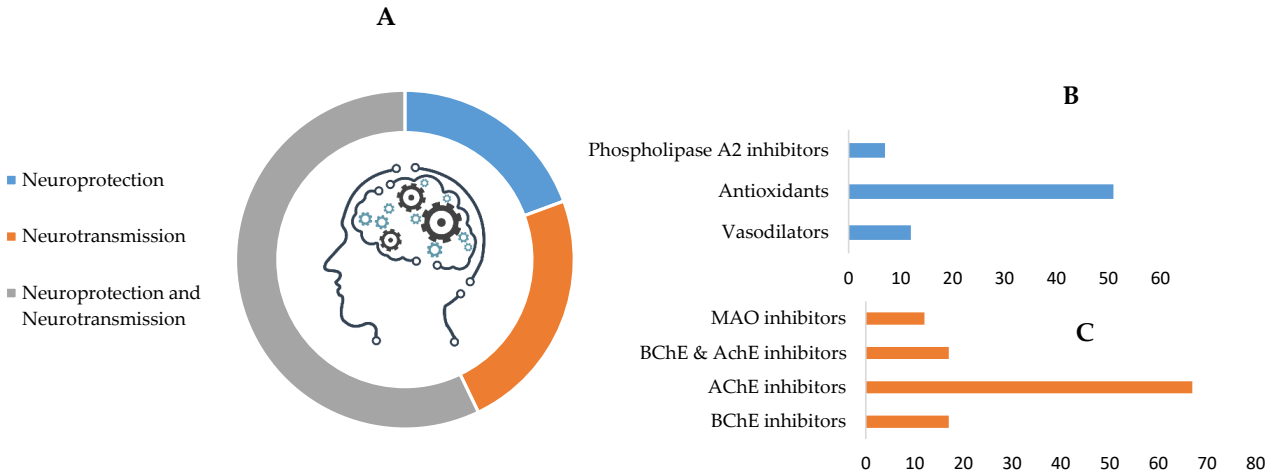


Figure 2. Summary of the main mechanisms by which botanicals may enhance cognition (**A**). Main relative contributions to neuroprotection (**B**) and neurotransmission (**C**) are highlighted. AChE—acetylcholinesterase; BChE—butyrylcholinesterase; MAO—monoamine oxidase.

Neuroprotection is associated with radical oxygen scavenger ability, reduction in inflammation and associated brain damage. Polyphenols, for instance, play an important part in reducing oxidative stress-induced inflammation and associated diseases. In fact, inflammation plays an important role in age-related cognitive disorders [50] and, as such, antioxidative molecules and the inhibitors of pro-inflammatory enzymes or cytokines, present in many (58%) of the plants considered, may improve cognition. As examples, *Bacopa monnieri* [51] has been associated with a reduction of radical oxygen associated inflammation and plants, such as *Foeniculum vulgare* [52] and *Centella asiatica* [53], inhibit the production of phospholipase A2. Crocin from *Crocus sativus* suppressed formation of brain inflammatory mediators, such as interleukin-1 and tumor necrosis factor-α [54].

On the other end, β-amyloid is a component of amyloid plaques characteristic of Alzheimer's, and T-tau and P-tau proteins are over phosphorylated in neurodegenerative disorders [50]. Inhibitors of aggregation/destruction of β-amyloid plaques or protection of T-tau and P-tau proteins (e.g., *Alpinia oxyphylla* [61]) were considered within the neuroprotective group, together with plants which reportedly prevent neuronal death (e.g., *Schisandra chinensis* [174]).

There is a strong link between reduced vasodilation (which can result in cerebrovascular lesions) and cognitive impairment and, ultimately, vascular dementia in elderly people [175]. Vasodilator-containing plants improve blood flow to the brain, reducing ischemia and therefore protecting the brain from injury and ameliorating cognition. *Angelica sinensis* [63], *Eleutherococcus senticosus* [91], and *Salvia miltiorrhiza* [24] are examples of such plants. Vinpocetin present in *Vinca minor* is also used as a neuroprotective cerebral vasodilator [20] and may interact with warfarin and other anticoagulants [176].

Many of the plants studied impact directly on neurotransmission (79%) by inhibiting acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and MAO (Figure 2C). Others inhibit catechol-*O*-methyltransferase (COMT; the enzyme responsible for the degradation of the catecholamine neurotransmitters) or show cholinergic activity (e.g., Z-ligustilide and ferulic acid from *Angelica sinensis* [18]). Noteworthy is the significant expression of plants capable of inhibiting AChE alone (67%) or in conjunction with BChE (17%), the majority of which contain alkaloids (e.g., assoanine, galantamine, lycorine, sanguinine and huperzine) and show promise in the treatment of Alzheimer's disease [17,22]. *Pancratium illyricum* roots and leaves are examples of good sources of anticholinergic alkaloids, including a particularly potent molecule, 11α-hydroxy-*O*-methylleucotamine [121]. Huperzine A is an example of a lead compound in the development of anticholinesterase drugs, which has shown higher oral bioavailability and blood–brain barrier penetration, as well as longer duration of activity, as compared to the approved drugs [22].

Table 1. Characterization of the plants purported as acting as cognition enhancers and main mechanism(s) of action. Bioactive molecules were selected based on reported activity in cognition; other phytochemicals present in the plant were omitted.

Plant	Main Bioactive(S) for Cognition	Effect on Brain/Cognition	References
Acorus calamus [+♦]	α-Asarone β-Asarone	Neurotransmission	[55–57]
Acorus gramineus	α-Asarone β-Asarone	Neuroprotection and Neurotransmission	[58]
Aframomum melegueta	Gingerol Shogaol Quercetin p-Kaempferol	Neuroprotection and Neurotransmission	[59,60]
Alpinia oxyphylla [■♦]	Protocatechuic acid	Neuroprotection and Neurotransmission	[61]
Anemarrhena asphodeloides [•■♦]	Timosaponin AIII	Neuroprotection and Neurotransmission	[58]
Angelica gigas [○]	Decursin Decursinol angelate	Neuroprotection and Neurotransmission	[58]
Angelica sinensis [•▲♦]	Z-ligustilide Coniferyl ferulate 11-Angeloylsenkyunolide F Ferulic acid	Neuroprotection and Neurotransmission	[18,62,63]
Asparagus adscendens	Shatavarin IV (Asparinin B) Conypododiol	Neuroprotection and Neurotransmission	[64,65]
Asparagus racemosus [+]	Shatavarin IV (Asparinin B) Sarsasapogenin	Neuroprotection and Neurotransmission	[57,66]
Atractylodes japonica [■]	Atractylenolide III	Neuroprotection	[67]
Atractylodes lancea [•■♦]	Atractylenolide III (Codonolactone) Stigmasterolβ-Sitosterol	Neurotransmission	[58]
Avena sativa	Avenanthramides A, B and C	Neuroprotection	[58]
Bacopa monnieri [*+]	Bacoside A and B	Neuroprotection and Neurotransmission	[51,68–70]
Bauhinia rufescens	D-pinitol (3-*O*-methyl-D-inositol) p-Coumaric acid Ferulic acid Hyperoside	Neuroprotection and Neurotransmission	[71]
Buxus hyrcana	Buxamine B	Neurotransmission	[22,72]
Buxus papillosa	Buxakashmiramine Cycloprotobuxine-C Cyclovirobuxeine-A Cyclomicrophylline-A *N*,*N*-dimethyl buxapapine	Neurotransmission	[22,72]
Camellia sinensis [•*♦]	Caffein Epigallocatechin-3-gallate Epicatechin gallate Methylliberine	Neuroprotection and Neurotransmission	[55,57,73,74]
Caragana chamiague [+]	(+)-α-Viniferin	Neurotransmission	[22]
Centella asiatica [•*▲+♦]	Asiatic acid	Neuroprotection and Neurotransmission	[55,57,66]

Table 1. *Cont.*

Plant	Main Bioactive(S) for Cognition	Effect on Brain/Cognition	References
Cinnamomum wilsonii (extract)	Cinnamaldehyde Eugenol	Neuroprotection and Neurotransmission	[75–78]
Citrus aurantium •■+♦	p-Synephrine	Neurotransmission	[79]
Citrus reticulata •■♦○	Nobiletin	Neuroprotection and Neurotransmission	[58]
Clitoria ternatea +	Kaempferol	Neuroprotection and Neurotransmission	[57,66]
Coffee arabica	Caffein Methylliberine Theacrine	Neuroprotection and Neurotransmission	[55,74,80,81]
Coleus forskohlii +	Forskolin (Colforsin)	Neuroprotection and Neurotransmission	[82]
Convolvulus pluricaulis +	Kaempferol Kaempferol-3-glucoside Caffeic acid Convolamine B-Sitosterol	Neuroprotection	[83]
Coptis chinensis •■▲♦	Berberine Coptisine Palmatine	Neurotransmission	[57]
Coptis japonica ■▲	Berberine	Neuroprotection	[57]
Corydalis speciosa	Palmatine	Neurotransmission	[22]
Crocus sativus •■▲+♦	Quercetin Crocins/picrocrocin Crocetin Safranal	Neuroprotection and Neurotransmission	[55,57,66]
Croton tonkinensis	Ent-kaurane	Neuroprotection and Neurotransmission	[16,84]
Curcuma longa •*■▲+♦	Curcumin	Neuroprotection and Neurotransmission	[55,57]
Cuscuta japonica	Hyperoside Kaempferol	Neuroprotection and Neurotransmission	[85]
Cynanchum atratum ♦	Cynatroside A Cynatroside B	Neurotransmission	[22]
Cyperus rotundus ■+♦	Quercetin Kaempferol Catechin	Neuroprotection and Neurotransmission	[85]
Dioscorea polystachya ■○	Diosgenin	Neuroprotection	[58]
Dioscorea oppositifolia •■♦	Diosgenin	Neuroprotection	[86,87]
Echium amoenum	Cyanidin-3-glucoside	Neuroprotection	[88,89]
Eleutherococcus senticosus•*■▲ (Siberian ginseng)	Syringin (Eleutheroside B)	Neuroprotection and Neurotransmission	[90–93]
Eucharis grandiflora	Sanguinine (*O*-Desmethylgalantamine)	Neuroprotection and Neurotransmission	[22]
Foeniculum vulgare •*■▲+♦	Caffeic acid Chlorogenic acid 1,8-Cineole	Neuroprotection and Neurotransmission	[52,94–96]
Galanthus nivalis	Galantamine	Neurotransmission	[22,57]

Table 1. *Cont.*

Plant	Main Bioactive(S) for Cognition	Effect on Brain/Cognition	References
Galanthus woronowii (or ikariae)	Galantamine Lycorine	Neurotransmission	[20,22,55]
Ginkgo biloba •*▲♦	Ginkgolide A Ginkgolide B Bilobalide Isorhamnetin Protocatechuic acid	Neuroprotection and Neurotransmission	[20,55,57,81,97]
Glycyrrhiza glabra •*■▲+♦	Glycyrrhizin Glycyrrhetinic acid	Neuroprotection	[57]
Glycyrrhiza uralensis •■▲♦	Isoliquiritigenin	Neuroprotection	[58]
Haloxylon recurvum	Haloxysterols A, B, C, D	Neurotransmission	[22]
Huperzia serrata	Huperzine A	Neuroprotection and Neurotransmission	[8,20,55,57]
Hypericum perforatum •*▲♦	Hypericin Hyperforin Biapigenin (I3,II8-biapigenin) Quercetin Chlorogenic acid Rutin Hyperoside Kaempferol	Neuroprotection and Neurotransmission	[98–102]
Ilex paraguariensis •	Chlorogenic acid Caffein Theobromine Quercetin Kaempferol	Neurotransmission	[22,57]
Lepidium meyenii○ (Maca Root Extract)	Quercetin β-Carbolines *N*-Benzylhexadecanamide *N*-Acetylbenzylamine *N*-3-Methoxybenzyl-linoleamide	Neuroprotection and Neurotransmission	[57,103–107]
Lespedeza bicolor	Catechin Rutin Daidzein Luteolin Naringenin Genistein	Neuroprotection and Neurotransmission	[22]
Lycopodium clavatum	α-Onocerin	Neurotransmission	[22]
Lycoris radiata	Galantamine	Neurotransmission	[22,57]
Mangifera indica +○	Mangiferin	Neuroprotection and Neurotransmission	[108]
Matricaria chamomilla •*▲	Chlorogenic acid Caffeic acid Catechin Rutin Luteolin Apigenin	Neuroprotection and Neurotransmission	[22]
Mauritia flexuosa	Rutin	Neuroprotection and Neurotransmission	[22,109]

Table 1. *Cont.*

Plant	Main Bioactive(S) for Cognition	Effect on Brain/Cognition	References
Melissa officinalis •▲	Luteolin Apigenin Rosmarinic acid Protocatechuic acid	Neuroprotection and Neurotransmission	[20,55,57]
Mentha spicata	Rosmarinic acid Salvianolic acid	Neuroprotection and Neurotransmission	[110,111]
Morinda lucida	Phytol Oleanolic acid Chlorogenic acid p-Coumaric acid Daidzein Rutin Naringin Quercetin Naringenin Genistein	Neuroprotection and Neurotransmission	[112–119]
Moringa peregrina	Rutin Myricetin β-Sitosterol	Neuroprotection and Neurotransmission	[22]
Mucuna pruriens +○	Gallic acid Genistein Levodopa (L-Dopa) Mucunadine Mucunine Prurienidine Prurienine β-Carbolines (Harmine) β-Sitosterol	Neuroprotection and Neurotransmission	[12,17,22,120]
Narcissus assoanus	Assoanine	Neurotransmission	[22]
Narcissus confusus	Galantamine Epinorgalantamine	Neurotransmission	[17,22,57]
Narcissus poeticus	11-Hydroxygalantamine	Neurotransmission	[22]
Paeonia lactiflora •■▲♦○	Paeonol	Neurotransmission	[22,58]
Panax ginseng •*■▲♦○	Ginsenosides Rb, Rc, Rd, Rg1	Neuroprotection	[8,55,57,58,81]
Pancratium illyricum	11-α-hydroxy-*O*-methylleucotamine Galantamine Sanguinine Lycorine	Neuroprotection and Neurotransmission	[8,20,55,57,58,81,121]
Paullinia cupana•○ (Guarana)	Caffein	Neuroprotection and Neurotransmission	[81,122,123]
Peganum harmala	β-Carbolines (Harmine, 9-Methyl-9B-Carboline)	Neuroprotection and Neurotransmission	[124–127]
Peltophorum pterocarpum	Hyperoside Quercetin-3-*O*-β-D-glucuronide	Neuroprotection and Neurotransmission	[116]
Phyllanthus emblica+♦ *(Emblica officinalis)*	Ellagic acid Gallic acid Chebulagic acid Apigenin Quercetin Corilagin Luteolin Phyllanthin	Neuroprotection and Neurotransmission	[57,128–130]

Table 1. *Cont.*

Plant	Main Bioactive(S) for Cognition	Effect on Brain/Cognition	References
Piper nigrum •*+♦	Piperine	Neuroprotection	[131,132]
Platycladus orientalis ♦	15-Methoxypinusolidic acid	Neurotransmission	[57,58,133]
Polygala tenuifolia •■♦	Tenuifoliside B Tenuifoliside C Tenuifolin Polygalaxanthone III	Neuroprotection and Neurotransmission	[134–140]
Puerariae lobate •*■♦	Daidzein Puerarin	Neuroprotection	[141]
Rehmannia glutinosa ■▲♦○	Catalpol	Neuroprotection	[58,142,143]
Rhizoma acori +♦	Eugenol β-Asarone	Neuroprotection	[144,145]
Rhodiola rosea *○	Rosavin Rosin Rosarin Salidroside	Neuroprotection and Neurotransmission	[146–148]
Ribes nigrum• (Blackcurrant)	Myricetin Quercetin Isorhamnetin	Neuroprotection and Neurotransmission	[22,149]
Rosmarinus officinalis •*▲	Caffeic acid Chlorogenic acid Oleanolic acid Rosmarinic acid Ursolic acid α-Pinene Eucalyptol (Cineole) Luteolin Protocatechuic acid	Neuroprotection and Neurotransmission	[22]
Salvia lavandulaefolia •	Eucalyptol α-Pinene	Neuroprotection and Neurotransmission	[20,22,55,57,150]
Salvia miltiorrhiza •*■♦○	Tanshinone I Tanshinone IIA Tanshinone IIB Salvianolic acid	Neurotransmission	[24,151,152]
Sarcococca saligna	Sarsalignenone Vaganine Sarcocine Sarcodine Sarcorine Isosarcodine	Neurotransmission	[22]
Saussurea costus •■	Apigenin Quercetin	Neurotransmission	[22,58]
Schisandra chinensis •■▲♦○	Schisandrin B (Gomisin N)	Neuroprotection and Neurotransmission	[57,58]
Scrophularia buergeriana	E-Harpagoside 8-*O*-E-p-methoxycinnamoylharpagide Harpagide	Neuroprotection and Neurotransmission	[153,154]

Table 1. *Cont.*

Plant	Main Bioactive(S) for Cognition	Effect on Brain/Cognition	References
Terminalia chebula ▲+♦○	Ellagic acid Tannic acid Chebulagic acid Corilagin Gallic acid 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose	Neuroprotection and Neurotransmission	[22,57,66]
Theobroma cacao •*■	Theobromine Caffein Catechin	Neuroprotection and Neurotransmission	[155–157]
Theobroma grandiflorum	Theacrine	Neuroprotection	[74]
*Trifolium pretense**▲ (Red clover)	Biochanin A	Neuroprotection	[158]
Trigonella foenum-graecum •*▲+♦○	Diosgenin	Neuroprotection and Neurotransmission	[159]
Vaccinium myrtillus•*▲ (Bilberry)	Cyanidin-3-*O*-β-glucoside	Neuroprotection	[160]
Vaccinium uliginosum L. (Bog bilberry)	Quercetin Rutin (Quercetin-3-rutinoside) Malvidin-3-glucoside Cyanidin-3-*O*-β-glucoside Delphinidin	Neuroprotection and Neurotransmission	[22,160]
Vaccinium angustifolium (Lowbush Blueberry or Wild blueberry)	Malvidin 3-glucoside Malvidin 3-galactoside Caffeic acid Cyanidin-3-*O*-β-galactoside Cyanidin-3-*O*-β-glucoside Cyanidin-3-*O*-β-arabinose Malvidin-3-*O*-β-arabinose Peonidin-3-*O*-β-arabinose Delphinidin-3-*O*-β-galactoside	Neuroprotection and Neurotransmission	[161]
Vinca minor	Vinpocetine	Neuroprotection and Neurotransmission	[20,162]
Vitex agnus-castus•*▲+○ (Chasteberry Extract)	Casticin	Neurotransmission	[163]
Vitis vinifera *+	Resveratrol Protocatechuic acid	Neuroprotection	[57,164]
Withania somnifera *▲+	Withaferin A Withanolide A, B Sitoindosides VII-X	Neuroprotection	[57,66,165–169]
Zingiber officinale Roscoe •*■▲+♦	Gingerol Shogaol	Neuroprotection and Neurotransmission	[22,57,170–173]

Plant listed in Ph.Eur (•), USP (*), JP (■), WHO monographs (▲), IP (+), PPRC (♦), (HMC)-USP (○). **List of plants excluded:** *Achyranthes aspera*; *Albizia adianthifolia*; *Allium sativum*; *Asparagus cochinchinensis*; *Astragalus membranaceus*; *Beta vulgaris*; *Boerhavia diffusa*; *Cannabis sativa* L; *Cassia occidentalis*; *Celastrus paniculatus*; *Chlorophytum borivilianum*; *Commiphora whighttii*; *Dipsacus asper*; *Euonymus alatus*; *Evodia rutaecarpa*; *Evolvulus alsinoides*; *Gastrodia elata*; *Indigo naturalis*; *Juncus effusus*; *Lavandula angustifolia*; *Lawsonia inermis*; *Ligusticum officinale*; *Ligusticum wallichii*; *Liriope muscari*; *Lycium barbarum*; *Lycopersicon esculentum*; *Magnolia officinalis*; *Nardostachys jatamansi*; *Nicotiana tobaccum*; *Paeonia suffruticosa*; *Petiveria aliácea*; *Physostigma venenosum*; *Piper betel*; *Piper methysticum*; *Pueraria tuberosa*; *Punica granatum*; *Pycnanthus angolensis*; *Rheum* spp.; *Ricinus communis*; *Terminalia arjuna*; *Terminalia bellirica*; *Tinospora cordifolia*; *Tripterygium wilfordii*; *Uncaria tomentosa*; *Vaccinium alaskaense How*; *Vaccinium cespitosum Michx.*; *Vaccinium membranaceum* L.; *Vaccinium ovalifolium* Sm; *Valeriana officinalis*; *Xanthoceras sorbifolia*; *Zanthoxylum armatum*; *Ziziphus jujuba*.

