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Invited review

Multipotent natural agents to combat Alzheimer's disease. Functional spectrum and structural features[1]

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Abstract

With the accelerated aging of human society, Alzheimer's disease (AD) is becoming one of the biggest threats to human health. Since multiple pathogenetic factors are implicated in the disease, the current hitting-one-target therapeutic strategy has proved inefficient to AD. As a result, finding multipotent agents that aim at multiple targets is attracting more and more attention. Although multifunctional anti-AD agents can be created by incorporating two or more pharmacophores in one scaffold, naturally occurring multipotent agents also attracted much attention. In this review, we first describe the functions of some typical naturally originated multipotent anti-AD compounds, then summarize their structural features and reveal that phenolics with certain flexibility predominate in these agents, which are of significance to find novel multipotent drugs to combat AD and other neurodegenerative diseases as well.

Introduction

Since the discovery of Alzheimer's disease (AD) in 1907, considerable effort has been devoted to combating the disease. However, up to now, there is no effective therapeutics. With the accelerated aging of human society, AD is becoming one of the biggest threats to human health[1–3]. Although the etiology of AD is not very clear, multiple pathogenetic factors have been identified for the disease, which include amyloid-β (Aβ) peptide and/or τ protein aggregation, excessive metal ions (*eg*, Cu^{2+}, Zn^{2+}, Fe^{3+}), oxidative stress and reduced acetylcholine (ACh) level, *etc*[1–8]. Besides, genetic factors and lifestyles, such as diet, exercise and cognitive stimulation, are also associated with AD development[9,10].

Despite the diverse pathogenetic factors involved in AD, the current anti-AD strategy depends largely on single-targeted drugs, especially acetylcholinesterase (AChE) inhibitors. As these drugs' effects are quite limited[11], more and more attention is given to fin d multiple-targeted agents to hit more than one target implicated in AD[12,13]. Although the new anti-AD strategy may be fulfilled by combining different anti-AD drugs in one pill (cocktail therapeutics)[14,15], an alternative approach that aims at multiple AD-targets with a single structure (termed multipotent agent) is also attractive, because of its advantages in reducing risks of drug-drug interactions and controlling pharmacokinetic behaviors[15].

Thanks to the continuing effort of medicinal chemists in the past decade, many multipotent anti-AD agents have been rationally designed by incorporating two or more pharmacophores in one scaffold, in which the pharmacophores for inhibiting AChE were most widely used[12,13]. For instance, Rosini *et al*[16] designed a hybrid compound (lipocrine) (Figure 1) by linking tacrine, an AChE inhibitor, and lipoic acid, a universal antioxidant. Rodríguez-Franco *et al* coupled tacrine to melatonin, a pineal neurohormone and a preventive antioxidant (Figure 1)[17]. These hybrid molecules exhibited markedly enhanced activity with respect to AChE inhibition and antioxidant properties compared with either of the original molecules[16,17]. By joining together the pharmaco-phores for inhibiting AChE and monoamine oxidases B (MAO-B), *ie*, carbamate and propargyl group, Sterling *et al*[18] also obtained novel dual inhibitors of AChE and MAO.

Despite the preliminary successes of synthetic hybrid agents, the latent risks in safety and bioavailability is a big

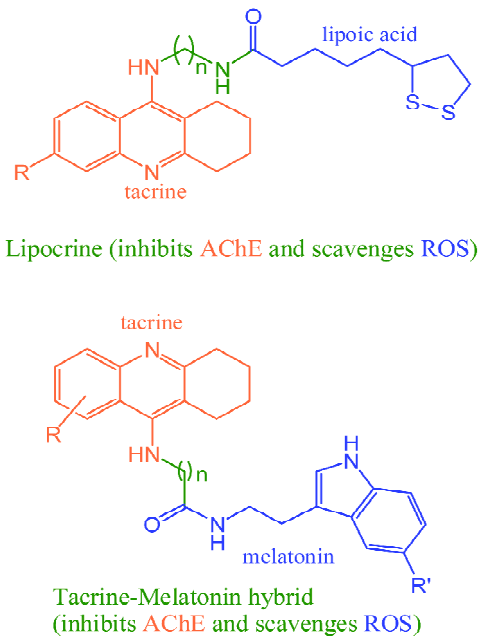


Figure 1. Synthetic multipotent agents to combat Alzheimer's disease.

concern in their further development. Thus, finding multipotent natural agents to combat AD is attracting more and more attention.

