BIOINFORMATICS STUDY OF NATURAL COMPOUNDS WITH PREDICTABLE ANTI-ALZHEIMER EFFECTS *VERSUS* DONEPEZIL

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Abstract. Alzheimer's disease is considered a severe, irreversible and progressive disorder with important cognitive and behavioral impairments. At present, the pharmacological management in Alzheimer disease is based on a few clinical approved drugs - memantine, donepezil, rivastigmine - with unclear molecular mechanisms, but severe reported side effects. Here, we present bioinformatics and cheminformatics tools in order to identify relevant structure-biological activity relationships of some natural compounds with possible anti-Alzheimer's disease activity. Molecular descriptors and pharmacokinetics profiles of resveratrol, kaempferol and ginkgolide B were calculated and evaluated against donepezil similar features.

Key words: Alzheimer's disease, donepezil, kaempferol, ginkgolide B), resveratrol, blood-brain barrier (BBB), central nervous system (CNS).

INTRODUCTION

Histopathological analyses have drawn attention to the great number of patients suffering from Alzheimer's disease (AD). These analyses confirm the diagnosis which up to that time represented a state of senility [9].

Research has shown that memory impairment in repeated cases, such as amnesia, may be considered an early symptom of Alzheimer's dementia syndrome. Neuropathological studies have shown that the first affected brain structures are present in the temporal lobe, namely the hippocampus, which is important in the formation of long-term memory, as well as the entorhinal cortex, which is important for short-term memory [18].

Early manifestation of progressive neurodegeneration of AD is determined by the onset of symptoms during the mild phase of the disease and its presence may represent a long-term predisposition to a psychiatric illness that is thought to have a

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genetic component. In patients who have a genetic predisposition for this disease one considers that the age of onset tends to be conserved within the family [17].

After the initial description of AD, many researchers have studied it carefully in order to find the pathological processes that intervene in the onset and evolution of the disease. Two major processes involved in the onset and progression of AD are the accumulation of amyloid β peptides and tau proteins [14].

Due to the link between pain and the neurotransmitter acetylcholine, acetylcholinesterase has become an important drug target in AD. These have a fundamental role for patients who have the disease in its incipient stage. Donepezil is a potent acetylcholinesterase inhibitor and has been shown to be effective in treating AD, it manages to maintain relatively constant acetylcholine levels in the brain. Thus, treatment with donepezil slows down the evolution of the disease [11]. However, recently studies show that inhibitory substances isolated from plants have promising effects for AD therapy [2].

Currently, the limited potential of pharmacological therapy in AD management led to an increasing interest for disease pathology and significant progress was made in identifying new therapeutic targets. Over the last decade, various pharmaceutical active compounds extracted from plants showed a beneficial effect in the treatment of AD [5, 24].

Natural compounds are better tolerated by the organism and have a lower incidence of side effects. Natural compounds are generally small molecule compounds that can be very well absorbed in the intestine and can also break through the blood brain barrier and reach the target site with increased efficiency and accuracy. Because they are natural compounds, the administered dose can be very high without harming the patient [16]. Natural compounds used in this study are: resveratrol, ginkgolide B and kaempferol [21].

In AD, resveratrol, a natural compound, is well tolerated by the patient. Resveratrol can have many molecular effects such as anti-inflammatory and antioxidant action, as well as anti-amyloid β aggregation. Resveratrol also promotes autophagy, thus removing toxic intraneuronal protein aggregates. Another effect of resveratrol is to facilitate the activation of microglia by determining long-term adaptive immunity [11]. Studies carried out by Ahlemeyer and Krieglstein on cell cultures from rat neurons have shown that ginkgolide B has the property to protect neurons from glutamate damage and have been able to reduce serum-induced apoptosis. From this study it appears that ginkgolide B may have neuroprotective and antiapoptotic effects in mouse neurons [1]. Clinical studies have shown that postmenopausal estrogen therapy protects cells against the toxic effects of amyloid β. Because of this, estrogens have become a possible treatment for AD [6]. Kaempferol is a natural substance isolated from mint and pumpkin. This substance has been shown to have a protective effect on cells against the toxic effects of amyloid β plaque accumulation, which is one of the causes of AD [4].

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Here, molecular descriptors, as critical pharmacological features and pharmacokinetics profiles, of resveratrol, kaempferol and ginkgolide B were calculated and evaluated versus donepezil similar features [15].

MATERIALS AND METHODS

The drug discovery process is expensive and time consuming, including both preclinical and clinical phases. Computational methods and bioinformatics data are versatile and useful tools for the elucidation of both drug discovery and novel therapeutic features of natural compounds, thus lowering the development costs and accelerating the process [3, 15].