Quercetin and β-carbolines (e.g., harmine) from *Mucuna pruriens* and *Peganum harmala* strongly inhibit MAO [126]. Antidepressant and anxiolytic activity have also been associ-

ated with *Rhodiola rosea* [148], *Hypericum perforatum* [177], and *Rosmarinus officinalis* [178], amongst many other plants.

Glutamine is an excitatory neurotransmitter, an energy substrate, the precursor of the neurotransmitter amino acids glutamate of γ-aminobutyric acid (GABA), as well as a potent neurotoxin [179]. As such, glutamate homeostasis is paramount, and several plants (e.g., *Hypericum perforatum* [98] and *Mangifera indica* [108]) reportedly regulate glutamate signaling through NMDA receptor antagonism.

Perhaps the most striking plant for its levodopa contents is *Mucuna pruriens*, whose therapeutic utility of the many seed constituents in neuroprotection and treatment of Parkinson's disease has been reviewed by Kasture [12].

Estrogen-like effects of phytochemicals (e.g., biochanin A, which requires P450-catalyzed metabolism to generate the active phytoestrogens daidzein and genistein, in *Trifolium pratense* and isoliquiritigenin in *Glycyrrhiza uralensis*) may also contribute to reduced cognitive decline and improve cerebrovascular function in postmenopausal women [158,180].

Caffein, present in *Paullinia cupana* and *Coffee arabica*, is a central nervous system stimulant and an adenosine receptor antagonist, increasing acetylcholine and dopamine transmission in the brain [181], which acts as an energizer, reducing fatigue and promoting wakefulness. In addition, the structurally similar alkaloids, theacrine and methylliberine, also identified in the seeds and leaves of *Coffee arabica* [74], are believed to potentiate and synergize with caffein, also enhancing mood, energy, focus, and motivation, but showing less side effects. *Camellia sinensis* catechins (epigallocatechin-3-gallate and epicatechin gallate) present antioxidant and anti-inflammatory activity and are capable of crossing the blood–brain barrier, acting as neuroprotectors [73].

Additionally, plants often present vitamins (e.g., A, B1, B2, B3, B12, C and E), as well as minerals, including calcium, zinc, potassium, copper, manganese, sodium, and iron, among others. These act, for instance, as antioxidants and enzyme cofactors, also contributing to cognition enhancement.

As a result of the different mechanisms described, plants (and bioactives) are frequently categorized based on their target application, such as mood support, improved mental focus, alertness and memory, stress reduction, neurostimulation, antidepressants, anxiolytics, anti-Parkinsonians, etc.

4. Chemical Characterization of Nootropic Bioactive Compounds

Phytochemicals are plant-derived bioactive, non-nutrient chemicals, which can be found in plant foods (e.g., fruits, vegetables and grains) and food supplements. They encompass a group of secondary metabolites and are part of the plant's adaptation mechanism to the environment. Phytochemicals are responsible for the health benefits attributed to botanicals and the purported prevention or risk reduction of chronic diseases, such as dementia, Alzheimer's, or Parkinson's.

The bioactive compounds identified in botanicals for cognitive enhancement, as described in the previous section, were classified according to their chemical structure [182–185] (Figure 3). Phytochemicals may also be categorized according to their different functions in the body, such as antioxidants, anti-inflammatory, neuroprotective, etc., reflecting their mechanism of action, previously discussed. Mixed classifications are sometimes found in literature. Noteworthy is the relative contribution of alkaloids (25%), terpenes/terpenoids (21%), flavonoids (20%), and phenolic acids (12%), as shown in Figure 4A. Compounds with reduced expression were grouped as "others" (Figure 4A), except for the amino acid levodopa, which, due to its relevance, is emphasized. Again, quinone derivatives (e.g., hypericin, a naphtodianthrone and Z-ligustilide, a benzoquinone derivative; Figure 3) and the family of flavonoids are highlighted (Figure 4A) and detailed in Figure 4B due to their outstanding brain health-promoting potential.

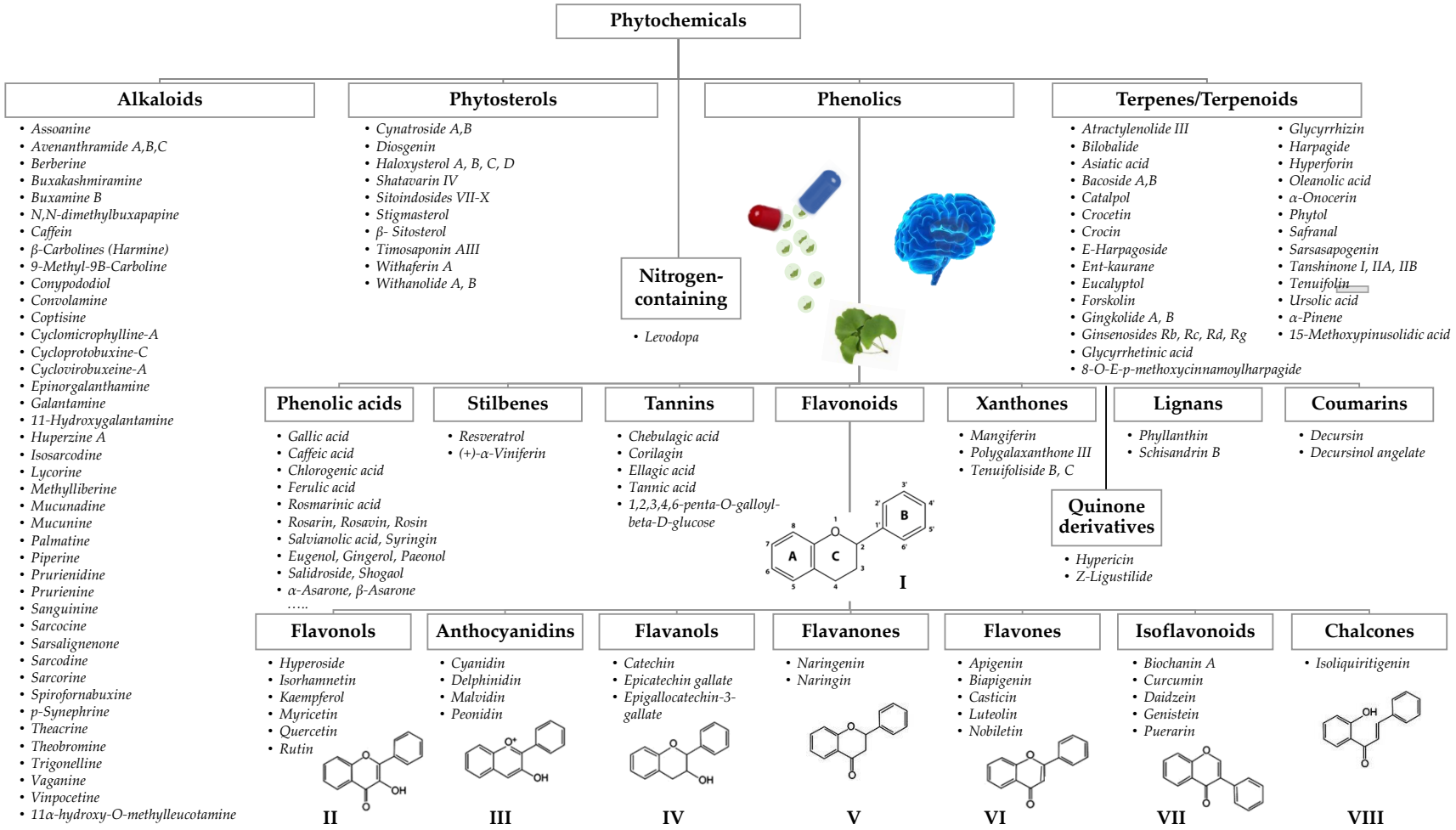


Figure 3. Classification of phytochemicals found in botanicals used in cognitive enhancement. For clarity, compounds, which due to the reduced expression were grouped as "others", are not represented; in a similar fashion, a shortened list of phenolic acids and only the aglycone part of flavonoids are shown. The structural backbone of flavonoids (**I**) comprises two phenyl rings (**A**,**B**) and a heterocyclic ring (**C**); the flavonoid family is classified into different groups, such as flavonols (**II**), anthocyanidins (**III**), flavanols (**IV**), flavanones (**V**), flavones (**VI**), isoflavonoids (**VII**), and chalcones (**VIII**), according to the degree of oxidation and substituent chemistry.

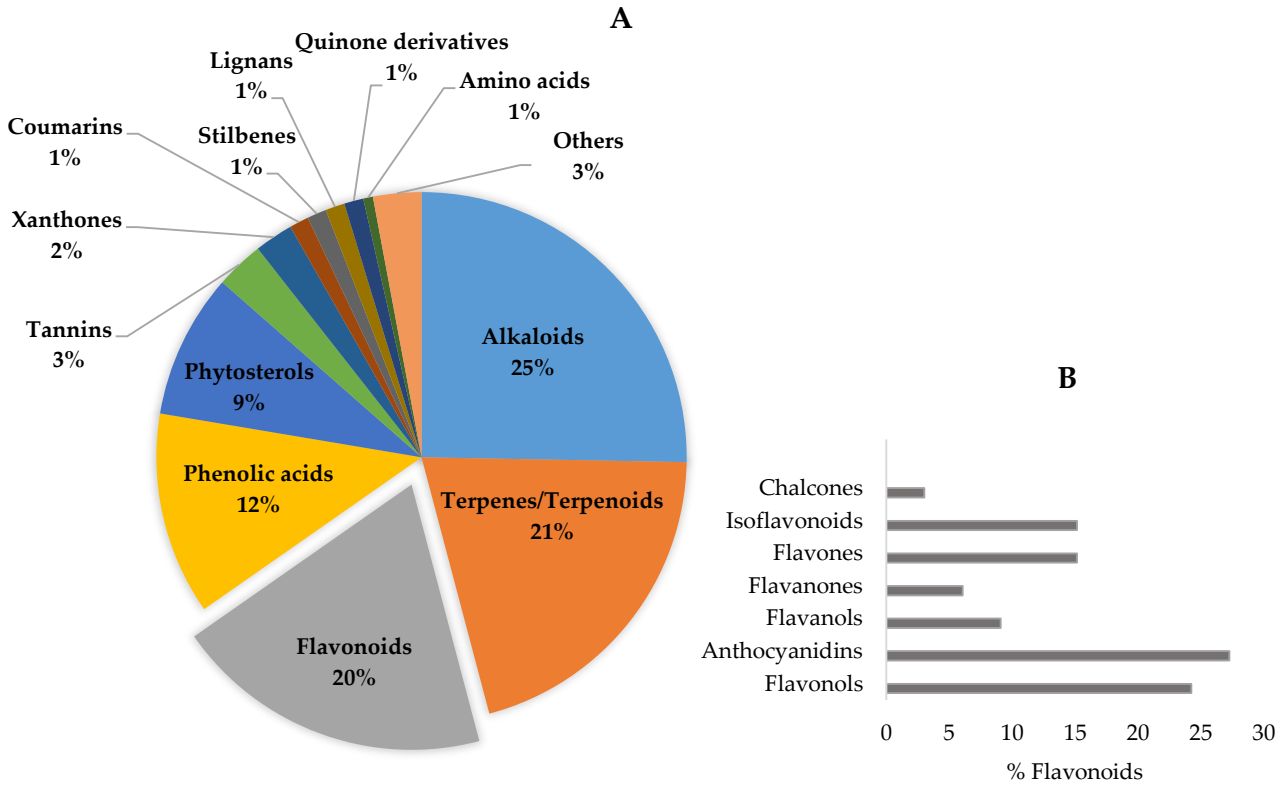


Figure 4. Phytochemicals in botanicals for cognitive enhancement (n = 170) by chemical class, evidencing the contribution of flavonoids (**A**). Phenolic compounds represent 42% of the total. On the inset (**B**), the relative percentage of the different types of flavonoids is presented.

Alkaloids are a heterogeneous group of naturally occurring chemical compounds, the majority of which contain nitrogen, usually in a heterocyclic ring [186]. Many are toxic and marketed as drugs. Reported actions, which may improve cognition, include antinociceptive, anticholinergic, sympathomimetic, anti-inflammatory, and antioxidant activities, as well as the ability to stimulate the central nervous system and cerebellum, have been extensively reviewed by Debnath et al. [187]. Many of the alkaloids found in our study show anticholinergic activity (56%), in line with reports by other authors [22,188].

Terpenes/terpenoids are the second most prevalent type of bioactives found (Figure 4A). Terpenes are water insoluble and made from single or multiple isoprene units joined together in different combinations to produce a variety of compounds [189]. Terpenoids derive from terpenes, usually by oxidation, and the terms are often used interchangeably. These are strong-smelling compounds and the major components of essential oils. Terpenes show psychoactive [190], anti-inflammatory, and antioxidant effects but some, in particular monoterpenes, are cytotoxic [191]. In plants, the majority of non-alkaloid AChE inhibitors are terpenoids; α-pinene from *Salvia lavandulaefolia* and tanshinones from *Salvia miltiorrhiza* are examples of such compounds [23].

Phenolic compounds represent 42% of the total bioactives identified (Figure 4A) and include simple phenols (e.g., phenolic acids—either hydroxycinnamic or hydroxybenzoic acids—and coumarins) and polyphenols (e.g., tannins, stilbenes, and flavonoids, which are the most representative group). As an example, decursin, a coumarin from *Angelica gigas*, has shown cholinesterase inhibitory activity [23].

Flavonoids show anti-inflammatory properties and reduce oxidative stress, among other direct roles on cognition [192]. Along with carotenoids (tetraterpenes; e.g., crocetin), flavonoids are responsible for the vivid colors of fruits and vegetables. They are found in plants in the aglycone form, polymerized (procyanidins), or linked to sugars in different po-

sitions, such as glycosides [15]. The general chemical structure of flavonoids is presented in Figure 3. A relation between structure and activity is possible to establish and, furthermore, the number and type of the sugar residues (glycone) impact oral bioavailability.

Naringenin (and its precursor naringin), is a flavanone, present in citrus and grapefruits, involved in different signaling pathways mainly related to neuroprotection [193]. Naringin attenuates inflammatory response (its potential to alleviate COVID-19 symptoms has recently been reported [194]), and it is believed to show anti-AChE activity as well [195]. The use of naringenin is, however, compromised due to poor oral bioavailability and accessibility to the brain [193].

Phytosterols are structurally related to cholesterol and encompass plant sterols and stanols, mainly present in vegetable oils, nuts, and cereals [196]. They have been linked to cholesterol lowering properties, but are also present in nootropic food supplements. Withaferin A and withanolides A and B, from *Withania somnifera*, are examples of neuroprotective sterols [165].

Our literature search revealed the presence in botanicals (e.g., *Mucuna pruriens*) of one amino acid well known for its activity in cognition: levodopa (L-DOPA), a precursor of dopamine with antiparkinsonian properties [12].

5. Interactions between Botanicals and Drugs

HDI are either pharmacokinetic, i.e., related to drug disposition, or pharmacodynamic, i.e., caused by changes in the drug's mechanism of action. Nonetheless, pharmacokinetic interactions are the most frequent. Only a brief summary is provided, since detailed characterization of drug targets is out of the scope of the present work.

5.1. Protein Targets as Key Points for Herb–Drug Interactions

Plants and herbal formulations contain several bioactive compounds, which increase the likelihood of HDI occurring with prescribed drugs, as reported in clinical practice [197]. On the other hand, drug's pharmacokinetic phases (absorption, distribution, metabolism, and elimination; ADME) require drug transformation and/or membrane crossing with the involvement of specific proteins, such as members of the CYP450 superfamily, and drug carriers.

HDI occurs when a botanical formulation interferes with the action of a co-administered drug. This can happen by action on several targets, such as enzymes, receptors, and transporters, causing changes in the drug's plasma profile, which can compromise therapeutic success or have fatal consequences, especially with narrow therapeutic margin drugs (HAM, as discussed before).

5.1.1. Cytochrome P450

CYP450 refers to a large family of enzymes responsible for the phase I metabolism of most drugs and other chemical compounds. CYP450 enzymes are grouped in families, with CYP1, CYP2, and CYP3 metabolizing the majority of xenobiotics. Although these enzymes can be found in several tissues, they are more abundant in the liver and small intestine. CYP3A, the most abundant, is implicated in many drug interactions [198].