Multipotent anti-AD agents derived from foods

In the past few years, some epidemiological investigations revealed that high consumption of some foods (or beverages) were inversely associated with AD incidence[19–25]. These foods include fruit and vegetable juices, green tea, wine, Mediterranean diet, curry spice turmeric and even cigarettes, all of which contain antioxidants, especially polyphenols. As it is well known that polyphenols are excellent antioxidants both as reactive oxygen species (ROS) scavengers and transition metal chelators[26,27], the anti-AD effects of these foods were naturally linked to their antioxidant potential. Nevertheless, accumulating evidence indicates that the excellent *in vitro* antioxidant activity of phenols can not necessarily be translated into *in vivo* therapeutic effects[28,29]. Thus, it is interesting to note that some antioxidants derived from these foods go beyond modulating ROS. Some representative examples are given as below.

Flavonoids Flavonoids are the most extensively studied polyphenols derived from fruit and vegetable juices and green tea. Multiple pharmacological effects have been identified for flavonoids, many of which are beneficial to combat AD. For instance, quercetin (Figure 2), the representative component of fruit and vegetable juices, can block Aβ- or τ-aggregation (IC_{50}s < 1 μmol/L)[30], inhibit monoamine oxidases A and B (MAO A and MAO B) with IC_{50}s of 0.01 μmol/L and 10.89 μmol/L, respectively[31,32]. In addition, quercetin can efficiently inhibit butyrylcholinesterase (BChE) (with an IC_{50} of 1 μmol/L)[33], a recently recognized potential target for treating AD[34]. As quercetin is highly bioavailable and can pass through the blood-brain barrier (BBB)[35,36], it seems partially responsible for the benefits of fruit and vegetable juices to AD.

(-)-Epigallocatechin gallate (EGCG) (Figure 2) is the representative component of green tea. Some potential anti-AD effects of EGCG have been identified as follows: i) it is a powerful Aβ-aggregation inhibitor with an IC_{50} of 0.18 μmol/L[30]; ii) it attenuates Aβ generation through activating α-secretase[37,38], inhibiting β-secretase (BACE1, with an IC_{50} of 1.6 μmol/L)[39] and reducing iron-regulated amyloid precursor protein expression[40]; iii) it inhibits MAO with an IC_{50} of 10 μmol/L[41]. All of these pharmacological effects are helpful to understand the preventive effects of green tea to AD.

Resveratrol Resveratrol (Figure 2) is a famous phenolic component extracted from red wine, which has been extensively studied in the past 15 years. Some pharmacological effects that are associated with AD treatment have been revealed. First, resveratrol can lower the levels of secreted and intracellular Aβ by promoting protease degradation of the peptide[42]. Second, resveratrol inhibits monoamine oxidase A (MAO-A) with an IC_{50} of 26.6 μmol/L[43]. Third, resveratrol can inhibit cyclooxygenase-1 (COX-1) with an IC_{50} of 24 μmol/L[44] and reduce cyclooxygenase-2 (COX-2) at mRNA level[45].

Olive oil phenols Mediterranean diet consists of olive oil, fruits, vegetables and fish, of which olive oil is of special interest and has been a research focus for decades. Many phenolic compounds have been identified from olive oil[46], some of which exhibit nonsteroidal anti-inflammatory drug-like activities that are beneficial to prevent AD. For instance, Beauchamp *et al* revealed that 25 μmol/L (-)-oleocanthal (Figure 2) inhibited 56.1%±3.2% and 56.6%±9.5% COX-1 and COX-2 activity, respectively[47]. In addition, Bazoti *et al* found that oleuropein (Figure 2) can form noncovalent complex with Aβ peptide or its oxidized form[48].