BIOINFORMATICS TOOLS

Freely accessible online databases (DrugBank [23], FooDB [2]) are of great help when studying the therapeutic potential of a natural compound. A brief description of them is presented below:

DrugBank [23] is an online, wide-range bioinformatics resource that accommodates information about drugs and drug targets. Because of its dual character (it is both a cheminformatics and bioinformatics tool), DrugBank contains comprehensive information regarding drug features (i.e. chemical, pharmaceutical and pharmacological characteristics), as well as detailed information about drug targets [23]. FooDB [25] is a freely accessible database comprising detailed computational, biochemical and physiological information about food constituents [13]. In this paper, we accessed DrugBank [23] database for the retrieval of information on donepezil, a synthetic compound presented above as important in the treatment of Alzheimer's disease and FooDB [25] to collect structural and functional features of natural compounds: resveratrol, kaempferol and ginkgolide B.

CHEMINFORMATICS TOOLS

In order to explore the therapeutic effect of natural compounds "druglikeness" and pharmacokinetics profiles, namely ADME-TOX (absorption, distribution, metabolism, excretion and toxicity), several cheminformatics tools were used. For this aim we accessed molinspiration [26], and pkCSM cheminformatics platform [27]. Molinspiration [26] provides a wide range of cheminformatics software tools, supporting molecule manipulation and processing [18]. In this paper, molinspiration [26] was used for the prediction of various physicochemical properties, necessary for assessing the drug-like character of chemical compounds. pkCSM [27] was used

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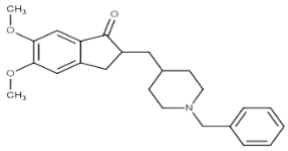
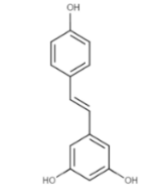
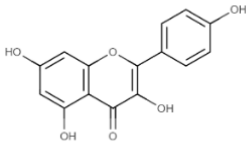
to predict pharmacokinetics (ADME-TOX): absorption, distribution, metabolism, excretion and toxicity) features of natural compounds versus donepezil.

MOLECULAR MODELING OF NATURAL STRUCTURES AND DONEPEZIL

In this study we used the 2D format of natural compounds - resveratrol, kaempferol and ginkgolide B and of the drug already used in clinical - donepezil. We used SMILES (Simplified Molecular Input Line Entry System) files obtained from DrugBank [23] database and FooDB [25]. The 2D chemical structure of the compounds and SMILES codes are presented in Table 1.

Table 1

The name of the compounds, the 2D structures and the SMILES codes

Compounds	**2D structure**	**SMILES code**
Donepezil		COC1=C(OC)C=C2C(=O)C(CC3CCN(CC4=CC=CC=C4)CC3)CC2=C1 [28]
Resveratrol		OC1=CC=C(\C=C\C2=CC(O)=CC(O)=C2)C=C1 [29]
Kaempferol		OC1=CC=C(C=C1)C1=C(O)C(=O)C2=C(O1)C=C(O)C=C2O [30]

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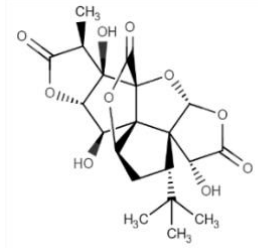
Ginkgolide B		CC1C(=O)OC2C(O)C34C5CC(C(C)(C)C)C33C(O)C(=O)OC3OC4(C(=O)O5)C12O [31]

CALCULATION OF MOLECULAR DESCRIPTORS OF RESVERATROL, KAEMPFEROL AND GINKGOLIDE B

In our paper several descriptors belonging to 2D descriptors were calculated These include physical properties such as: steric (subdivided van der Waals surface and volume, topological surface area), atom and bond counts (hydrophobic/polar, donor/acceptor atoms, rigid and rotatable bonds) and hydrophobicity (*logP*), etc. In the end, according with our previous study [6], we selected a few molecular descriptors (Table 2) that appear to be essential for the therapeutic effect of the natural compounds studied in this paper versus molecular descriptors for Donepezil.

Table 2

Short description of molecular descriptors used to predict the pharmacological action of both the natural compounds (resveratrol, kaempferol, ginkgolide B) and the synthetic compound, donepezil.

Descriptors	**Description**
Hidrophobicity (*logP*)	A compound's concentration in a given volume of n-octanol divided by its concentration in a given volume of water after octanol and water reached equilibrium.
Rotatable bonds	The number of rotatable bonds.
Polar surface area (*TPSA*)	The accessible surface calculated around all polar atoms, measured in Å$_2$.
H-bond acceptors	The number of hydrogen bonds acceptors atoms.
H-bond donors	The number of hydrogen bond donors atoms.
Molecular weight (*MW*)	The mass of a given molecule, measured in g/mol.