Regarding the drugs evaluated in the present work, 70% are substrates of CYP3A (mainly CYP3A4, but also CYP3A5 and CYP3A7). Based on in vitro, in silico, and in vivo studies largely documented [199], it is fairly safe to conclude that these enzymes are easily vulnerable to modulation by several compounds, including phytoconstituents. Indeed, many of the bioactives isolated from herbs may act as substrates, inducers, or inhibitors of several CYP enzymes. Hence, it is of the utmost importance to identify the enzymes targeted by these bioactives.

5.1.2. Uridine Diphosphate-Glucuronosyltransferases

Drug metabolism may include phase II conjugation reactions mediated by enzymes of the uridine diphosphate-glucuronosyltransferases (UGT) family, using UDP-glucuronic acid as a co-substrate. This conjugation ultimately facilitates drug elimination in urine

or bile by increasing its hydrophilicity. UGT members are liable to undergo induction or inhibition by various xenobiotics, such as flavonoids, with a consequent change in the pharmacokinetic profile (e.g., elimination half-life) [200].

5.1.3. Drug Carriers

A large number of drugs and other xenobiotics are organic anions or cations, and their pharmacokinetic disposition depends on special carriers. Drug carriers or transporters are the largest group of membrane proteins in the human body, which ensure the passage of molecules across membranes. The transporters are divided into two main families: ABC and SLC. Although many of the members can perform bidirectional transport, mostly ABC transporters mediate the efflux of drugs, whereas SLC are involved in the substrate uptake and are responsible for the cellular entry of many clinically important drugs. Both are expressed in various tissues, such as in the intestine, where they modulate absorption, in the liver and kidney, influencing the metabolism and excretion of drugs.

The two main ABC efflux pumps are multidrug resistance protein 1 (MDR1; P-gP) and BCRP. Both proteins limit the entry of several drugs (especially BDDCS Classes II-IV) in the central nervous system and have the potential to alter drug pharmacokinetics. BCRP serves two major drug transport functions, conditioning the distribution of its substrates into several organs, such as the brain, and eliminating its substrates from excretory organs.

SLC includes two superfamilies responsible for the transport of organic anions and cations: SLC21A (current designation, solute carrier organic anion transporter family, SLCO), comprising the organic anion transporting polypeptides (OATP), and SLC22A, which contains the organic anion/cation transporters (OAT/OCT) [201–203].

Following recommendations of the International Transporter Consortium (ITC) on transporters with relevance in drug interactions [204], the main transporters with impact on drug ADME are P-gP, BCRP, OATP1B1/1B3/2B1, OCT1/2, SLC47A, MRP, and bile salt export pump (BSEP). Hence, these are more likely to be involved in herb–drug or drug–drug interactions.

5.1.4. Other Targets

In addition to drug carriers UGT and CYP450 oxidative enzymes, which have a significant influence on pharmacokinetics of administered drugs, other targets may also be involved in HDI through pharmacodynamic processes, such as COX and MAO enzymes and NMDA receptor.

COX1 and COX2 catalyze the formation of prostaglandins, thromboxane, and levuloglandins. COX enzymes are clinically important, because they are inhibited by non-steroidal anti-inflammatory drugs, such as Di, also used as antipyretic and antithrombotic [205]. Therefore, the bioactives under evaluation, which exert an inhibitory or inductor effect on this group of enzymes, have the potential to affect the therapeutic efficacy of Di, through a HDI that may increase the risk of side effects [206].

MAO (A and B) is a widely distributed mitochondrial enzyme with high expression levels in gastro-intestinal and hepatic, as well as neuronal, tissues. The enzyme catalyzes the oxidative deamination of a variety of monoamines, both endogenous and exogenous, and has major roles in metabolizing released neurotransmitters and in detoxification of a large variety of endogenous and exogenous amines [207]. Whenever drugs and bioactives, taken concomitantly, share MAO-A and/or MAO-B as targets (e.g., Se, as substrate and Pr, as inhibitor), an HDI may occur with impact on the deamination of monoamines and the metabolization of neurotransmitters. Especially, the upregulation of MAO-A prompted increments of 5-hydroxyindoleacetic acid/5-hydroxytryptamine ratio (5-HIAA/5-HT) and oxidative stress, leading to nuclear factor-κB activation, inflammation, and apoptosis [208].

NMDA receptor is a ligand of glutamate, the primary excitatory neurotransmitter in the human brain. It plays an integral role in synaptic plasticity, which is a neuronal mechanism believed to be the basis of memory formation. NMDA receptors also appear to have involvement in a process called excitotoxicity, which may play a role in the pathophys-

iology of a variety of diseases such as Alzheimer's disease. Many drugs inhibit NMDA receptors, including Me, an uncompetitive NMDA antagonist, which is used in the treatment of Alzheimer's and off-label for Huntington's diseases [209]. Bioactive compounds, which are antagonists and inhibit NMDA receptors, can mimic Me activity.

5.2. Drugs Used in Elderly Patients

Aging is associated with an increase in chronic pathologies and, consequently, an increase in medication. Indeed, the number of elderly people who regularly take five or more medications (polypharmacy) has been rising in several countries. In the 2017 study by Page et al. [210], it was found that 36.1% of Australians over 70 years of age were polymedicated with five or more medications, representing about one million people. In the USA, between 2013 and 2016, the value rose to 40.9%, for people older than 65 [211]. Polypharmacy increases the risk of drug related interactions, which leads to clinical complications with significant damage to the patient and financial loss.

Propranolol (Pr), alprazolam (Al), sertraline (Se), metformin (Mt), diclofenac (Di), atorvastatin (At), tadalafil (Ta), memantine (Me), piracetam (Pi), and clopidogrel (Cl) were selected as representatives of the pharmacotherapeutic classes commonly prescribed in this age group.

Pharmacokinetic and pharmacodynamic processes are influenced by the transport of drugs through membranes and, eventually, by metabolism [212]. Crossing of membranes can occur either by passive diffusion or by active or facilitated transport mechanisms involving transporters. Metabolism, on the other hand, results from the action of enzymes. Transporters and enzymes are found essentially in the intestinal epithelium, liver, and kidneys, and can exist in many other tissues, such as the brain and heart. Changes in the expression and/or activity of transporters and enzymes can result in modification of the disposition of drugs with a compromise in effectiveness and safety [213].

Detailed knowledge of drug pharmacokinetics, especially of the involvement of targets such as enzymes, transporters, and receptors, allows understanding, anticipation, and prevention of interactions with other xenobiotics, such as phytochemicals [214]. Nevertheless, not all interactions may have clinical relevance, and to assess the real significance of each enzyme or transporter can be a lengthy and expensive process [215], hence the need for a simplified method to define whether enzymes and transporters are potentially important in the clinic [216].

BDDCS was developed to predict drug disposition and potential drug–drug interactions, mainly in the intestine and the liver [40]. The system classifies drugs based on the criteria of solubility and permeability, in order to establish the relevance of enzymes and transporters in determining drug disposition. For example, according to BDCSS, At is a Class II drug (exhibiting poor solubility and extensive metabolism), which may potentially exhibit an interaction with inhibitors of hepatic uptake transporters. In fact, as indicated in Table 2, the disposition of At involves several CYP enzymes and transporters.

Drugs in Class I and II have a disposition greatly influenced by metabolism (>70%), whereas classes III and IV drugs are mainly eliminated unchanged [43]. In short, these authors hypothesize that Class I drugs are very affected by enzymatic changes, but not by changes in transporters. On the other hand, Class II drugs can undergo major changes in disposition due to enzymatic and transport modifications. Class III drugs are unlikely to be affected by metabolic changes, but are susceptible to changes in absorption or efflux transport in various tissues. Finally, Class IV drugs (not represented in the drugs selected amongst the most prescribed, probably due to the fact that they represent about 5% of the approved drugs [38]) are substrate for P-gP and undergo extensive presystemic metabolization. Noteworthy is that BDDCS only allows for predictions, i.e., there will always be drugs with unanticipated behavior.

Table 2. Characteristics of the drugs used in the study. The main enzymatic targets (substrates, inhibitors, and inducers) are specified.

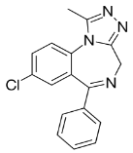
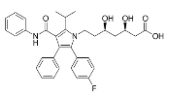
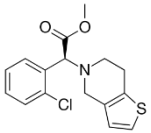
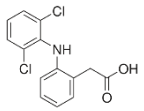
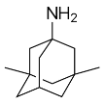
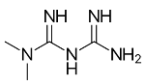
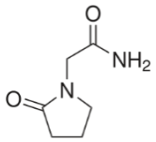
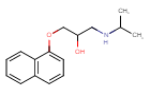
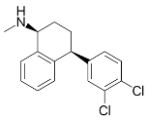
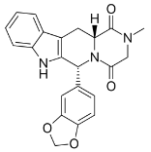
Drug Name and Chemical Structure	HAM	ATC Class (Code)	BDDCS Class	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
													BCRP	MRP	Pgp		PEPT; OCT; OAT, MATE, OATP		
Alprazolam 	Y	Benzodiazepine derivatives (N05BA12)	I	-	-	-	-	$3A4^{S\downarrow}$ $3A5^{S}$ $3A7^{S}$ $2C9^{S}$ $2C19^{S}$	-	-	-	-	-	-	-	-	-	-	[217–219]
Atorvastatin 	Y	HMG CoA reductase inhibitors (C10AA05)	II	-	-	S	-	$3A4^{S\uparrow}$ $3A5^{S}$ $3A7^{S}$ $2B6^{\uparrow}$ $2C8^{S\downarrow}$ $2C9^{\uparrow}$ $2C19^{\downarrow}$ $2D6^{\downarrow}$	-	$\downarrow$	-	-	S	1^{S} 2^{S} 4^{S} 5^{S}	S$\downarrow$	-	$21A3^{S}$ $21A6^{S\downarrow}$ $21A8^{S}$ $21A9^{S}$	$1A1^{S}$ $1A3^{S}$	[218–222]
Clopidogrel 	Y	Platelet aggregation inhibitors excl. heparin (B01AC04)	II	-	-	-	-	$1A2^{S}$ $3A4^{S}$ $3A5^{S}$ $2B6^{S\downarrow}$ $2C8^{\downarrow}$ $2C9^{S\downarrow}$ $2C19^{S}$	-	-	-	-	$\downarrow$	-	S	-	$21A8^{S}$ $22A1^{\downarrow}22A2^{\downarrow}$	-	[218,219, 223–225]
Diclofenac 	Y	Anti-inflammatory agents, non-steroids (S01BC03)	II	$\uparrow$	-	S	$1^{\downarrow}$ $2^{\downarrow}$	$1A2^{S}$ $3A4^{S\downarrow}$ $2B6^{S}$ $2C8^{S}$ $2C9^{S\downarrow}$ $2C18^{S}$ $2C19^{S}$ $2E1^{\downarrow}$	-	-	-	-	S	$1^{\downarrow}$ $4^{\downarrow}$	$\uparrow$	$\downarrow$	$21A6^{\downarrow}$ $21A8^{S}$ $21A14^{\downarrow}$ $22A11^{\downarrow}$ $22A6^{\downarrow}$ $22A8^{\downarrow}$	$1A3^{s}$ $1A9^{s}$ $2B4^{s}$ $2B7^{s}$	[218,219, 226,227]
Memantine 	N	Other anti-dementia drugs (N06DX01)	III	-	-	-	-	$2B6^{\downarrow}$ $2C19^{\downarrow}$	-	-	-	ANT	-	-	-	-	$15A1^{\downarrow}$ $15A2^{\downarrow}$ $22A8^{\downarrow}$ $22A1^{\downarrow}$ $22A2^{S\downarrow}$ $22A4^{S}$ $47A1^{S}$	-	[218,222, 228–231]
Metformin 	Y	Biguanides (A10BA02)	III		$\uparrow$	-	-	-	$\uparrow$	-	-	-	S	-	-	-	$22A1^{S}$ $22A2^{S\downarrow}$ $22A3^{S}$ $47A1^{S}$ $47A2^{S}$	-	[218,222, 232–235]

Table 2. *Cont.*

Drug Name and Chemical Structure	HAM	ATC Class (Code)	BDDCS Class	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
													BCRP	MRP	Pgp		PEPT; OCT; OAT, MATE, OATP		
Piracetam 	N	Other psychostimulants and nootropics (N06BX03)	III	-	-	-	-	-	-	-	-	-	-	-	0	-	-	-	[236]
Propranolol 	Y	β-blocking agents, non-selective (C07AA05)	I	-	-	-	-	1A1$^{\downarrow}$ 1A2^{S} 3A4^{S} 3A5^{S} 3A7^{S} 2C19^{S} 2D6$^{S\downarrow}$	-	-	A$^{\downarrow}$	-	-	-	S	-	22A2$^{\downarrow}$	-	[218,237–240]
Sertraline 	N	Selective serotonin reuptake inhibitors (N06AB06)	I	-	-	-	-	1A2$^{\downarrow}$ 3A4^{S} 2B6$^{S\downarrow}$ 2C9$^{S\downarrow}$ 2C19$^{S\downarrow}$ 2D6$^{S\downarrow}$ 2E1^{S}	-	-	A^{S} B^{S}	-	S	-	S$\downarrow$	-	6A2$^{\downarrow}$ 6A3$^{\downarrow S}$ 6A4$^{\downarrow S}$ 36A1$^{\downarrow}$	1A3^{S} 1A6^{S} 2B4^{S} 2B7^{S}	[217–219,241–243]
Tadalafil 	N	Drugs used in erectile dysfunction (G04BE08)	II	-	-	-	-	3A4^{S} 3A5^{S}	-	-	-	-	-	-	S	-	-	-	[218,219,244]

$^{\downarrow}$—target inhibition; $^{\uparrow}$—target induction; ^{s}—drug is substrate of the target; ^{ANT}—drug is a target antagonist; ^{0}—No effect; (¯)—Not reported; ABC—ATP-binding cassette; ALOX5—Arachidonate 5-lipoxygenase; AMPK—AMP-activated protein kinase; BCRP—Breast cancer resistance protein; BSEP—Bile salt export pump (ABCB11); COX—Cyclooxygenase; CYP—Cytochrome P450; GLP-1—Glucagon-like peptide-1; HMGCoAR—3-hydroxy-3-methyl-glutaril-CoA reductase; MAO—Monoamine Oxidase; MATE—Multi-antimicrobial extrusion protein; MRP—Multidrug resistance-associated protein; NMDA—*N*-methyl-D-aspartate; OAT—Organic anion transporter; OATP—Organic-anioN-transporting polypeptide; OCT—Organic cation transport; P-gP—Glycoprotein P; UGT—Uridine diphosphate-glucuronosyltransferase; PLA2G2A—Phospholipase A2 Group IIA; SLC—Solute Carriers (15A/PEPT; 22A1-3/OCT1-3; 22A4/OCTN1; 22A6,8,11/OAT1,3,4; 47A/MATE; 21A3/OATP1A2; 21A6,8/OATP1B1,3; 21A9/OATP2B1; 21A14/OATP1C1); PEPT—Peptide transporter. HAM—High-Alert Medications [44]; Y—yes; *N*—No; ATC—Anatomical Therapeutic Chemical [36]; BDDCS—Biopharmaceutics Drug Disposition Classification System [37–43].

The clinical significance of changes in drug disposition is also dependent on the type of drug. High-Alert Medications (HAM) bear a significant risk of causing harm to patients if errors or interactions occur, thus requiring extra caution. These drugs present narrow therapeutic indexes, and therefore, small changes in drug blood levels can result in critical, even life-threatening events.

Table 2 summarizes the different targets involved in the metabolism, transport, and action of the selected drugs and includes their BDDCS and HAM classifications. Details of the targets involved in the pharmacokinetics of the 10 drugs studied can be found in the Supplementary Material.

Generally, drugs act as substrates of enzymes and drug carriers. The top six targets are four enzymes of CYP P450 (CYP3A4, CYP3A5, CYP2C9, and CYP2C19) and two efflux pumps from the ABC transporters family (P-gP and breast cancer resistance protein-BCRP). CYP3A4 metabolizes all the Class I and Class II drugs (Pr, Se, Al, At, Cl, Di, and Ta); CYP3A5 is involved in the metabolism of Pr, Al, At, Ta, and Cl and CYP2C19 metabolizes Pr, Al, Se, Di, and Cl, whereas it is inhibited by At and Me; CYP2C9 is induced by At and metabolizes Se, Al, Di, and Cl; with respect to transporters, Pr, Se, At, Ta, and Cl are substrates of P-glycoprotein, and Di induces its expression. Finally, Se, Mt, Di, and At are substrates of BCRP transporter, which is inhibited by Cl. Other enzymes are also inhibited by the drugs, such as CYP2B6 (Se, Me, and Cl) and CYP2D6 (Pr, Se, and At).

Regarding uptake transporters, such as the solute carrier family, there are several members involved in drug disposition. For example, organic-anioN-transporting polypeptide (OATP) OATP1B3 (SLC21A8) is an uptake transporter exclusively expressed in the liver on the basolateral side of hepatocytes. Together with OATP1B1 (SLC21A6), it is responsible for the hepatic uptake of some important drug classes, including the BDDCS Class II, At, Cl, and Di, thus mediating drug interactions.

SLC22A2 (organic cation transporter 2-OCT2) facilitates the transport of cationic compounds, including many drugs such as Mt. SLC22A2 is inhibited by four of the 10 drugs studied (Pr, Mt, Me, and Cl).

Di, Se, and At are the most promiscuous drugs, being related to 29 (14, as a substrate), 26 (16, as a substrate), and 26 (17, as a substrate) targets, respectively (Figure 5). In addition, At and Di are HAM and are classified as Class II drugs, making their disposition more likely to depend on both enzymes and transporters. Thus, these drugs have a higher risk of clinically relevant interactions with bioactive agents, which share the same targets. On the other hand, Pi is the drug with the lowest probability of HDI, since it does not share any target with the phytochemicals under study.