Curcumin Curcumin (Figure 2), a yellow-orange pigment extracted from curry spice turmeric, has long been used as a food additive in India. Many pharmacological effects have been identified for this pigment[49]. Besides its famous transition metal-chelating ability and anti-inflammatory activity[50–52], curcumin holds Aβ aggregation-blocking poten-

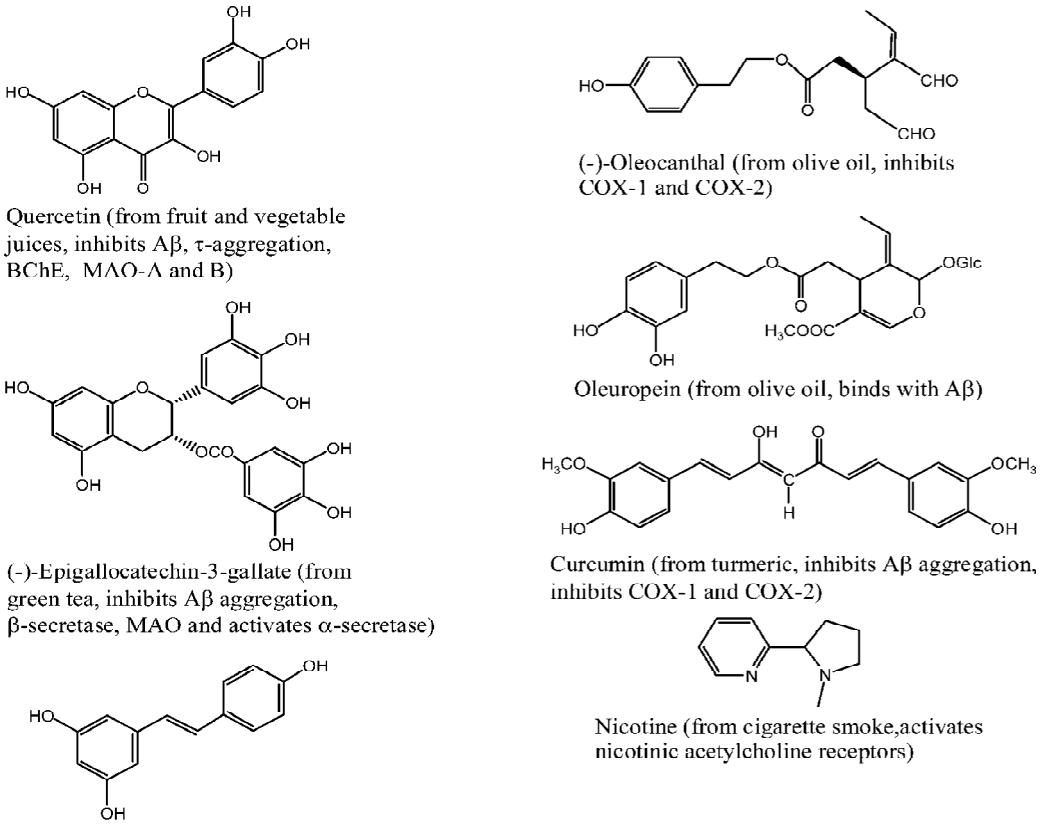


Figure 2. Food-derived multipotent agents to combat Alzheimer's disease. Only the activities that go beyond modulating ROS and metals are listed in parentheses.

tial (with an IC_{50} of < 1 μmol/L)[30] and COX-1-, COX-2-inhibiting activities (with IC_{50}s of 18.8 μmol/L and 15.9± 7.9 μmol/L, respectively).[53,54]

Nicotine Nicotine (Figure 2) is the predominant component of cigarette smoke, which is considered responsible for the cigarettes' benefits to AD. Recently, Zhao and co-workers revealed that nicotine attenuated the β-amyloid neurotoxicity through regulating metal (copper and zinc) homeostasis[55] and activating nicotinic acetylcholine receptors[56,57]. Combining experimental findings and theoretical calculation results, we indicated that the copper(II)-nicotine chelates hold SOD-like activity, which may play a role in the neuroprotective effects of nicotine[58].