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ESTABLISHING THE DRUG PROFILES "DRUGLIKENESS" OF NATURAL COMPOUNDS

Lipinski's "rule of five" is an essential criterion for identifying the chemical compounds likely to present pharmacological action in the biological systems. In accordance with the mentioned rule, the druglikeness of a compound is determined by the following physicochemical properties, computed with the help of the above mentioned cheminformatics tools: (i) a maximum number of 5 hydrogen bond donors and 10 hydrogen bond acceptors, (ii) a molecular mass lower than 500 Daltons, (iii) the octanol-water partition coefficient *logP* not greater than 5, (iv) no more than 10 rotatable bonds and (v) topological polar surface area (*TPSA*) equal or less than 140 $Å_2$ [8, 10, 19].

Veber's rule refers to the properties of a compound to be administered orally. Its characteristics are: 10 or fewer rotatable bonds, less than 12 H bond donors or acceptors in total, a polar surface area of less than 140 $Å_2$. Bioavailability represents an important rule for the drug development process because oral administration is easier for the patient compared to injection [7, 22].

PREDICTED ADME-TOX PHARMACOKINETIC PROFILES

Computational prediction of ADME-TOX properties (absorption, distribution, metabolism, excretion and toxicity) is essential for the drug discovery process. Most frequently, the toxicity of a given compound can be a deal-breaker for the development of novel pharmacological agents. Computational toxicity estimations are not only faster than the experimental determination of toxic doses in animals, but can also help reduce the costs and usage of great numbers of animal test subjects. In addition to toxicity, ADME-TOX also provides information about the absorption, distribution, metabolism and excretion of a certain compound.

pkCSM [27] is a freely accessible online tool used to determine predictive classification models for the ADME-TOX properties.

By using the cheminformatic tool, pkCSM [27], we have selected the following parameters from the predictive ADME-TOX modules: (1) Absorption – Intestinal absorption (human % absorbtion). A molecule with an absorbance of less than 30% is considered to be poorly absorbed; (2) Distribution – (i) BBB permeability (Numeric (*logBB*)), *logBB* more than 0.3 indicates good BBB permeability, a value lower than −1 indicates low BBB permeability; (ii) CNS permeability (Numeric (*logPS*)) – *logPS*: values higher than −0.2 indicate a compound that can penetrate the CNS, a value lower than –3 indicates a compound unable to penetrate the CNS; (3) Toxicity – (i) AMES toxicity (mutagenic potential of a drug), (ii) carcinogenity and (iii) hepatotoxicity [10,12].

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RESULTS

STRUCTURE-BIOLOGICAL ACTIVITY RELATIONSHIP (SAR) OF NATURAL COMPOUNDS *VERSUS* DONEPEZIL

Based on comparative analysis of the molecular mechanism and of the molecular targets of various natural compounds, we selected three natural compounds that are present in spices and in the typical plant foods commonly used by humans. The chosen natural compounds are: kaempferol, resveratrol and ginkgolide B. We compared the molecular features of natural compounds with identical molecular features described for donepezil, a drug used in the treatment of AD and approved by the FDA (U.S. Food and Drug Administration) in order to define the structure-biological activity relationship (SAR). Donepezil is a cholinesterase inhibitor that has the effect of alleviating the symptoms of AD in its moderate and severe stages. This synthetic medicine loses its efficiency with time, for this reason once the body becomes accustomed to the drug the daily dose needs to be modified.

In Table 3 we presented the critical molecular features which recorded significant variations during compounds series.

Table 3

Molecular properties of natural compounds (resveratrol, ginkgolide B, kaempferol) and synthetic compound donepezil

Compunds	***LogP***	***TPSA*(Å$_2$)**	***MW*(g/mol)**	***NrotB***
Donepezil	4.10	38.78	379.5	6
Resveratrol	2.99	60.68	228.25	2
Ginkgolide B	–2.38	148.83	424.4	1
Kaempferol	2.17	111.12	286.24	1

LogP or hydrophobicity is the ability of the compound to pass through the membrane. Our results show that resveratrol (2.99) and kaempferol (2.17) presented a value of *logP* similar to donepezil (*logP* = 4.10), but different for ginkgolide B. This natural compound appeared to be more hydrophilic than donepezil.

MW represents the molecular weight, and if it has a lower value than 500 g/mol it manages to diffuse more easily through the membrane. However, there is a risk that the compound will remain stuck in the membrane. We can notice a large

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variation of molecular weights throughout our compounds series from 228.25 (resveratrol) to 424.4 (ginkgolide B).