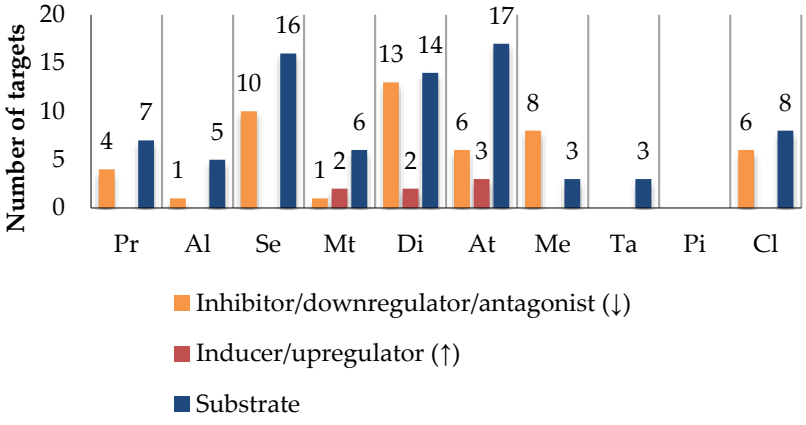


Figure 5. Effect of drugs on targets. The number of shared targets between drugs and bioactives was taken as a measure of potential interaction. Propranolol (Pr), alprazolam (Al), sertraline (Se), metformin (Mt), diclofenac (Di), atorvastatin (At), tadalafil (Ta), memantine (Me), piracetam (Pi), and clopidogrel (Cl).

5.3. Target Modulation by Bioactives

Given the importance of the above mentioned entities as potential targets for HDI and considering the fact that all of them are somehow involved with the drugs under study, a literature review was undertaken, in order to characterize the relationship between each of the bioactives isolated from the plants used for cognitive enhancement and neuroprotection and those targets. A total of 55 targets, including drug carriers, receptors (e.g., NMDA), UGT, CYP, and other enzymes (e.g., MAO, COX, ALOX5, 3-hydroxy-3-methyl-glutaril-CoA reductase-HMGCoAR) were analyzed, and the results are displayed on Table 3.

Bioactives interfere in the targets, mainly by inhibition (Figure 6), and the six most frequently inhibited are CYP3A4 (n = 67; 39%), P-gP (n = 51; 30%), COX2 (n = 48; 28%), CYP2C9 (n = 47; 28%) and CYP1A2 (n = 45; 26%), and BCRP (n = 30; 18%). These are of particular importance for the pharmacokinetic profile (or pharmacodynamic in case of COX2) of multiple drugs, as it was also observed for the majority of the drugs under study. Moreover, P-gP and BCRP are amongst the most relevant transporters for drug interactions [204], and CYP enzymes, particularly 3A and 2C families, play a major role in the disposition of many drugs and have been associated with HDI [245].

The bioactives responsible for the inhibition of the six most affected targets are shown in Figure 7. The location of the targets is purely indicative, since they are expressed in several other tissues.

By comparison of the type of interaction that drugs and bioactives have on the 55 targets analyzed, a high degree of overlap is evident, with drugs acting mostly as substrates of enzymes and transporters, whereas bioactives act as inhibitors of the same targets. As an example, from the top six targets of drugs and bioactives, four are shared: two enzymes of CYP P450 (CYP3A4 and CYP2C9) and two efflux pumps from the ABC transporter family (P-gP and BCRP). Hence, whenever drugs and herbal formulations are associated, the modulation that bioactive compounds can exert on targets may lead to therapeutic failure or toxicity.

The number of targets affected by the herbal bioactives largely depends on the type of the latter. On the one hand, one fourth of the 170 bioactives studied did not show any influence in any of the 55 targets (see Supplementary Material). On the other hand, some have the capacity to modulate several different targets. Naringenin, for example, modulates 20 targets (13 inhibitions and seven inductions), while epigallocatechin-3-gallate (EGCG) and quercetin both affect a total of 19 targets, mainly by inhibition. The higher the number of targets affected, the higher the potential for interaction.

Table 3. Characterization of the identified phytochemicals in terms of origin and main enzymatic targets (substrates, inhibitors, and inducers).

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
11-Angeloylsenkyunolide F *	*A. sinensis*	—	—	—	—	3A4$^{\uparrow}$ 2D6$^{\uparrow}$	—	—	—	—	—	—	—	—	—	—	[246]
Apigenin *	*M. chamomilla* *M. officinalis* *P. emblica* *S. costus*	—	—	—	—	1A2$^{\downarrow}$ 2C9$^{\downarrow}$ 2C19$^{\downarrow}$ 3A4$^{\downarrow}$	—	—	—	—	↓	—	↓	—	21A6$^{\downarrow}$ 21A8$^{\downarrow}$ 21A9$^{\downarrow}$ 22A8$^{\downarrow}$ 22A11$^{\downarrow}$ 22A4$^{\downarrow}$	1A1$^{\uparrow}$	[200,247–253]
α-Asarone	*A. calamus* *A. gramineus*	—	—	—	2$^{\downarrow}$	1A1$^{\downarrow}$ 3A4$^{\downarrow}$ 2B6$^{\downarrow}$ 2C8$^{\downarrow}$ 2C9$^{\downarrow}$ 2C19$^{\downarrow}$ 2D6$^{\downarrow}$ 2E1$^{\downarrow}$	—	↓	A$^{\downarrow}$ B$^{\downarrow}$	Ant	—	—	↓	—	—	—	[254–260]
β-Asarone	*A. calamus* *A. gramineus* *R. acori*	—	↑	—	2$^{\downarrow}$	3A4$^{\downarrow}$	—	—	A$^{\downarrow}$ B$^{\downarrow}$	—	—	—	↓	—	—	—	[255,259,261]
Asiatic acid *	*C. asiatica*	—	—	—	—	3A4$^{\downarrow}$ 2D6$^{\downarrow}$ 2C9$^{\downarrow}$	—	—	—	—	—	—	S	—	—	—	[262–265]
Assoanine	*N. assoanus*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Atractylenolide III *	*A. japonica* *A. lancea*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2B7$^{\downarrow}$	[266]
Avenanthramide A *	*A. sativa*	—	—	—	2$^{\downarrow}$	—	—	—	—	—	—	—	↓	—	—	—	[267,268]
Avenanthramide B *	*A. sativa*	—	—	—	2$^{\downarrow}$	—	—	—	—	—	—	—	↓	—	—	—	[268]
Avenanthramide C *	*A. sativa*	—	↑	—	2$^{\downarrow}$	—	—	—	—	—	—	—	↓	—	—	—	[268,269]
Bacoside A * and B *	*B. monnieri*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{\downarrow}$ 2C9$^{\downarrow}$ 2C19$^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	[270]
N-Acetyl Benzylamine *	*L. meyenii*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
N-Benzylhexadecanamide *	*L. meyenii*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Berberine *	*C. chinensis* *C. japonica*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{S\downarrow}$ 2C9$^{\downarrow}$ 2D6$^{\downarrow}$	—	—	—	—	↓	—	↓↑^{S}	—	21A8^{S}	—	[271–277]
Biapigenin *	*H. perforatum*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{\downarrow}$ 2C9$^{\downarrow}$ 2D6$^{\downarrow}$	—	—	A$^{\downarrow}$	Ant	—	—	S	—	—	—	[124,200,278,279]
Bilobalide *	*G. biloba*	—	—	—	—	1A1$^{\uparrow}$ 1A2$^{\uparrow}$ 3A4$^{\uparrow}$ 2B6$^{\uparrow}$ 2C9$^{\uparrow}$ 2E1$^{\uparrow}$	—	—	—	↓	—	—	—	↓	6A2$^{\downarrow}$ 22A6$^{\downarrow}$ 22A8$^{\downarrow}$	—	[218,280–282]

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Biochanin A *	*T. pratense*	—	—	—	2$^{\downarrow}$	3A4$^{\downarrow}$	—	—	B$^{\downarrow}$	$\downarrow$	$\downarrow$S	—	$\downarrow$	—	21A6$^{\downarrow}$ 21A8$^{\downarrow}$	—	[245,248,283–287]
Buxakashmiramine	*B. papillosa*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Buxamine B	*B. hyrcana*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Caffeic acid *	*C. pluricaulis* *F. vulgare* *M. chamomilla* *M. officinalis* *R. officinalis* *V. angustifolium*	—	—	—	1,2$^{\downarrow}$	1A1$^{\downarrow}$ 3A4$^{\downarrow}$ 2C9$^{\downarrow}$ 2C19$^{\downarrow}$ 2D6$^{\downarrow}$	—	—	—	—	$\uparrow$	—	—	$\downarrow$	—	—	[288–291]
Caffein *	*C. arabica* *I. paraguariensis* *P. cupana* *T. cacao* *C. sinensis*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{\downarrow}$	—	—	—	—	$\downarrow$	—	—	—	—	—	[292,293]
β-Carbolines (Harmine) *	*L. meyenii* *M. pruriens* *P. harmala*	—	—	—	—	1A1$^{\downarrow}$ 1A2$^{\downarrow}$ 2C9$^{\downarrow}$ 2C19$^{\downarrow}$ 2D6$^{\downarrow}$ 2E1$^{\downarrow}$	—	—	A$^{\downarrow}$ B$^{\downarrow}$	—	$\downarrow$	2$^{\uparrow S}$	—	—	—	—	[124,126,294–296]
9-Methyl-9B-Carboline *	*P. harmala*	—	—	—	—	3A4$^{\downarrow}$ 2D6$^{S\downarrow}$	—	—	A$^{\downarrow}$ B$^{\downarrow}$	—	—	—	0	—	—	—	[127,296,297]
Casticin *	*V. agnus-castus*	—	—	—	—	3A4$^{\downarrow}$ 2C9$^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	[298]
Catalpol *	*R. glutinosa*	—	—	—	—	3A4$^{\uparrow\downarrow}$ 2C9$^{\uparrow\downarrow}$ 2E1$^{\downarrow}$	—	$\downarrow$	—	—	—	—	$\uparrow$	—	—	—	[292,299–301]
Catechin *	*C. rotundus* *L. bicolor* *M. chamomilla* *T. cacao*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{\downarrow}$ 2C9$^{\downarrow}$	—	—	—	—	—	—	$\downarrow$	—	47A1$^{\downarrow}$ 47A2$^{\downarrow}$ 22A1$^{\downarrow}$ 22A2$^{\downarrow}$ 21A3$^{\downarrow}$ 21A6$^{\downarrow}$	—	[302,303]
Chebulagic acid *	*T. chebula* *P. emblica*	—	—	—	2$^{\downarrow}$	—	—	—	—	—	—	—	$\downarrow$	—	—	—	[304,305]
Chlorogenic acid *	*F. vulgare* *H. perforatum* *I. paraguariensis* *M. chamomilla* *M. lucida* *R. officinalis*	—	$\uparrow$	—	2$^{\downarrow}$	1A2$^{\downarrow}$ 3A4^{o} 2E1$^{\downarrow}$	—	$\downarrow$	B$^{\downarrow}$	—	—	—	—	$\downarrow$	22A6$^{\downarrow}$ 22A8$^{\downarrow}$	—	[306–311]
1,8-Cineole (eucalyptol) *	*F. vulgare* *S. lavandulaefolia* *R. officinalis*	—	—	—	—	3A4^{S}	—	—	—	—	—	—	S	—	—	—	[312]
Cinnamaldehyde *	*C. wilsonii*	—	$\uparrow$	—	2$^{\downarrow}$	1A2$^{\downarrow}$ 2E1$^{\downarrow}$	—	—	B^{S}	Ant	—	—	$\downarrow$	—	—	—	[75,313–317]
Coniferyl ferulate *	*A. sinensis*	—	—	—	—	3A4$^{\uparrow}$ 2D6$^{\uparrow}$	—	—	—	—	—	—	$\downarrow$	—	—	—	[246,318]
Convolamine *	*C. pluricaulis*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Conypododiol	*A. adscendens*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Coptisine	*C. chinensis*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{\uparrow}$ 2C9$^{\uparrow}$ 2D6$^{\downarrow}$	—	—	A$^{\downarrow}$ B$^{\downarrow}$	—	—	—	S$^{\uparrow}$	—	22A1$^{S\downarrow}$ 22A2$^{S\downarrow}$	—	[272–274,319,320]
p-Coumaric acid *	*B. rufescens* *M. lucida*	—	↑	—	2$^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	—	[321,322]
Corilagin *	*T. chebula* *P. emblica*	—	—	—	—	—	—	—	—	—	—	2$^{\uparrow}$	—	—	—	2B4$^{\uparrow}$	[323]
Crocetin *	*C. sativus*	—	—	—	—	—	—	—	—	Ant	—	1$^{\downarrow}$ 2$^{\downarrow}$	S	—	—	—	[324–326]
Crocin *	*C. sativus*	—	—	—	1$^{\downarrow}$ 2$^{\downarrow}$	3A4$^{\downarrow}$ 3A5$^{\downarrow}$ 3A7$^{\downarrow}$ 2B6$^{\downarrow}$	—	—	A$^{\downarrow}$ B$^{\downarrow}$	—	—	1$^{\downarrow}$ 2$^{\downarrow}$	↓	—	—	—	[327–329]
Curcumin *	*C. longa*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{\downarrow}$ 2B6$^{\downarrow}$ 2C9$^{\downarrow}$ 2D6$^{\downarrow}$	—	—	—	—	↑↓	1$^{\downarrow}$ 2$^{\downarrow}$	↓	—	21A6$^{\downarrow}$ 21A8$^{\downarrow}$	1A1$^{\downarrow}$ 1A6$^{\downarrow}$ 1A9$^{\downarrow}$	[247,330–339]
Cyanidin-3-*O*-β-arabinose *	*V. angustifolium*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	[340]
Cyanidin-3-*O*-β-galactoside *	*V. angustifolium*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{\downarrow}$ 2C9$^{\downarrow}$	—	—	—	—	S	—	0	—	—	—	[341,342]
Cyanidin-3-*O*-β-glucoside *	*E. amoenum* *V. angustifolium* *V. uliginosum L.*	—	—	—	2$^{\uparrow}$	3A4$^{\downarrow}$ 2C9$^{\downarrow}$	—	—	—	—	S	—	—	↓	21A9$^{\downarrow}$	—	[341,343–345]
Cyclomicrophylline A	*B. papillosa*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cycloprotobuxine-C	*B. papillosa*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cyclovirobuxeine-A	*B. papillosa*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cynatroside A	*C. atratum*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Cynatroside B	*C. atratum*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Daidzein *	*L. bicolor* *M. lucida* *P. lobata*	—	—	—	—	1A1^{S} 1A2^{S} 3A4$^{\downarrow}$	—	—	—	—	↓S	1$^{\uparrow}$	↑	—	—	1A1^{S} 1A9^{S}	[245,285,346–349]
Decursin *	*A. gigas*	—	—	—	—	1A1$^{\downarrow}$ 1A2$^{\downarrow}$	—	—	—	—	—	2$^{\downarrow}$	↓	—	—	—	[247,350]
Decursinol angelate *	*A. gigas*	—	—	—	—	1A1$^{\downarrow}$ 1A2$^{\downarrow}$ 3A4^{S} 2C19^{S}	—	—	—	—	—	—	S	—	—	—	[350–352]
Delphinidin *	*V. uliginosum L.*	—	—	—	—	3A4$^{\downarrow}$ 2B6$^{\downarrow}$ 2C9$^{\downarrow}$	—	—	—	—	↓	—	—	—	21A8$^{\downarrow}$	—	[341,344,353]
Delphinidin-3-*O*-β-galactoside *	*V. angustifolium*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Diosgenin *	*D. polystachya* *D. oppositifolia* *T. foenum-graecum*	—	—	—	$2^{\uparrow}$	$3A4^{\downarrow}$	—	—	—	—	—	—	S	—	—	—	[354–356]
Ellagic acid *	*T. chebula* *P. emblica*	—	—	—	—	$1A1^{\uparrow\downarrow}$ $2B6^{\downarrow}$ $2E1^{\downarrow}$	—	—	—	—	↓	—	S	—	$22A6^{\downarrow}$ $22A11^{\downarrow}$	—	[357–362]
Ent-kaurane *	*C. tonkinensis*	—	↑	—	$2^{\downarrow}$	—	—	—	—	—	—	—	↓	—	—	—	[363–365]
Epicatechin gallate (ECG) *	*C. sinensis*	—	—	—	—	$1A1^{\downarrow}$ $1A2^{\downarrow}$ $3A4^{\downarrow}$	—	—	—	—	—	—	↓	—	$21A6^{S\downarrow}$ $21A8^{\downarrow}$	—	[366–369]
Epigallocatechin-3-gallate (EGCG) *	*C. sinensis*	—	—	—	—	$1A1^{\downarrow}$ $1A2^{\downarrow}$ $3A4^{\downarrow}$ $3A5^{\downarrow}$ $2B6^{\downarrow}$ $2C8^{\downarrow}$ $2C9^{\downarrow}$ $2C19^{\downarrow}$ $2D6^{\downarrow}$ $2E1^{\downarrow}$	—	—	—	—	↓	—	S↓	—	$21A6^{\downarrow}$ $21A8^{S\downarrow}$ $21A9^{\downarrow}$ $22A1^{\downarrow}$ $22A2^{\downarrow}$ $47A1^{\downarrow}$ $47A2^{\downarrow}$	—	[248,302,303,345,367,370–376]
Epinorgalantamine	*N. confusus* *G. woronowii*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Eugenol *	*C. wilsonii* *R. acori* *R. officinalis*	—	↓	—	$2^{\downarrow}$	$1A1^{\downarrow}$ $2E1^{S}$	—	0	$A^{\downarrow}$	↓	—	—	$0\downarrow$	—	—	$1A1^{\uparrow}$	[77,247,377–383]
Ferulic acid *	*A. sinensis* *B. rufescens*	—	—	—	—	$1A1^{\uparrow}$ $1A2^{\uparrow S}$ $3A4^{\uparrow S}$ $2B6^{\uparrow S}$ $2C8^{\uparrow S}$ $2C9^{\uparrow S}$ $2C19^{\uparrow S}$ $2D6^{\uparrow S}$	—	—	$B^{\downarrow}$	Ant	—	—	↓	—	—	$1A1^{S}$ $2B7^{S}$	[246,384–387]
Forskolin *	*C. forskohlii*	—	↓	—	$2^{\downarrow}$	$3A4^{S\uparrow}$ $2C^{\uparrow}$ $2B6^{\uparrow}$	↑	—	—	↑	—	—	s↓	—	—	—	[388–397]
Galantamine *	*G. nivalis* *G. woronowii* *L. radiata* *N. confusus* *P. illyricum*	—	—	—	—	$3A4^{S\,0}$ $2D6^{S}$	—	—	—	—	—	—	↓	—	—	$1A1^{S}$	[398–402]
11-Hydroxy Galantamine *	*N. poeticus*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Gallic acid *	*M. pruriens* *P. emblica* *T. chebula*	—	—	—	$2^{\downarrow}$	$3A4^{\downarrow}$ $2D6^{\downarrow}$	—	—	$A^{\downarrow}$	—	—	—	↓	—	$21A8^{\downarrow}$	$2B7^{\uparrow}$	[403–409]
Genistein *	*L. bicolor* *M. lucida* *M. pruriens*	—	↑	—	$2^{\downarrow}$	$1A1^{\downarrow}$ $1A2^{\downarrow S}$ $3A4^{\uparrow}$ $2C8^{\downarrow}$ $2C9^{\downarrow}$ $2D6^{\downarrow}$	—	↓	$A^{\downarrow}$ $B^{\downarrow}$	↓	$\downarrow S$	$1^{\downarrow}$ $2^{\downarrow S}$	↓	—	$21A6^{\downarrow S}$	—	[218,285,369,374,409–415]
Gingerol *	*A. melegueta* *Z. officinale Rosc.*	—	—	—	—	$3A4^{\downarrow}$ $2C9^{\downarrow}$ $2C19^{\downarrow}$	—	—	—	—	—	—	↓	—	—	—	[416,417]