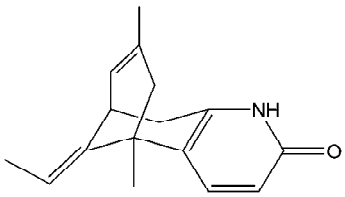
Multipotent anti-AD agents derived from herbs

It is not surprising to note that in addition to foods, some herbal medicines, such as *G Biloba*, *Huperzia serrata*, *Salvia officinalis*, *Melissa officinalis*, also hold anti-AD potential, as revealed by some preliminary clinical trials[59–64]. Some ingredients responsible for the anti-AD effects have been identified from these herbs.

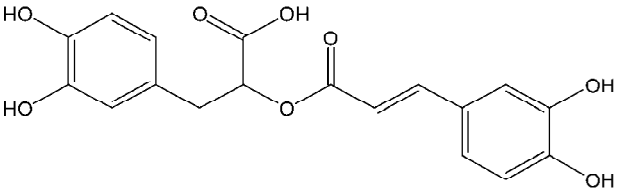
Extract EGb761 (extract G biloba 761), prepared from the leaves of *G biloba* and comprising flavonoids and terpene lactones, was a hot spot of medicinal research in the past two decades. EGb761 has many pharmacological effects in favor of the fight against AD, which include inhibiting Aβ aggregation, attenuating apoptosis, preventing membrane lipid from oxidation and resisting inflammation[65].

Huperzine A (HupA) (Figure 3), an alkaloid isolated from Chinese herb *Huperzia serrata*, is also a potent multipotent anti-AD agent, with activities of inhibiting AChE (with an IC_{50} of 0.082 μmol/L)[60], mitigating oxidative stress, regulating the expression of apoptotic proteins Bcl-2, Bax, p53, and caspase-3, interfering with amyloid precursor protein metabolism and so on, which definitely benefits the neuro-protection[60,61].

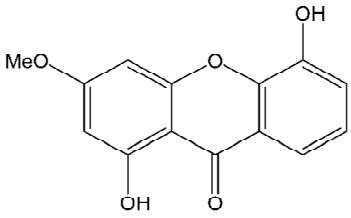
Rosmarinic acid (Figure 3) is likely to be one of the major active ingredients of *Salvia officinalis* and *Melissa officinalis*,



Huperzine A (from *Huperzia serrata*, inhibits AChE, attenuates oxidative stress, regulates the expression of apoptotic proteins Bcl-2, Bax, p53 and caspase-3)



Rosmarinic acid (from *Salvia officinalis* and *Melissa officinalis*, antioxidative, anti-Aβ aggregation and antiapoptotic)



Xanthone (from *Chironia krebsii*, inhibits MAO-A, MAO-B and AChE)

Figure 3. Herb-derived multipotent agents to combat Alzheimer's disease.