Significant variation of molecular descriptors was recorded from topological polar surface. It varies from 38.78 $Å_2$ (donepezil) to 148.83 $Å_2$ (ginkgolide B). Our results suggested that donepezil and resveratrol are described by similar polar surfaces, but ginkgolide B shows a different polar surface.

NrotB (the number of rolling links) represents the ability of the compound to change its conformation. Using this parameter, you can decide if the compounds are flexible. If they have many rotating links, they can no longer pass through the membrane due to steric conflicts. Our results suggested a large difference among natural compounds and donepezil regarding molecular flexibility.

PREDICTED "DRUGLIKENESS" FEATURES OF NATURAL COMPOUNDS

In our study, the features of possible drugs respected by natural compounds, resveratrol, ginkgolide B and kaempferol was analyzed. Our results are presented in Table 4. Our results revealed that all four natural compounds respected the Lipinski's rules. Veber's rule has as its characteristics hydrophobicity which is important because it shows the possibility of small compounds to pass through the plasma membrane. It also recommends a low number of donor atoms and electron acceptors and a low number of rotating bonds, so that the molecule cannot change too much its conformation.

As can be seen in Table 4, the tested compounds comply with Veber's rule except for ginkgolide B, which has a higher polar molecular surface value. The biodisponibility score is 0.55.

Table 4

Lipinski's and Veber's rules calculated with molinspiration [26] for resveratrol, ginkgolide B and kaempferol

Compound	Lipinski's rule	Veber's rule
Donepezil	Yes	Yes
Resveratrol	Yes	Yes
Ginkgolide B	Yes	NO (TPSA>140)
Kaempferol	Yes	Yes

PREDICTED ADME-TOX PROFILES

Using *in silico* tools (pkCSM [27]), we evaluated the predictive ADME-TOX profiles of resveratrol, ginkgolide B and kaempferol *versus* donepezil (Table 5).

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Table 5

Predictive ADME features for resveratrol, ginkgolide B and kaempferol versus donepezil

Compound	**Human intestinal absorption (% absorbed)**	**BBB permeability (Numeric (*logBB*))**	**CNS permeability (Numeric (*logPS*))**
Resveratrol	89.057	–0.41	–2.098
Ginkgolide B	59.984	–0.893	–3.493
Kaempferol	75.342	–1.234	–2.368
Donepezil	94.77	0.428	–1.466

Intestinal absorption is a very important parameter in terms of drug design. Its value for natural compounds resveratrol is similar of the synthetic compound, donepezil. The value of kaempferol is slightly lower than that of the other compounds, but it is close to 70%, which can be considered satisfactory. Not the same result was obtained for ginkgolide B, which presents a low intestinal absorption.

According to the results obtained in Table 5, we can appreciate the ability of the compounds to cross the blood-brain barrier and to perform the function for which they are studied. From these tables we can see that these compounds have a moderate value of BBB.

Resveratrol and kaempferol are likely to slowly penetrate the central nervous system, but not ginkgolide B. Its CNS permeability value shows that it cannot enter. Donepezil enters the central nervous system very well with a CNS value of less than –2.

Table 6

Toxicity features of for resveratrol, ginkgolide B and kaempferol versus donepezil

Compound	**AMES**	**Hepatotoxicity**	**Cardiotoxicity**
Resveratrol	NO	NO	NO
Ginkgolide B	NO	NO	NO
Kaempferol	NO	NO	NO
Donepezil	NO	NO	NO

Testing the toxicity assessment using PkCSM [20] we assessed that all natural compounds, represented by resveratrol, kaempferol and ginkgolide B, as well

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as donepezil have no activity in terms of AMES toxicity, hepatotoxicity and cardiotoxicity.

CONCLUSIONS

Following the analysis of the physico-chemical properties of the compounds we observed that all the tested compounds comply with the Lipinski's rule and have a bioavailability score of 0.55. Veber's rule are fullfield by the compounds, which can be administered orally, except ginkgolide B.

Resveratrol has a moderate probability of going through the blood-brain barrier and reaching the central nervous system.

Kaempferol has an important action in neuroinflammation, but a very large amount of the compound must be administred in order to reach the central nervous system, because it fails to pass well through the blood-brain barrier. However, it could be a good drug because of its anti-neuroinflammatory action.

Ginkgolide B, although it is a larger compound compared to the other compounds tested, it has the ability to pass very well through the membrane and cross the BBB. Although it presents a violation in the case of oral bioavailability with higher TPSA value, this compound may be effective in the treatment of Alzheimer's disease.

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