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Ginkgolide A *	*G. biloba*	—	—	—	$2^{\downarrow}$	$3A4^{\downarrow}$ $2C9^{\downarrow}$	—	—	—	↓	—	—	↑	↓	$6A2^{\downarrow}$ $22A6^{\downarrow}$ $22A8^{\downarrow}$	—	[218,281,418–420]
Ginkgolide B *	*G. biloba*	—	—	—	—	$3A4^{\downarrow}$ $2C9^{\downarrow}$	—	—	—	—	—	—	↑	↓	$6A2^{\downarrow}$ $22A6^{\downarrow}$ $22A8^{\downarrow}$	—	[218,281,418]
Ginsenoside Rb *	*P. ginseng*	—	—	—	—	$1A1^{\uparrow}$ $1A2^{\downarrow}$ $3A4^{\downarrow}$ $2C9^{\downarrow}$	—	—	—	—	↓	—	—	—	$21A8^{S}$	—	[421–423]
Ginsenoside Rc *	*P. ginseng*	—	—	—	—	$3A4^{\downarrow}$ $2C9^{\downarrow}$	—	—	—	—	—	—	—	—	$21A8^{S}$	—	[421,423]
Ginsenoside Rd *	*P. ginseng*	—	—	—	—	$3A4^{\downarrow}$ $2C9^{\downarrow}$ $2C19^{\downarrow}$ $2D6^{\downarrow}$	—	—	—	—	↓	—	—	—	$21A8^{S}$	—	[421,423]
Ginsenoside Rg *	*P. ginseng*	—	—	—	—	$1A1^{\uparrow}$ $1A2^{\downarrow}$ $3A4^{\downarrow}$ $2C9^{\downarrow}$ $2D6^{\downarrow}$	—	—	—	—	S	—	—	—	$21A8^{S}$	—	[421–423]
1,2,3,4,6-Penta-*O*-galloyl-β-D-glucose *	*T. chebula*	—	—	—	$2^{\downarrow}$	—	—	—	—	—	—	—	↓	—	—	—	[424,425]
Glycyrrhetinic acid *	*G. glabra*	—	—	—	—	—	—	—	—	—	—	—	—	—	$21A9^{\downarrow}$	—	[426]
Glycyrrhizin *	*G. glabra*	—	—	S	—	$3A4^{\downarrow}$ $2D6^{\downarrow}$	—	—	—	—	—	—	↑↓	—	$21A8^{\downarrow}$	—	[247,257,427–429]
Haloxysterol A *, B *, C *, D *	*H. recurvum*	—	—	—	$2^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	—	[430]
Harpagide *	*S. buergeriana*	—	—	—	—	$3A4^{0}$	—	—	—	—	—	—	—	—	—	—	[431]
8-*O*-E-p-Methoxy Cinnamoyl Harpagide	*S. buergeriana*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
E-Harpagoside *	*S. buergeriana*	—	—	—	$1^{\downarrow 0}$ $2^{\downarrow 0}$	$3A4^{0}$	—	—	—	—	—	—	↓	—	—	—	[431–434]
Huperzine A *	*H. serrata*	—	—	—	—	$1A2^{\uparrow}$ $3A4^{\uparrow 0}$	—	—	—	—	—	—	S	—	—	—	[435–437]
Hyperforin *	*H. perforatum*	↓	—	—	$1^{\downarrow}$ 2^{0}	$2D6^{\downarrow 0}$ $2C9^{\downarrow}$ $3A4^{\downarrow}$ $3A5^{\downarrow}$ $1A2^{\downarrow}$ $2C19^{\downarrow}$	—	—	A^{0}	Ant	↓	$2^{\uparrow}$	↑↓	—	$21A6^{\downarrow}$ $21A8^{\downarrow}$ $21A9^{\downarrow}$	$1A1^{\uparrow\uparrow}$	[98,124,202,278,438–449]
Hypericin *	*H. perforatum*	—	↑	—		$2D6^{\downarrow 0}$ $2C9^{\downarrow}$ $3A4^{\downarrow}$ $1A2^{\downarrow}$ $2C19^{\downarrow}$	—	—	$A^{\downarrow 0}$ $B^{\downarrow 0}$	Ant	↓	$1^{\uparrow}$	↑	—	$21A9^{\downarrow S}$	$1A6^{\downarrow}$	[102,124,278,336,442–444,447,450–455]

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Hyperoside *	*B. rufescens* *C. japonica* *H. perforatum* *P. pterocarpum*	—	—	—	—	2D6↓ 2C9↓	—	—	—	—	—	—	S	—	—	—	[289,456]
Isoliquiritigenin *	*G. uralensis*	—	—	—	—	1A2↓ 3A4↓ 2C9↓ 2C19↓	—	—	—	—	—	—	—	—	—	—	[457]
Isorhamnetin *	*G. biloba* *R. nigrum*	—	—	—	—	1A2↓ 3A4↓	—	—	—	—	—	2↓	S↑↓	—	21A8↓	—	[200,247,249,458,459]
Isosarcodine	*S. saligna*	—	—	—	2↓	—	—	—	—	—	—	—	—	—	—	—	[430]
p-Kaempferol *	*A. melegueta* *C. pluricaulis* *C. japonica* *C. rotundus* *H. perforatum* *I. paraguariensis*	—	—	—	—	1A2↓ 3A4↓ 2C9↓ 2C19↓	—	—	—	Ant	—	—	↓S	—	21A8↓ 21A9↓ 22A4↓ 22A8↓	1A1↑	[200,218,250,251,374,460–463]
Kaempferol-3-glucoside *	*C. ternatea* *C. pluricaulis*	—	—	—	—	—	—	—	—	—	—	—	—	—	21A6↓ 21A8↓	—	[345,463]
11 α-Hydroxy-*O*-methylleucotamine	*P. illyricum*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
N-3-methoxybenzyl-linoleamide (macamide) *	*L. meyenii*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Levodopa *	*M. pruriens*	—	—	—	—	—	—	—	—	Ant	—	—	S	—	—	—	[464,465]
Luteolin *	*L. bicolor* *M. chamomilla* *M. officinalis* *P. emblica* *R. officinalis*	—	↑	—	2↓	1A2↓ 3A4↓ 3A5⁰ 2B6↓ 2C8↓ 2C9↓ 2C19↓ 2D6↓ 2E1↓	—	↓	A↓ B↓	—	↓	—	—	—	—	1A1↓S 1A9↓ 2B7↓	[276,466–472]
Lycorine	*G. woronowii* *P. illyricum*	—	—	—	—	3A4⁰	—	—	—	—	—	—	0	—	—	—	[342,473]
Malvidin 3-galactoside *	*V. angustifolium*	—	—	—	—	3A4↓ 2C9↓	—	—	—	—	↓S	—	↓	—	21A6↑	—	[341,353,474]
Malvidin 3-glucoside *	*V. angustifolium* *V. uliginosum L.*	—	—	—	—	3A4↓ 2C9↓	—	—	—	—	↓	—	↓	—	21A6↑	—	[341,353,474]
Malvidin-3-*O*- β -arabinose *	*V. angustifolium*	—	↑	—	—	—	—	—	—	-	—	—	—	—	—	—	[475]
Mangiferin *	*M. indica*	—	—	—	—	1A1↓ 1A2↓ 3A4↓ 2C8↓ 2B6↓ 2D6↓	—	—	—	—	—	—	↓	—	—	1A1↓ 1A9↓ 2B7↓	[198,476,477]
Methylliberine *	*C. arabica*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Mucunadine *	*M. pruriens*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Mucunine *	*M. pruriens*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Myricetin *	*M. peregrina* *R. nigrum*	—	—	—	—	1A2$^{\downarrow}$ 3A4$^{\downarrow}$ 2D6$^{\downarrow}$	—	—	—	—	↓	1$^{\downarrow}$	↓S	—	21A6$^{\downarrow}$	—	[218,247,248,276,478]
Naringenin	*L. bicolor* *M. lucida*	—	↑	—	2$^{\downarrow}$	1A2$^{\downarrow 0}$ 3A4$^{\downarrow}$ 2B6^{0} 2C9$^{\downarrow}$ 2C19$^{\downarrow}$ 2D6^{0} 2E1^{0}	—	↓	A$^{\downarrow}$ B$^{\downarrow}$	—	↓	—	↓	—	22A6$^{\downarrow}$ 21A6$^{\downarrow}$ 21A8$^{\downarrow}$ 21A9$^{\downarrow}$	1A1$^{\uparrow}$ 1A3$^{\uparrow}$ 1A6$^{\uparrow}$ 1A9$^{\uparrow}$ 2B4$^{\uparrow}$ 2B7$^{\uparrow}$	[200,218,247,253,479–488]
Naringin *	*M. lucida*	—	↑	—	2$^{\downarrow}$	3A4$^{\downarrow\uparrow}$ 1A2$^{\downarrow}$	—	↓	A$^{\downarrow}$	—	↑	—	↓	—	21A9$^{\downarrow}$	—	[200,253,338,483,487,489–493]
N,*N*-dimethyl buxapapine	*B. papillosa*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Nobiletin *	*C. reticulata*	—	—	—	2$^{\downarrow}$	1A1$^{\downarrow\uparrow}$ 1A2$^{\downarrow\uparrow}$ 3A4$^{\downarrow}$	—	—	A$^{\downarrow}$ B$^{\downarrow}$	—	↓	1$^{\downarrow}$	↓	—	21A8$^{\downarrow}$ 21A9$^{\downarrow}$	—	[208,247,337,487,494–497]
Oleanolic acid *	*M. lucida* *R. officinalis*	—	↑	—	2$^{\uparrow}$	1A2$^{\downarrow}$ 3A4$^{\downarrow}$	—	↓	A$^{\downarrow}$	—-	↓	1$^{\downarrow}$	0	—	—	—	[276,498–503]
α-Onocerin *	*L. clavatum*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
p-Synephrine *	*C. aurantium*	—	—	—	—	1A2^{0} 3A4$^{\downarrow}$ 2D6^{0} 2E1^{0}	—	—	A^{S} B^{S}	—	—	—	↓	—	—	—	[79,504–506]
Paeonol *	*P. lactiflora*	—	—	—	2$^{\downarrow}$	1A2^{S}	—	—	A$^{\downarrow}$ B$^{\downarrow}$	—	↓	—	S	—	—	—	[507–511]
Palmatine	*C. chinensis* *C. speciosa*	—	—	—	2$^{\downarrow}$	1A1$^{\downarrow}$ 1A2^{S} 3A4$^{\uparrow}$ 2D6^{S}	—	—	A$^{\downarrow}$	—	—	—	↑	—	—	—	[274,512–515]
Peonidin-3-*O*-β-arabinose *	*V. angustifolium*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
D-Pinitol	*B. rufescens*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
15-Methyl Pinusolidic acid *	*P. orientalis*	—	—	—	—	—	—	—	—	A	—	—	—	—	—	—	[133]
Phyllanthin *	*P. emblica*	—	—	—	—	1A2^{0} 3A4$^{\downarrow}$ 2C9^{0} 2D6^{0} 2E1^{0}	—	—	—	—	—	2^{0}	↓	—	—	—	[516,517]
Phytol	*M. lucida*	—	↑	—	2$^{\downarrow}$	—	—	↓	—	—	—	—	—	—	—	—	[518–520]
α-Pinene *	*R. officinalis* *S. lavandulaefolia*	—	—	—	2$^{\downarrow}$	2B6$^{\downarrow}$	—	—	—	Ant	—	—	—	—	—	—	[521–523]

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Piperine *	*P. nigrum*	—	—	—	—	1A2↑ 3A4↓ 2C9↓ 2E1↓	—	—	—	—	↓	—	↓	—	22A2↓	1A1↓	[524–526]
Polygalaxanthone III *	*P. tenuifolia*	—	—	—	—	2E1↓	—	—	—	—	—	—	—	—	—	—	[527]
Protocatechuic acid *	*A. oxyphylla* *G. biloba* *M. officinalis* *R. officinalis* *V. vinifera*	—	—	—	—	1A1↓ 1A2↓ 2C9↓ 2E1↓	—	—	—	—	—	—	—	—	—	—	[245,528]
Prurienidine *	*M. pruriens*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Prurienine *	*M. pruriens*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Puerarin *	*P. lobata*	—	↑	—	2↓	1A1↑ 1A2↑ 3A4↓ 2B6↓ 2C9↓ 2D6↓ 2E1↓	—	↓	—	↓	—	—	↑	—	—	1A1↑	[529–537]
Quercetin *	*A. melegueta* *C. sativus* *C. rotundus* *H. perforatum* *I. paraguariensis* *L. meyenii* *M. lucida* *P. emblica* *R. nigrum* *S. costus* *V. uliginosum L.*	—	—	—	—	1A1↓ 1A2↓ 3A4↓ 2C8↓ 2C9↓ 2C19↓ 2D6↓	—	—	A↓	Ant	↑S	1↓ 2↓	↓S	—	21A6↓ 21A8↓ 21A9↓ 22A6↓	1A1↑ 1A6↑	[24,200,218, 247,289,338, 374,462,487, 488,538–542]
Quercetin-3-*O*-β-D-glucuronide	*P. pterocarpum*	—	—	—	2↓	3A4↓	—	—	—	—	—	2↓	↓	—	21A8↓ 21A9↓	1A1↓	[539,543]
Resveratrol *	*V. vinifera*	—	—	—	—	1A1↓S 1A2↓ 3A4↓ 2C9↓ 2C19↓ 2D6↓	↑	↓	A↓	↓	↑S	2S	↓	—	21A8S	—	[218,298,338, 544–551]
Rosarin *	*R. rosea*	—	—	—	—	1A2↓ 3A4↓ 2C9↓ 2D6↓	—	—	A0 B0	—	—	—	—	—	—	—	[552,553]
Rosavin *	*R. rosea*	—	—	—	—	1A2↓ 3A4↓ 2C9↓ 2D6↓	—	—	A0 B0	—	—	—	—	—	—	—	[552,553]
Rosin *	*R. rosea*	—	—	—	—	1A2↓ 3A4↓ 2C9↓ 2D6↓	—	—	A0 B0	—	—	—	—	—	—	—	[552,553]

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Rosmarinic acid *	*M. officinalis* *M. spicata* *R. officinalis*	—	—	—	—	3A4$^{\downarrow}$ 2C9$^{\downarrow}$ 2C19$^{\downarrow}$ 2D6$^{\downarrow}$ 2E1$^{\downarrow}$	—	—	—	—	↓	—	↓	—	—	1A1$^{\downarrow}$	[416,554,555]
Rutin *	*H. perforatum* *L. bicolor* *M. chamomilla* *M. flexuosa* *M. lucida* *M. peregrina* *V. uliginosum L.*	—	↑	—	2$^{\downarrow}$	1A1$^{\uparrow}$ 3A4$^{\downarrow}$	—	↓	B$^{\downarrow}$	—	↓	—	↓	—	21A6$^{\downarrow}$ 21A8$^{\downarrow}$ 21A9$^{\downarrow\uparrow}$	—	[24,248,253,345,426,556–563]
Safranal *	*C. sativus*	—	—	—	—	2B6$^{\uparrow}$	—	—	—	—	↓	—	↓	—	—	—	[247,328,564]
Salidroside *	*R. rosea*	↓	—	—	1$^{\downarrow}$ 2$^{\downarrow}$	1A2$^{\uparrow}$ 3A4$^{\downarrow}$ 2B6$^{\uparrow}$ 2C9$^{\uparrow}$	—	—	A$^{\downarrow}$ B$^{\downarrow}$	↑	—	1$^{\downarrow}$	↓	↓	—	—	[565–570]
Salvianolic acid *	*M. spicata* *S. miltiorrhiza*	—	—	—	2$^{\downarrow}$	1A2$^{\downarrow}$ 3A4$^{\downarrow}$	—	—	—	—	↑	—	↓	—	21A8^{S}	—	[571–574]
Sanguinine	*E. grandiflora* *P. illyricum*	—	—	—	—	3A4^{0}	—	—	—	—	—	—	—	—	—	—	[399]
Sarcocine	*S. saligna*	—	—	—	—	—	—	—	—	—	—	—	—	—	15A1^{S} 15A2^{S}	—	[575]
Sarcodine	*S. saligna*	—	—	—	2$^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	—	[430]
Sarcorine	*S. saligna*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Sarsalignenone	*S. saligna*	—	—	—	2$^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	—	[430]
Sarsasapogenin *	*A. racemosus*	—	—	—	—	—	—	—	A$^{\downarrow}$ B$^{\downarrow}$	—	—	—	—	—	21A6^{S}	—	[369,576]
Schisandrin B *	*S. chinensis*	—	—	—	—	3A4$^{\downarrow}$ 3A5$^{\downarrow}$ 2B6$^{\uparrow}$ 2E1^{S}	—	—	—	—	—	—	↓	—	21A6$^{\uparrow}$	—	[577–581]
Shatavarin IV *	*A. adscendens* *A. racemosus*	—	—	—	—	—	—	—	A$^{\downarrow}$ B$^{\downarrow}$	—	—	—	—	—	—	—	[582]
Shogaol *	*A. melegueta* *Z. officinale Rosc.*	—	—	—	1$^{\downarrow}$ 2$^{\downarrow}$	1A2$^{\downarrow}$ 2C9$^{\downarrow}$ 2C19$^{\downarrow}$	—	—	—	↓	—	—	—	—	—	1A1^{S} 1A3^{S} 2B7^{S}	[583–586]
Sitoindosides VII-X *	*W. somnifera*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
β-Sitosterol *	*A. lancea* *C. pluricaulis* *M. peregrina* *M. pruriens*	—	↑	—	2$^{\downarrow}$	3A4^{0} 3A5^{0} 2C19^{0}	—	↓	—	—	↓	—	0	—	—	—	[587–592]
Spirofornabuxine	*B. hyrcana*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Stigmasterol *	*A. lancea*	—	—	—	—	3A4$^{\downarrow}$ 3A5$^{\downarrow}$	—	—	—	—	—	—	↓	—	—	—	[590,593]