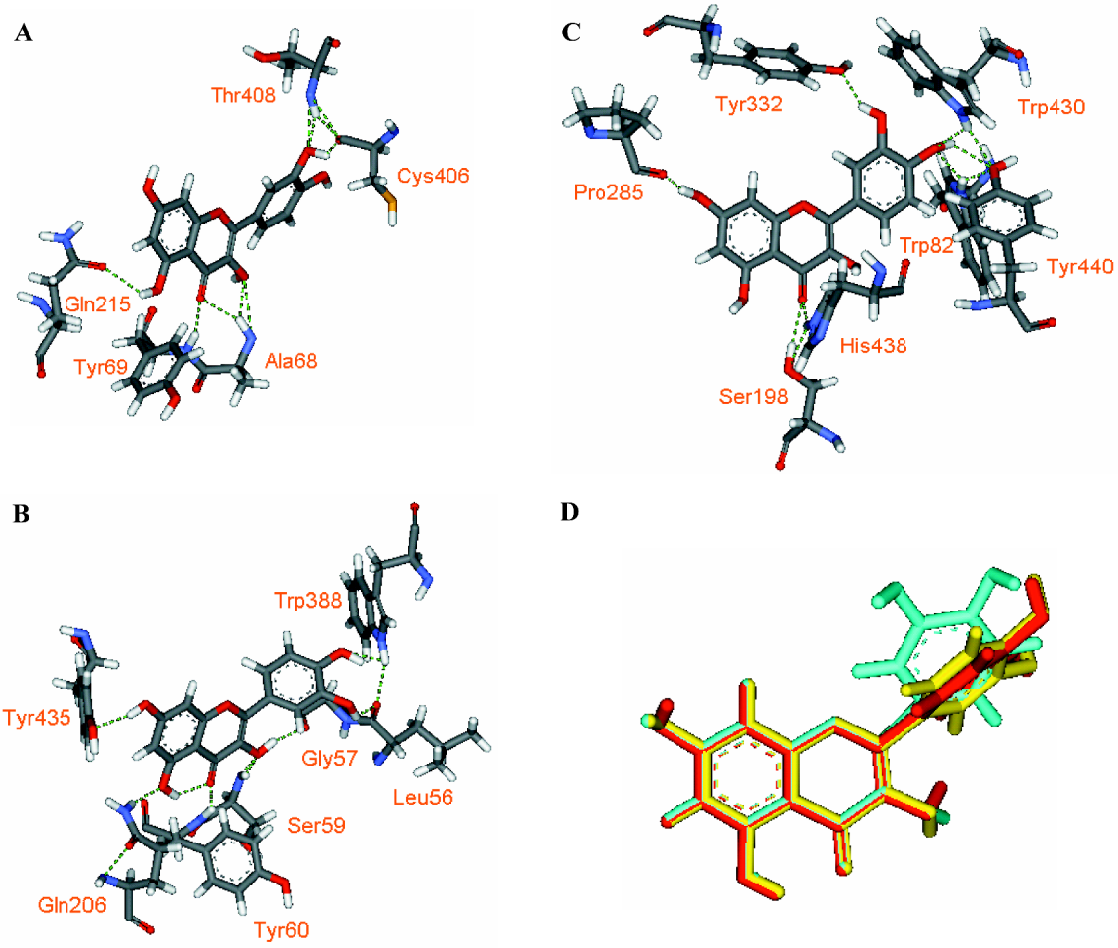


Figure 4. Close-up views of binding modes of quercetin with MAO-A (A), MAO-B (B) and BChE (C) and superimposed quercetin structures in conformations of binding with MAO-A (in yellow), MAO-B (in red) and BChE (in cyan) (D). The hydrogen bonds are marked in green dotted lines.

which exhibits a combination of antioxidative, anti-Aβ aggregation and antiapoptotic effects[66].

Recently, xanthones, a special kind of flavonoids that spread widely in nature, were also found possessing high anti-AD potential. Indeed, some xanthone-containing herbs, such as *Polygala tenuifolia*, show benefits to prevent AD[67]. A representative of multipotent anti-AD xanthone is presented in Figure 3. It can inhibit MAO-A (with an IC_{50} of 0.04 μmol/L), MAO-B (with an IC_{50} of 33.0 μmol/L) and AChE (with a K_i of 16.0 μmol/L)[68,69]. Because of the perfect conjugation of the ring system and the electron-withdrawing property of 1,4-pyrone (the central ring)[70,71], xanthones are weaker electron donors than flavonoids[72], which implies that xanthones are safer than flavonoids with respect to the prooxidant potential.