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Syringin *	*E. senticosus*	-	-	-	$2^{\downarrow}$	$2C9^{\downarrow}$ $2E1^{\downarrow}$	—	—	—	—	—	—	S	—	—	—	[93,594]
Tannic acid *	*T. chebula*	—	—	—	$2^{\downarrow}$	$1A2^{\downarrow}$ $3A4^{\downarrow}$ $2B6^{\downarrow}$	—	—	—	—	—	$1^{\downarrow}$ $2^{\downarrow}$	$\downarrow$	—	$21A6^{S\downarrow}$	—	[333,369,595–598]
Tanshinone I *	*S. miltiorrhiza*	—	—	—	—	$1A1^{\uparrow}$ $1A2^{\uparrow\downarrow}$ $2C9^{\downarrow}$ $2E1^{\downarrow}$	—	—	—	—	$\downarrow$	—	$S\downarrow$	—	—	$1A1^{o}$ $1A3^{0}$ $1A9^{0}$ $2B7^{0}$	[24,599–602]
Tanshinone IIA *	*S. miltiorrhiza*	—	—	—	$2^{\downarrow}$	$1A1^{\uparrow}$ $1A2^{\uparrow\downarrow}$ $3A4^{\uparrow\downarrow}$ $2C9^{\downarrow}$ $2E1^{\downarrow}$	—	—	—	—	$\downarrow$	—	$\downarrow$	—	—	$1A1^{o}$ $1A3^{0}$ $1A9^{0}$ $2B7^{0}$	[24,599–601,603]
Tanshinone IIB *	*S.miltiorrhiza*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tenuifolin *	*P.tenuifolia*	—	—	—	$2^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	—	[604]
Tenuifoliside B *	*P. tenuifolia*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tenuifoliside C *	*P. tenuifolia*	—	—	—	—	$2E1^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	[527]
Theacrine *	*C. arabica* *T. grandiflorum*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Theobromine *	*T. cacao*	—	—	—	—	$1A2^{S}$ $3A4^{0}$ $2C9^{0}$ $2C19^{0}$ $2D6^{0}$	—	—	—	—	—	—	0	—	—	—	[218,605]
Timosaponin AIII *	*A. asphodeloides*	—	$\uparrow$	—	$2^{\downarrow}$	—	—	—	—	—	—	—	$\downarrow$	—	—	—	[606]
Trigonelline *	*T. foenum-graecum*	—	—	—	—	$1A2^{\downarrow}$ $3A4^{0}$ $2B6^{0}$ $2C8^{0}$ $2C19^{0}$ $2D6^{\downarrow}$ $2E1^{0}$	—	$\uparrow$	—	—	$\uparrow$	—	—	—	—	—	[607,608]
Ursolic acid *	*R. officinalis*	—	—	—	$2^{\downarrow}$	$1A2^{\downarrow}$ $3A4^{\downarrow S}$ $2C8^{\downarrow}$ $2C9^{\downarrow S}$ $2C19^{\downarrow}$ $2D6^{\downarrow}$	—	—	$A^{\downarrow}$	—	$\downarrow$	1^{0}	—	—	$21A6^{\downarrow}$ $21A8^{\downarrow}$ $21A9^{\downarrow}$ $22A8^{\downarrow}$	—	[276,409,501,609–613]
Vaganine	*S. saligna*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(+)-α-Viniferin *	*C. chamiague*	—	—	—	—	$3A4^{S}$	—	—	—	—	—	—	S	—	—	—	[218]
Vinpocetine *	*V. minor*	—	—	—	—	$3A4^{S}$	—	—	—	—	—	—	—	—	—	—	[614]
Withaferin A *	*W. somnifera*	—	—	—	—	$1A1^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	[615]

Table 3. *Cont.*

Bioactive	Plant Sources	ALOX5	AMPK	BSEP	COX	CYP	GLP-1	HMGCoAR	MAO	NMDA	ABC			PLA2G2A	SLC	UGT	References
											BCRP	MRP	PgP		PEPT; OCT; OAT, MATE, OATP		
Withanolide A *	*W. somnifera*	—	—	—	—	$1A1^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	[615]
Withanolide B *	*W. somnifera*	—	—	—	—	$1A1^{\downarrow}$	—	—	—	—	—	—	—	—	—	—	[615]
Z-Ligustilide *	*A. sinensis*	—	—	—	—	$1A1^{\downarrow}$ $3A4^{\uparrow}$ $2D6^{\uparrow}$	—	—	—	—	—	—	—	—	—	—	[246,616]

*—Phytochemicals found in food supplements; $^{\downarrow}$—target inhibition; $^{\uparrow}$—target induction; ^{s}—bioactive is substrate of the target; ^{Ant}—Bioactive is a target antagonist; ^{0}—No effect; (-)—Not reported; ABC—ATP-binding cassette; ALOX5—Arachidonate 5-lipoxygenase; AMPK—AMP-activated protein kinase; BCRP—Breast cancer resistance protein; BSEP—Bile salt export pump (ABCB11); COX—Cyclooxygenase; CYP—Cytochrome P450; GLP-1—GlucagoN-like peptide-1; HMGCoAR—3-hydroxy-3-methyl-glutaril-CoA reductase; MAO—Monoamine Oxidase; MATE—Multi-antimicrobial extrusion protein; MRP—Multidrug resistance-associated protein; NMDA—*N*-methyl-D-aspartate; OAT—Organic anion transporter; OATP—Organic-anioN-transporting polypeptide; OCT—Organic cation transport; P-gP—Glycoprotein P; UGT—Uridine diphosphate-glucuronosyltransferase; PLA2G2A—Phospholipase A2 Group IIA; SLC—Solute Carriers (15A/PEPT; 22A1-3/OCT1-3; 22A4/OCTN1; 22A6,8,11/OAT1,3,4; 47A/MATE; 21A3/OATP1A2; 21A6,8/OATP1B1,3; 21A9/OATP2B1; 21A14/OATP1C1); PEPT—Peptide transporter; association of two symbols ($^{\uparrow\downarrow}$ or $^{\downarrow 0}$ or $^{\uparrow 0}$) for the same target, refers to conflicting information reported in literature.

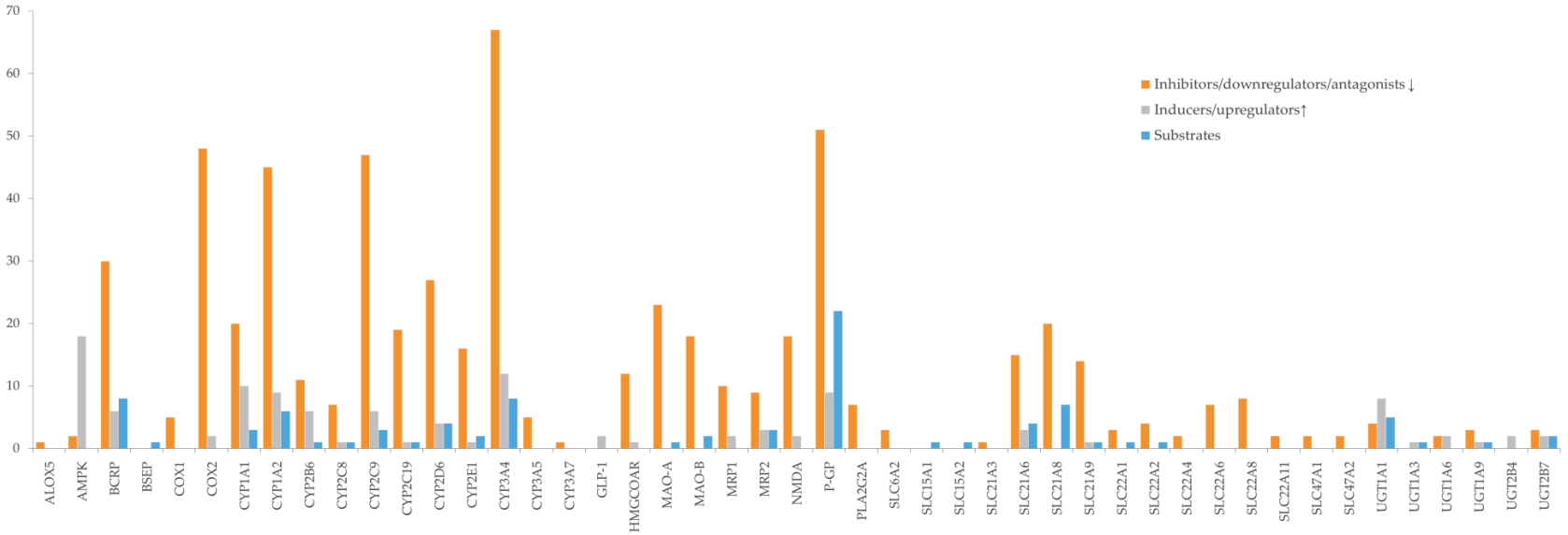


Figure 6. Effect of bioactives on targets (enzymes, transporters, and receptors).

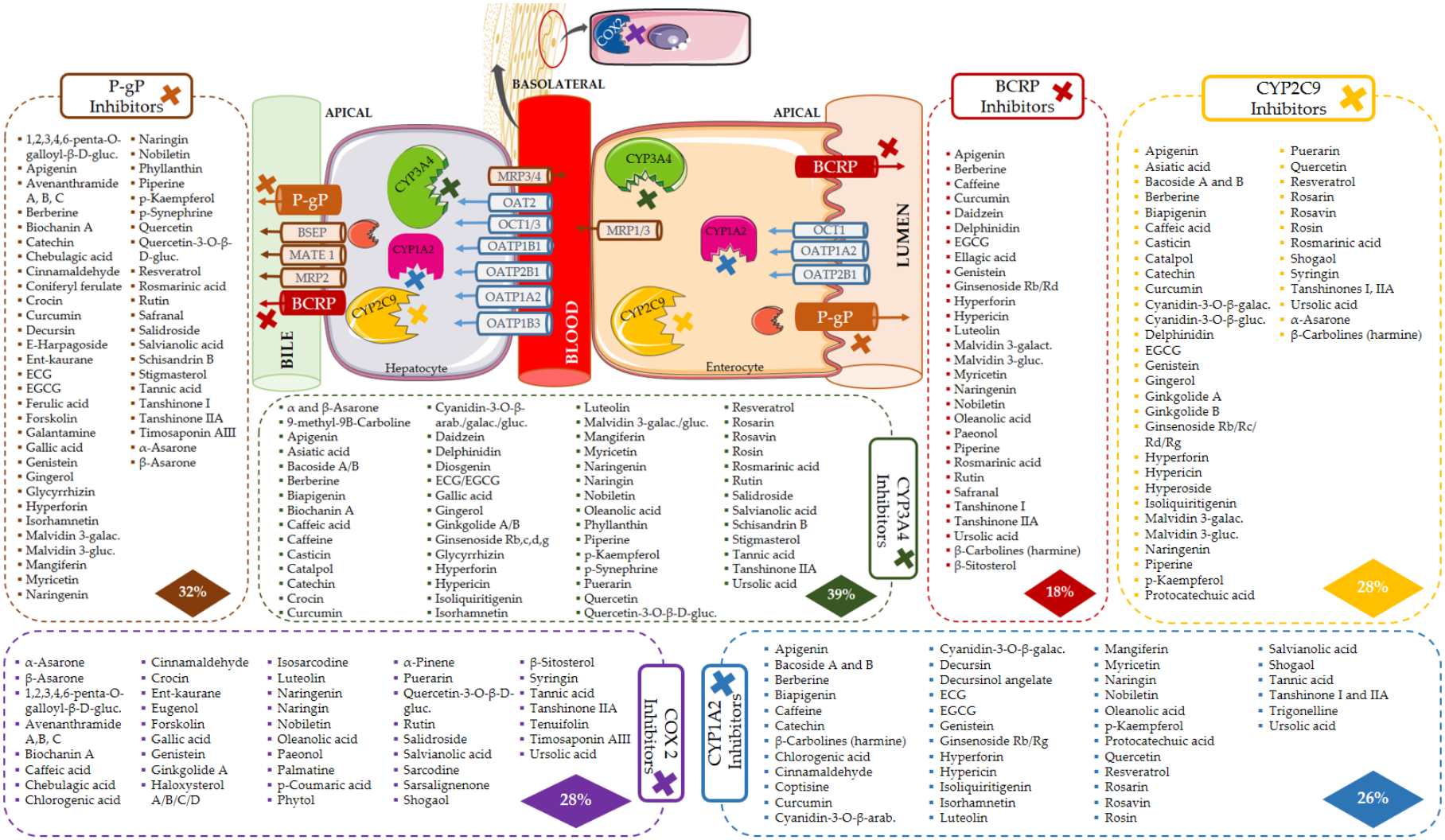


Figure 7. Bioactives that inhibit the six most affected targets (COX2, CYP1A2, CYP3A4, CYP2C9, BCRP, and P-gP). Location of the targets is indicative, since they are expressed in several other tissues.

5.4. Assessment of HDI Potential

In order to understand the potential consequences of combining each bioactive with the drugs, a crossed analysis was performed searching for matches between the targets of which the drugs are substrate and that are simultaneously inhibited, or induced, by the bioactive. Whenever a match was found in at least one target for a specific drug and a specific bioactive, the latter was considered a potential HDI agent, regardless of the direction of modulation (inhibition or induction). Otherwise, if the roles of the drug and the bioactive were reversed, that is, the drug assumed the role of inhibitor/inducer of a specific target of which the bioactive was a substrate, the interaction was considered to be of a different nature, because, in this case, it is the drug that changes the disposition of the bioactive. However, this type of interaction was disregarded in the present study.

Furthermore, situations were identified in which the drug and the bioactive modulate the same target, either in the same direction (both inhibit/induce) or in opposite directions (one induces and the other inhibits the target).

Half of the drugs have at least one of their targets inhibited or induced by more than 80 of the bioactives found in plants used for cognition enhancement. Se and Cl have over 100 bioactive agents as potential modulators of their metabolism, transport, or therapeutic action (Figure 8).

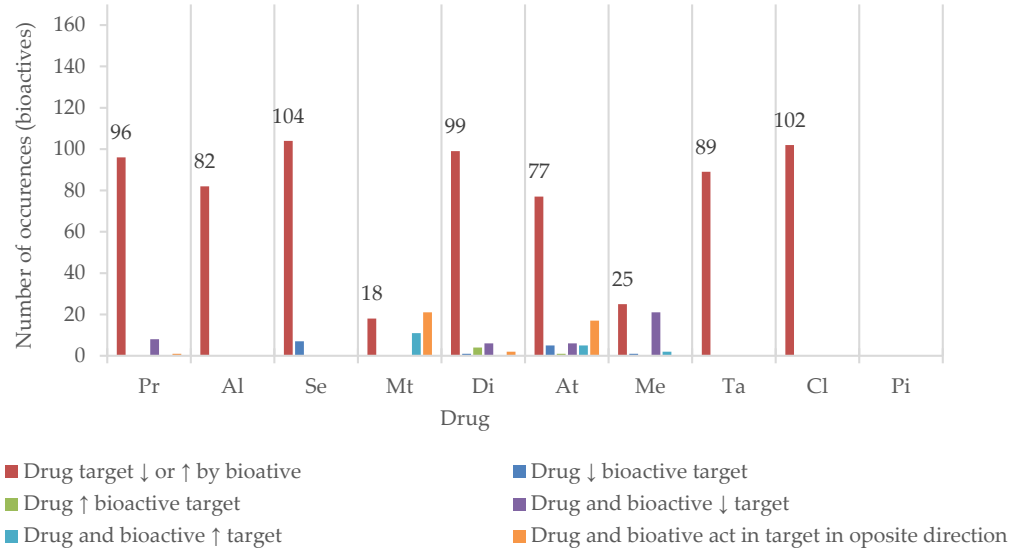


Figure 8. Number of bioactives sharing at least one target with the drugs (↓—inhibition; ↑—induction). Propranolol (Pr), alprazolam (Al), sertraline (Se), metformin (Mt), diclofenac (Di), atorvastatin (At), tadalafil (Ta), memantine (Me), piracetam (Pi), and clopidogrel (Cl).

However, since the risk of HDI is naturally related to the number of shared targets between a given bioactive and a specific drug, only the bioactives that cause induction/inhibition of at least four targets were selected for more detailed analysis. The potential HDI of these with the 10 drugs under study is summarized in a double entry table (Table 4). Hence, a total of 75 bioactive agents met the inclusion criteria (minimum of four targets affected), and 95 were excluded. Of the 95 excluded, only 42 have no action on any of the 55 targets analyzed. Thus, the exclusion of bioactives does not guarantee the absence of interactions with any of the drugs under study; simply, the probability of their occurrence was considered lower. Pi was excluded from the detailed analysis for not sharing any target with any bioactive (Figure 8).

Table 4. Hypothesized interactions between selected bioactives (those inducing/inhibiting at least four of the 55 targets studied) and drugs. Interaction was considered if at least one target was simultaneously affected by bioactive and drug, while sequentially fulfilling criteria 1 and 2 (see text for details). Piracetam is not shown, since it does not interact with any of the bioactives under study.

Bioactive	Drug								
	Pr	**Al**	**Se**	**Mt**	**Di**	**At**	**Me**	**Ta**	**Cl**
Apigenin	x	x	x	x	x	x	x	x	x
α-Asarone	x	x	x	-	x	x	x	x	x
β-Asarone	x	x	x	▲	x	x	-	x	x
Bacoside A	x	x	x	-	x	x	▼	x	x
Bacoside B	x	x	x	-	x	x	▼	x	x
Berberine	x	x	x	x	x	x	-	x	x
Biapigenin	x	x	x	-	x	x	x	x	x
Bilobalide	x	x	x	-	x	x	x	x	x
Biochanin A	x	x	x	-	x	x	x	x	x
Caffeic acid	x	x	x	x	x	x	▼	x	x
β-Carbolines (Harmine)	x	x	x	x	x	x	▼	-	x
9-Methyl-9B-Carboline	x	x	x	-	x	x	-	x	x
Catalpol	x	x	x	-	x	x	-	x	x
Catechin	x	x	x	x	x	x	x	x	x
Chlorogenic acid	x	-	x	▲	x	x	▼	-	x
Cinnamaldehyde	x	x	x	▲	x	x	x	x	x
Coptisine	x	x	x	x	x	▲	x	x	x
Crocin	x	x	x	-	x	x	▼	x	x
Curcumin	x	x	x	x	x	x	▼	x	x
Cyanidin-3-*O*-β-glucoside	x	x	x	-	x	x	-	x	x
Daidzein	x	x	x	x	x	x	-	x	x
Decursin	x	-	x[&]	-	x	x	-	x	x
Delphinidin	x	x	x	x	x	x	▼	x	x
Ellagic acid	▼	-	x	x	x	x	▼	-	x
ECG	x	x	x	-	x	x	-	x	x
EGCG	x	x	x	x	x	x	x	x	x
Eugenol	▼	-	x	◄►	▼	x	x	-	x
Ferulic acid	x	x	x	-	x	x	x	x	x
Forskolin	x	x	x	▲	x	x	x	x	x
Gallic acid	x	x	x	-	x	x	-	x	x
Genistein	x	x	x	x	x	x	x	x	x
Gingerol	x	x	x	-	x	x	▼	x	x
Ginkgolide A	x	x	x	-	x	x	▼	x	x
Ginkgolide B	x	x	x	-	x	x	▼	x	x
Ginsenoside Rb	x	x	x	x	x	x	-	x	x

Table 4. *Cont.*

Bioactive	Drug								
	Pr	**Al**	**Se**	**Mt**	**Di**	**At**	**Me**	**Ta**	**Cl**
Ginsenoside Rd	x	x	x	x	x	x	▼	x	x
Ginsenoside Rg	x	x	x	-	x	x	-	x	x
Glycyrrhizin	x	x	x	-	x	x	-	x	x
Hyperforin	x	x	x	x	x	x	x	x	x
Hypericin	x	x	x	x	x	x	x	x	x
Isoliquiritigenin	x	x	x	-	x	x	▼	x	x
Isorhamnetin	x	x	x	-	x	x	-	x	x
p-Kaempferol	x	x	x	-	x	x	x	x	x
Luteolin	x	x	x	x	x	x	▼	x	x
Malvidin 3-galactoside	x	x	x	x	x	x	-	x	x
Malvidin 3-glucoside	x	x	x	x	x	x	-	x	x
Mangiferin	x	x	x	-	x	x	▼	x	x
Myricetin	x	x	x	x	x	x	-	x	x
Naringenin	x	x	x	x	x	x	▼	x	x
Naringin	x	x	x	x	x	x	-	x	x
Nobiletin	x	x	x	x	x	x	-	x	x
Oleanolic acid	x	x	x	x	x	x	-	x	x
Paeonol	▼	-	x	x	x	x	-	-	-
Palmatine	x	x	x	-	x	x	-	x	x
Piperine	x	x	x	x	x	x	x	x	x
Protocatechuic acid	x	x	x	-	x	◄►	-	-	x
Puerarin	x	x	x	▲	x	x	▼	x	x
Quercetin	x	x	x	x	x	x	x	x	x
Quercetin-3-*O*-β-D-glucuronide	x	x	x	-	x	x	-	x	x
Resveratrol	x	x	x	x	x	x	x	x	x
Rosarin	x	x	x	-	x	x	-	x	x
Rosavin	x	x	x	-	x	x	-	x	x
Rosin	x	x	x	-	x	x	-	x	x
Rosmarinic acid	x	x	x	x	x	x	▼	x	x
Rutin	x	x	x	x	x	x	-	x	x
Salidroside	x	x	x	-	x	x	x	x	x
Salvianolic acid	x	x	x	x	x	x	-	x	x
Schisandrin B	x	x	x	-	x	x	▲	x	x
Shogaol	x	x	x	-	x	▼	x	-	x
β-Sitosterol	-	-	x[#]	x	x	x	-	-	-
Tannic acid	x	x	x	-	x	x	▼	x	x
Tanshinone I	x	x	x	x	x	x	-	x	x

Table 4. *Cont.*

Bioactive	Drug								
	Pr	**Al**	**Se**	**Mt**	**Di**	**At**	**Me**	**Ta**	**Cl**
Tanshinone IIA	x	x	x	x	x	x	-	x	x
Trigonelline	x	-	x	x	x	x	-	-	x
Ursolic acid	x	x	x	x	x	x	▼	x	x

X—Drug is substrate of at least one target, which is induced/inhibited by the bioactive; direction of interaction is not disclosed; x[&]—The bioactive only inhibits P-gP; x[#]—The bioactive only inhibits BCRP; ▼—Drug and bioactive are inhibitors of at least one shared target; ▲—Drug and bioactive are inducers of at least one shared target; ◄►—Drug and bioactive act at least in one target, in opposite direction; — no interaction in any of the targets.

For the construction of Table 4, the targets shared between each drug and each bioactive were analyzed, based on two sequential criteria: (1) targets of which the drug is a substrate; (2) targets of which the drug is a modulator. If at least one target fulfilled criterion 1, the interaction was considered and identified in the table with an x, regardless of inhibition or induction; when no target met criterion 1, the analysis proceeded to targets modulated by the drug (criterion 2), considering the following types of interaction: (a) the drug and bioactive modulate the target in the same or opposite directions and (b) the drug modulates at least one target of which the bioactive is a substrate. For clarity, the following example illustrates application of type 2 criteria: both Di and eugenol are inhibitors of COX2 and Di inhibits CYP2E1, of which eugenol is a substrate; therefore, Di inhibits the metabolism of the bioactive and was identified with ▼. Finally, when none of the criteria were met, it was considered that there was no interaction.

In terms of chemistry, the majority of bioactives with potential to cause HDI belong to the phenolic group (50; 67%), followed by terpenes (17; 23%) and alkaloids (7; 9%) (Figure 9). Phenolic compounds, such as the isoflavonoids (daidzein, genistein, biochanin A, etc.) have already been reported as inhibitors of several CYP enzymes (e.g., the noncompetitive inhibition of CYP2C9 caused by genistein and daidzein [245]). Both flavonoids and terpenoids have the ability to modulate ABC transporters [192,617], which can be advantageous for drugs with poor absorption, but can also lead to toxic plasma drug concentrations, especially for narrow therapeutic window drugs.

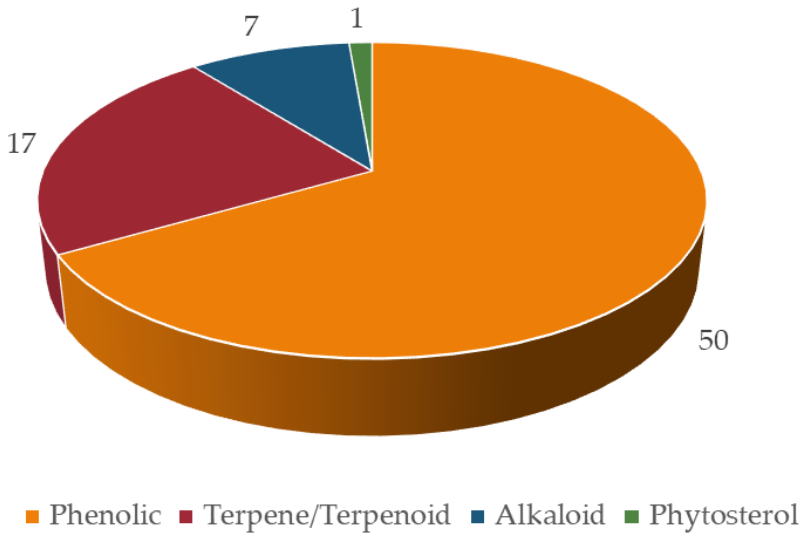


Figure 9. Number of bioactives inducing/inhibiting at least four targets, according to chemical class.

Amongst the 50 phenolic compounds listed in Table 4, apigenin, EGCG, genistein, hypericin, quercetin, caffeic acid, catechin, cinnamaldehyde, curcumin, delphinidin, luteolin,

naringenin, puerarin, rosmarinic acid, and resveratrol show the capacity to interfere with all nine drugs. For the remaining groups, the terpenoids forskolin, ginsenoside Rd, hyperforin, and ursolic acid and the alkaloids coptisine and piperine showed similar capacity. On the other hand, β-sitosterol only has the potential to modulate disposition of three of the nine drugs (Mt, Di and At). The effect of β-sitosterol on Se disposition was not considered, since the target affected is BCRP, and Se is a BDDCS class I drug and therefore unlikely to depend on efflux carriers. The noncompetitive inhibition of CYP2C9 by genistein can change the disposition of Al, Se, Di, and Cl. Aside from this effect on CYP2C9, genistein modulates 16 other targets, inhibiting for instance CYP1A1/2, COX2, HMGCoAR, BCRP, P-gP, MAO-A, and MAO-B, among others.

Some drugs may also potentiate or antagonize the modulation of bioactives acting on shared targets. For example, At induces CYP2C9, whereas the same CYP is inhibited by biapigenin, catechin, cyanidin-3-*O*-β-glucoside, ginkgolide A, ginkgolide B, ginsenoside Rg, protocatechuic acid, rosarin, rosavin, and rosin. On the other hand, Mt significantly increases glucagoN-like peptide-1 (GLP-1) levels, an effect that can be potentiated by forskolin. In the case of At, a drug used to slow the production of cholesterol in the body by inhibiting HMG-CoAR, several of the bioactives studied (e.g., β-sitosterol, rutin, resveratrol, naringenin genistein, chlorogenic acid, oleanolic acid, luteolin, catalpol, and α-asarone) also inhibit the same enzyme. Finally, a drug may cause changes on the disposition of the bioactive by modulating targets of which the latter is a substrate. This is the case of Di, which inhibits CYP2E1, an enzyme involved in the metabolism of eugenol and schisandrin B. Se inhibits CYP1A2, which metabolizes palmatine, daidzein, and paeonol.

As discussed before, drugs belonging to BDDCS class I (Pr, Se and Al) are more sensitive to changes in CYP, whereas class II drugs (At, Cl, Di and Ta) are affected by both CYP and drug carriers; for drugs in classes III and IV, modulation of CYP has a minimal effect [43]. Hence, the disposition of class II drugs may be at greater risk of being modified by co-administration of herbal formulations. On the other hand, for class I drugs in which the only targets shared with bioactives are transporters, the probability of the interaction having clinical significance is low, because, although the drug can use the transporter, its disposition does not depend on it. This is the case of Se combined with decursin or β-sitosterol, where the sole interaction point is the inhibition of P-gP by decursin and the inhibition of BCRP by β-sitosterol. In these cases, the risk of significant interaction is considered low. Likewise, if an interaction is identified between a bioactive and a class III drug, exclusively due to CYP modulation, the risk of clinical significance is low. This was not the case for any of our two BDDCS class III drugs (Mt and Me), since none of them were reported to be a substrate of any CYP enzyme.

For the remaining BDDCS class II drugs (Di, At, Ta, and Cl), all interactions are considered relevant, regardless of whether the affected targets are CYP enzymes, transporters, or other receptors. Furthermore, drugs are substrates of multiple targets, thus increasing the risk of serious interaction, with a multiplicity of plants/bioactives, which will be of more concern if the drug belongs to the HAM group. Among the nine drugs studied, Di and At meet a series of criteria, sufficient to be considered at risk for potential clinically significant interactions with the bioactives used in cognitive enhancement. Specifically, both are BDDCS class II drugs, belong to the HAM group, share targets with the 75 bioactives under study (only considering the bioactives modulating at least four different targets), and are substrates of 14 and 17 targets, respectively. Additionally, Di inhibits 13 targets and induces two, whereas At inhibits six targets and induces three (Figure 5). These drugs were therefore chosen for an in depth study, presented in the following sections.

5.4.1. Diclofenac

Di is a nonsteroidal anti-inflammatory drug used to treat pain and inflammatory diseases. It acts by inhibiting COX1 and COX2. Di is mainly metabolized by several CYP enzymes: CYP1A1, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, and CYP3A4. Di is a substrate of BSEP/ABCB11, BCRP, and OATP1B3 (Table 2). The official label of the

drug indicates lethargy, drowsiness, nausea, vomiting, epigastric pain, and gastrointestinal bleeding, as symptoms of overdose.

According to our results, Di is at great risk for HDI by modulation (mostly inhibition) of CYP enzymes, drug carriers (both efflux and uptake transporters), and COX enzymes (Figure 10). CYP1A2, CYP2C9, and CYP3A4 are the targets most susceptible to HDI, which can result in a decreased metabolization of the drug, and toxicity may occur. OATP1B3 (SLC21A8) is an uptake transporter exclusively expressed in the liver on the basolateral side of hepatocytes, responsible for the uptake of Di (Figure 7). The inhibition of this transporter results in less exposition of the drug to the metabolization site in the liver. OATP3 is inhibited by 19 bioactives, 16 of them being phenolic and three terpenes (Figure 11), such as EGCG, naringenin, quercetin, curcumin, hyperforin, apigenin, ursolic acid and p-kaempferol, among others. EGCG has been reported to inhibit diclofenac 4′-hydroxylation [618].

Moreover, naringenin and ursolic acid have the capacity to inhibit the six most affected Di targets (CYP1A2, CYP2C9, CYP2C19, CYP3A4, BCRP, and OATP1B3) and also COX2 synergistically with the mechanism of action of Di. In fact, a total of 48 (of the 170 bioactives) have the ability to inhibit COX2. All of these HDI may result in toxic levels of Di. Several authors have reported HDI involving Di [619,620]. For example, cinnamaldehyde (COX2 and CYP1A2 inhibitor) enhanced analgesia of a low dose of Di [206]. The authors hypothesized that cinnamaldehyde could increase Di absorption by increasing gastrointestinal blood flow by vasodilatation. Our results suggest that the inhibition of CYP1A2 and additional inhibition of COX2 could help explain those results. The same explanation could fit to the results of Matejczyk et al. [621], where the association of Di with chlorogenic acid resulted in increased toxicity to *E. coli* K-12. Resveratrol has shown to significantly interact with Di, probably due to CYP2C9 inhibition [622]. Our findings are in line with those conclusions, since resveratrol inhibits CYP2C9, CYP1A2, CYP2C19, CYP3A4, and OATP1B3 (SLC21A8), all contributing to the observed pharmacokinetic changes. A similar effect on CYP2C9 was found with association of Di with genistein [245]. Therefore, it is reasonable to conclude that bioactives with potential to inhibit CYP2C9 and COX2 (please refer to Figure 7 for additional examples) have a great chance to originate clinically relevant HDI and should not be associated with Di.

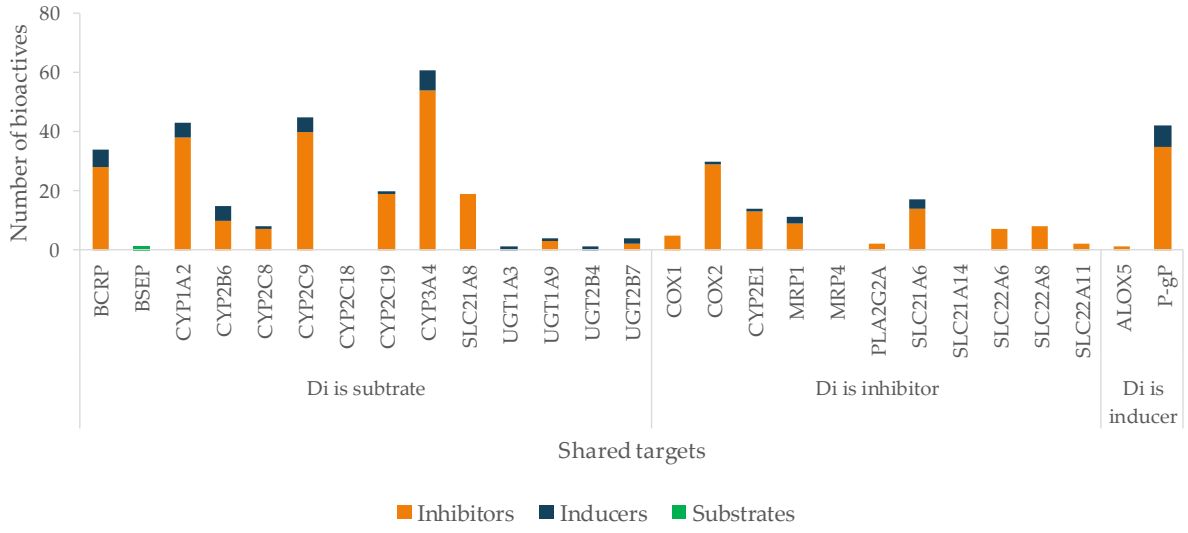


Figure 10. Number of bioactives affecting the shared targets with Di and respective mode of interaction (induction/inhibition). For clarity and due to relevance, bioactives were considered as substrates only for BSEP.

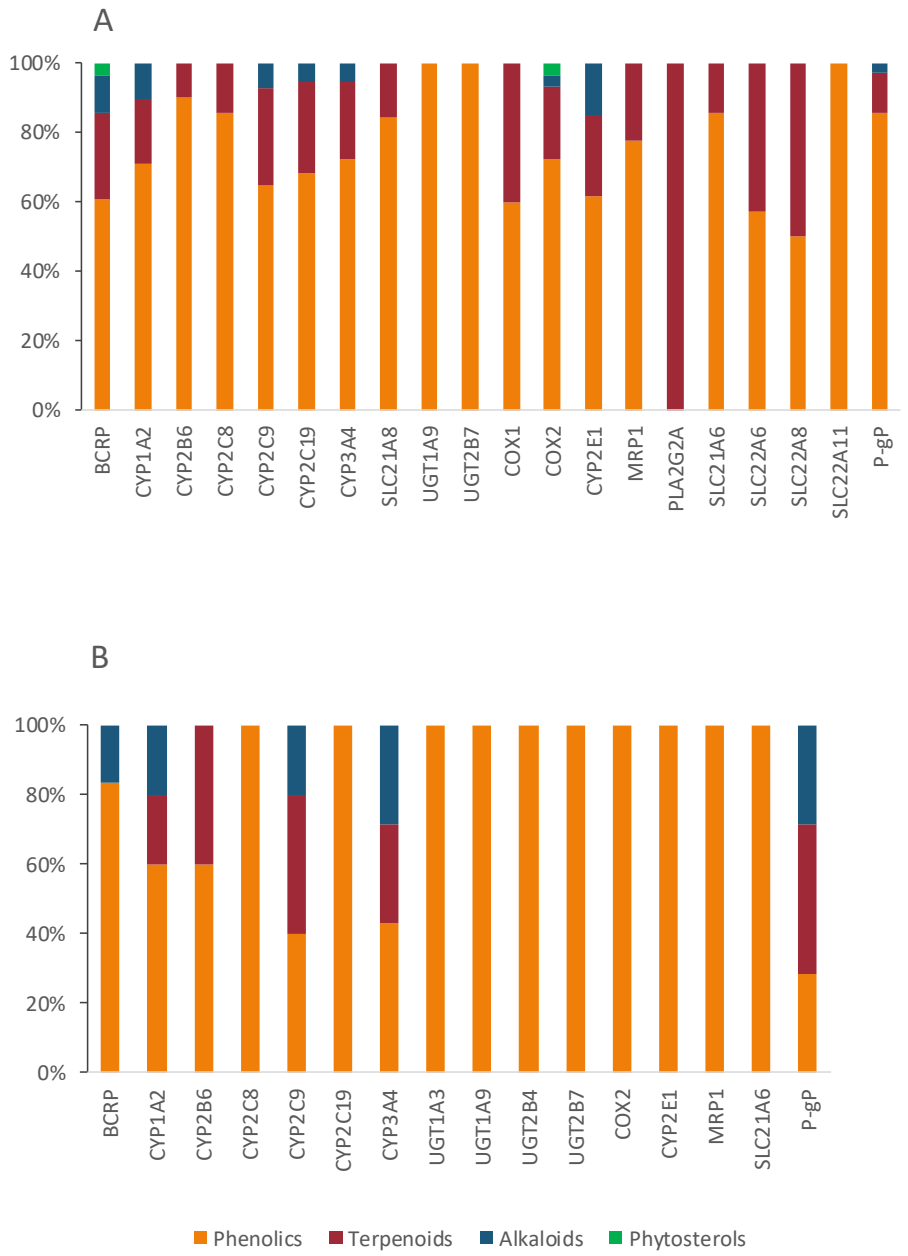


Figure 11. Characterization of the bioactives inhibiting (**A**) or inducing (**B**) Di shared targets, according to chemical class.

BSEP is a uni-directional efflux transporter expressed in the liver, involved in the elimination of bile salts from the hepatocyte [623]. In the case of inhibition, bile salts will not be cleared and ultimately accumulate in the liver, causing cholestasis and liver injury [624]. Di and At are BSEP substrates, as well as glycyrrhizin. No reports were found on bioactives/plant inhibition of BSEP, but the fact that those three molecules may compete for the transporter must not be ignored and is highlighted in Figures 10 and 11. Since no bioactive interfered with BSEP, neither by induction nor by inhibition, they were not represented; bioactives were considered as substrates only for BSEP of which Di is also a substrate and may indicate some sort of competition.

5.4.2. Atorvastatin

At is a lipid lowering drug included in the statin group (lipophilic statin), considered the first-line treatment for dyslipidemia and in prevention of cardiovascular events. At can

cause moderate side effects, but also, although rarely, serious side effects such as liver problems and kidney failure, as well as myopathy, which can progress to rhabdomyolysis, a potentially life-threatening complication. As reported in the drug label, the most common side effects include cold symptoms such as runny nose, sneezing, and coughing, diarrhea, heartburn, joint pain, forgetfulness, and confusion.

The mechanism of action of At is due to competitive inhibition of the HMG-CoAR, the enzyme involved in the hepatic synthesis of cholesterol, through the production of mevalonate [625]. At is mainly metabolized by CYP3A4, 3A5, 3A7, and 2C8 enzymes, and it is also a substrate of BSEP, MRPs, P-gP, and BCRP, four SLC transporters and UGTs (Table 2). All of these targets contribute to At disposition, and, therefore, changes in any of them may modify At plasma profile and compromise the therapeutic outcomes. The great variety of CYP enzymes and efflux and uptake transporters of which At is a substrate, typical of a BDDCS class II drug, makes it more likely to suffer HDI, especially concerning since At is a HAM. In fact, amongst the bioactives under study, several have the potential to modulate most of those targets. For instance, there are 28 inhibitors of BCRP, 54 of CYP3A4, 35 of P-gP, 19 of SLC21A8, and 14 of SLC21A6 (Figure 12). Most bioactives have the potential to modulate multiple At targets, such as naringenin (inhibits BCRP, CYP3A4, HMGCoAR, P-gP, SLC21A6, SLC21A8, and SLC21A9 and induces UGT1A1 and UGT1A3), quercetin (inhibits CYP2C8, CYP3A4, MRP1, MRP2, P-gP, SLC21A6, SLC21A8, and SLC21A9 and induces UGT1A1 and BCRP), and EGCG (inhibits BCRP, CYP2C8, CYP3A4, CYP3A5, P-gP, SLC21A6, SLC21A8, and SLC21A9). Hence, if co-administered with At, they can cause pharmacokinetic and pharmacodynamic changes, with the possibility of compromising the efficacy and safety of the drug. Regarding HMGCoAR, naringenin, genistein, α-asarone, luteolin, resveratrol, rutin, naringin, chlorogenic acid, oleanolic acid, catalpol, β-sitosterol, and phytol may potentiate the inhibitory effect of At, since they are all inhibitors of the enzyme. Naringin proved to be a bioenhancer towards At, since the co-administration of both of them resulted in higher At plasma levels in rats. This effect was associated with the inhibition of CYP3A4 and P-gP by naringin [626].

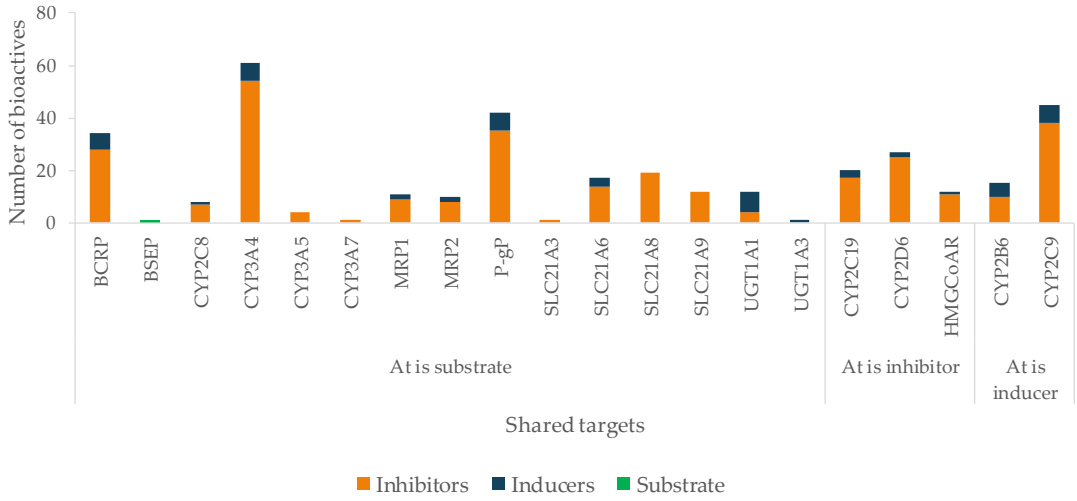


Figure 12. Number of bioactives affecting the shared targets with At and respective mode of interaction (induction/inhibition). For clarity and due to relevance, bioactives were considered as substrates only for BSEP.

The alkaloid berberine has been used as a cholesterol-lowering agent through a mechanism different from that of statins [627]. In the study of Feng et al. [628] the association of berberine with At had a greater inhibitory effect of CYP3A4 than the drug alone. Additionally, Glycyrrhizin and At are both substrates of BSEP, and they could compete for the binding site of BSEP, as discussed earlier for Di, which is a BSEP substrate as well.

OATP1B1 (SLC21A6), OATP1B3 (SLC21A8), and OATP2B1(SLC21A9) are the most relevant uptake transporters of At. OATP1B1 is inhibited by 14 bioactives (naringenin, EGCG, ECG, quercetin, genistein, curcumin, hyperforin, apigenin, ursolic acid, rutin, catechin, tannic acid, biochanin A, and myricetin); OATP1B3 is inhibited by 19 bioactives (EGCG, ECG, naringenin, quercetin, curcumin, hyperforin, apigenin, ursolic acid, nobiletin, p-kaempferol, rutin, naringin, biochanin A, gallic acid, quercetin-3-*O*-β-D-glucuronide, delphinidin, salvianolic acid, isorhamnetin, and glycyrrhizin) and OATP2B1 by 12 bioactives (EGCG, naringenin, naringin, quercetin, hypericin, hyperforin, apigenin, ursolic acid, nobiletin, p-kaempferol, quercetin-3-*O*-β-D-glucuronide, and cyanidin-3-*O*-β-glucoside). On all three carriers, more than 80% of the inhibitors are phenolic, and the remaining are terpenes (Figure 13A). Inducers are scarce (Figure 12) and mainly phenolic. Exceptionally, the MRP2 is not induced by any phenolic, but by one terpene (hyperforin) and one alkaloid (β-carboline) (Figure 13B). At and curcumin have been reported to act synergistically in lipid lowering effect [629].

Figure 13. Characterization of the bioactives inhibiting (**A**) or inducing (**B**) At shared targets, according to chemical class.

Flavonoids like apigenin, quercetin, and kaempferol have been reported to competitively inhibit OATP1B1 [250]. This, in addition to CYP3A4 inhibition, could alter the pharmacokinetics and pharmacodynamics of At [253]. Hyperforin, a terpenoid, has been

related to cause an increased efflux ratio of At in Caco-2 cells transcellular transport through the inhibition of OATP2B1 [443].

The number of HDI possibilities is overwhelming if we consider the huge number of plants reported to have an effect on cognition, the vast quantity of different bioactives present in each plant, and the complex network of targets involved in both drug and bioactive disposition and action. Moreover, drugs and bioactives can interact with the targets in different ways (substrates, inducers, inhibitors, and combinations of them, such as substrate and inhibitor of a given target). Nevertheless, not all HDI has a clinically significant impact on patients' health. The data used to build up our HDI prediction tool has limitations (detailed in Section 6), such as the lack of definition of minimum amount of bioactive necessary to cause HDI, the fact that many data come from in vitro and/or animal studies, which do not always translate to humans, and the fact that no information is provided on the strength of the effect on targets [630]. On the other hand, bioactives studied in the present work are not usually taken alone, but rather included in food supplements (hence, briefly discussed in the following section), in association with other bioactives (for the same therapeutic goal or otherwise). The net effect of such a combination is not easy to predict, but it seems reasonable to speculate that the risk for HDI increases.

5.5. Food Supplements

Food supplements containing the phytochemicals identified in the plants were searched online to assess the prevalence of the potential interactions with drugs. Many of the plants/bioactives (about 80%) are indeed found in commercially available supplements, used for cognitive enhancement and identified in Table 3 with an asterisk.

Products are advertised as brain tonics, nootropics, memory boosters, cognitive enhancers, memory protectors, memory enhancers, and cognition strengtheners, to support memory or improve brain attention, brain health, and cognitive function, concentration, and focus.

It is very common to encounter extracts of the plants rather than a specific bioactive. Additionally, mixtures derived from many different plants are the norm. As examples, NEUROTHERA™ [631] is a food supplement claiming to "Offer combined cognitive function benefits of 11 key neuronutrients" including extracts of *Withania somnifera* (root), *Vaccinium corymbosum* (Blueberry fruit concentrate), *Ginkgo biloba* (leaf), and *Eleutherococcus senticosus* (root); Maxgars Memory Booster [632] includes in the formula 14 different plants: *Bacopa monnieri*, *Centella asiatica*; *Withania somnifera*, *Terminalia arjuna*, *Terminalia bellirica*, *Phyllanthus emblica*, *Terminalia chebula*, *Convolvulus pluriens*, *Mucuna pruriens*, *Acorus calamus*, *Cyperus rotundus*, *Cassia occidentalis*, *Chlorophytum borivilianum*, and *Asparagus racemosus*.

The most common dosage forms are hard gelatin capsules, tablets, and soft gels, depending on the solubility of the bioactive/extract/tincture. Formulation and manufacturing processes (e.g., to avoid degradation, improve bioavailability, or correct organoleptic properties) are sometimes patent protected [633].

To safeguard consumers, who often confuse food supplements and drugs, the first should undergo a thorough, systematic monitorization, which would allow for the collection of reliable information on the safety of these products and thus the development of guidelines for its safe and effective use, as postulated for herbal medicines [634].

6. Final Remarks

Phytochemicals (bioactives) found in plants and food supplements are used as cognitive enhancers. Since they are part of the plant defense mechanism against predators, they can be toxic and interact with drugs sharing the same targets. The occurrence of the potential risks depends on exposure levels, which may be high, especially when various food supplements are taken simultaneously. To safely assess potential toxicity and HDI, the right daily dose of the bioactive should be established, standardized, and strictly controlled in food supplements.

The potential of such compounds to affect the pharmacokinetics or pharmacodynamics of drugs usually used by the elderly, a particularly sensitive age group due to polymedication, has not been studied yet. Thus, based on the documented reports available in literature for the interaction potential on targets, including enzymes, transporters, and receptors, an attempt has been made to postulate their HDI potential.

Limitations to the study relate to: (a) counting every reported action on target, regardless of whether they were obtained in vivo (animals or humans), in vitro, or in silico studies; (b) published studies are sometimes contradictory, in which case interaction was disregarded; (c) not every possible HDI mechanism has been contemplated (e.g., competitive binding to plasma proteins); and (d) the intensity of interactions is unknown, because they are dependent on dose and presence of other constituents in the plant matrix or food supplements. In fact, our study has considered the bioactives individually, and that might be misleading. Plants are sometimes used as a whole, or in the form of extracts, which contain very complex mixtures of compounds affecting the targets in diverse manners. Moreover, many food supplements contain cocktails of different plants, further hampering evaluation of the potential hazards.

Although efficacy evidence may be feeble (e.g., because studies were done in vitro, in animals, or in a limited number of individuals), the fact is that many of the plants studied are sold as food supplements and show potential for interacting with drugs, compromising the safety and efficacy of the latter. In fact, our study shows that HDI should not be ignored, strengthening the idea that when a patient starts a therapeutic regimen, or a new drug, these should be carefully assessed.

Plants containing alkaloids seem to be particularly involved in neurotransmission regulation, while polyphenols present the highest potential of neuroprotection and HDI (67% of the 75 bioactives affecting at least four targets are phenolic). Our research suggests that many herbs/bioactives interact with the drugs under study through a complex cytochrome P450 (mainly CYP3A4, CYP1A2, and CYP2C9) and/or transport mechanism, mainly involving P-glycoprotein, BCRP (ABCG2) and OATP1B3 carriers (SLC21A8). Approximately 30% of all the bioactives studied modulate CYP2C9 and CYP1A2, and the number rises to 45% when the target is CYP3A4 (70% of the drugs studied are substrates of this enzyme). In terms of transport, P-gP is the most involved carrier, modulated by 36% of the 170 bioactives studied, followed by BCRP (21%) and OATP1B3 (12%), in line with other reviews [630]. Additionally, we found COX2 to be a critical target for HDI (30%), which may be of particular concern for anti-inflammatory drugs such as Di. On the other hand, drugs may also affect the bioactive disposition. In our study, 89 of the 170 bioactives (52%) are substrates of at least one shared target with the 10 drugs.

Naturally, not every target modulation identified results in changes with clinical significance. Furthermore, a cellular transporter–enzyme interaction may not translate into an in vivo clinically relevant interaction. However, the higher the number of targets affected, the bigger the likelihood of interaction and of that interaction having clinical significance due to potentiation of effects.

Nevertheless, in this work we have created a database of interactions of 170 bioactives with 10 drugs, which may help doctors when prescribing, nutritionists in clinical practice, and pharmacists when counselling in the community or hospital pharmacy. Though only a limited number of drugs were selected, this work constitutes a helpful tool to anticipate interaction potential with other drugs affecting the same targets.

Supplementary Materials: The following are available online at https://www.mdpi.com/1999-4923/13/1/124/s1, Figure S1: Number of drugs interacting with the different targets (enzymes, transporters and receptors) as substrates, inducers/upregulators and inhibitors/downregulators/antagonists. Figure S2. Frequency of target modulation by bioactives, as a measure of HDI potential.

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A.I.F. have conceptualized, analyzed the data, written, and made the scientific review and editing of the final version of the paper. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

ABC	ATP-binding cassette
ABCG2	ATP Binding Cassette Subfamily G Member 2
AChE	Acetylcholinesterase
ADME	Absorption, distribution, metabolism and elimination
Al	Alprazolam
ALOX5	Arachidonate 5-lipoxygenase
AMPK	AMP-activated protein kinase
At	Atorvastatin
ATC	Anatomical Therapeutic Chemical
BChE	Butyrylcholinesterase
BCRP	Breast cancer resistance protein
BDDCS	Biopharmaceutics Drug Disposition Classification System
BSEP	Bile salt export pump
Cl	Clopidogrel
COMT	Catechol-*O*-methyltransferase
COX	Cyclooxygenase
CYP	Cytochrome P450
Di	Diclofenac
ECG	Epicatechin gallate
EGCG	Epigallocatechin-3-gallate
GABA	γ-Aminobutyric acid
GLP-1	Glucagon-like peptide-1
HAM	High-Alert Medications
HDI	Herb–drug interactions
5-HI	5-hydroxyndoleacetic acid
5-HT	5-hydroxytryptamine
HMC	Herbal Medicines Compendium
HMGCoAR	3-hydroxy-3-methyl-glutaril-CoA reductase;
IP	Indian Pharmacopoeia
ITC	International Transporter Consortium
JP	The Japanese Pharmacopoeia
L-DOPA	Levodopa
MAO	Monoamine oxidase
MATE	Multi-antimicrobial extrusion protein
MDR1	Multidrug resistance protein 1
Me	Memantine
MRP	Multidrug resistance-associated protein
Mt	Metformin
NMDA	*N*-methyl-D-aspartate
OAT	Organic anion transporter
OATP	Organic-anion-transporting polypeptide
OCT	Organic cation transport
PEPT	Peptide transporter
P-gP	Glycoprotein P
Ph.Eur	European Pharmacopoeia

Pi	Piracetam
PLA2G2A	Phospholipase A2 Group IIA
PPRC	Pharmacopoeia of People's Republic of China
Pr	Propranolol
Se	Sertraline
SLC	Solute Carriers
SLCO	Solute carrier organic anion transporter
Ta	Tadalafil
UGT	Uridine diphosphate-glucuronosyltransferase
USP	United States Pharmacopoeia
WHO	World Health Organization

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