Structural features of naturally occurring multipotent anti-AD agents

From the structures of rational designed and naturally occurring multipotent anti-AD agents, it can be found that both kinds of compounds are different in scaffold, that is, the latter shows a seamless framework (Figures 2 and 3), while the former is composed of two or more isolated parts, linked by spacers of different lengths, with each part aiming at a particular target (Figure 1). So, it is of significance to explore the natural strategy of "designing" multipotent anti-AD agents.

Through examining the structures of above-mentioned multipotent natural agents, we can find that most of them are phenolics. It is well known that phenolic hydroxyls are the most potent groups to neutralize ROS through donating H-atoms[73] and also effective to chelate transition metal ions[26]. However, the present description shows that natural phenolics go beyond scavenging ROS or chelating transition metals. They can inhibit various enzyme's activities and prevent protein aggregation. The major underlying reason may be that phenolic hydroxyls are H-bond acceptors and H-bond donors simultaneously, which facilitates the binding with protein targets. This explanation is supported by a meta-analysis on phenol-protein binding patterns which revealed that more than 70% phenolic hydroxyls form intermolecular hydrogen bonds (IHBs) with targeted proteins[28]. Another feature of the naturally occurring multipotent anti-AD agents is that their structures contain more than one conjugated rings (most are phenolic rings) and most of the conjugated systems are still flexible. Thus, these molecules reach a good balance between rigidity and flexibility, which must benefit their binding with various targets. To illustrate the importance of these structural features in binding diverse target proteins, some multipotent agents were docked

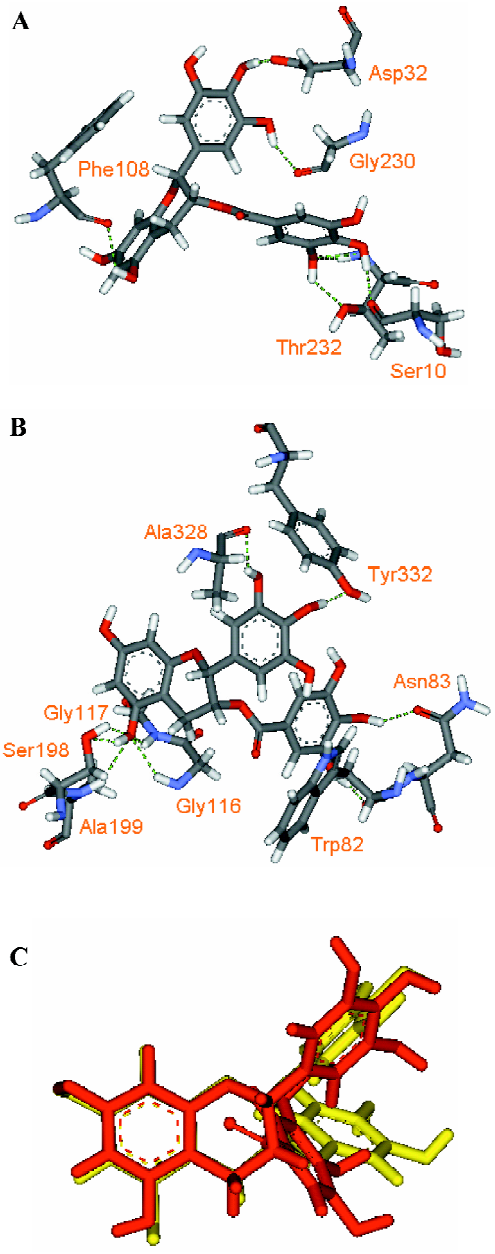


Figure 5. Close-up views of binding modes of EGCG with BACE1 (A) and MAO-B (B) and superimposed EGCG structures in conformations of binding with BACE1 (in yellow) and MAO-B (in red) (C). The hydrogen bonds are marked in green dotted lines.

with corresponding targets. As shown in Figures 4–8, the phenolic hydroxyls indeed tend to form IHBs with surrounding residues and the flexible structures favor the binding between agents and proteins. Finally, since *p*-stacking plays an important role in protein amyloid formation[30,74], the aromaticity of phenolic ring is favorable to prohibit amyloid fibril formation[75].

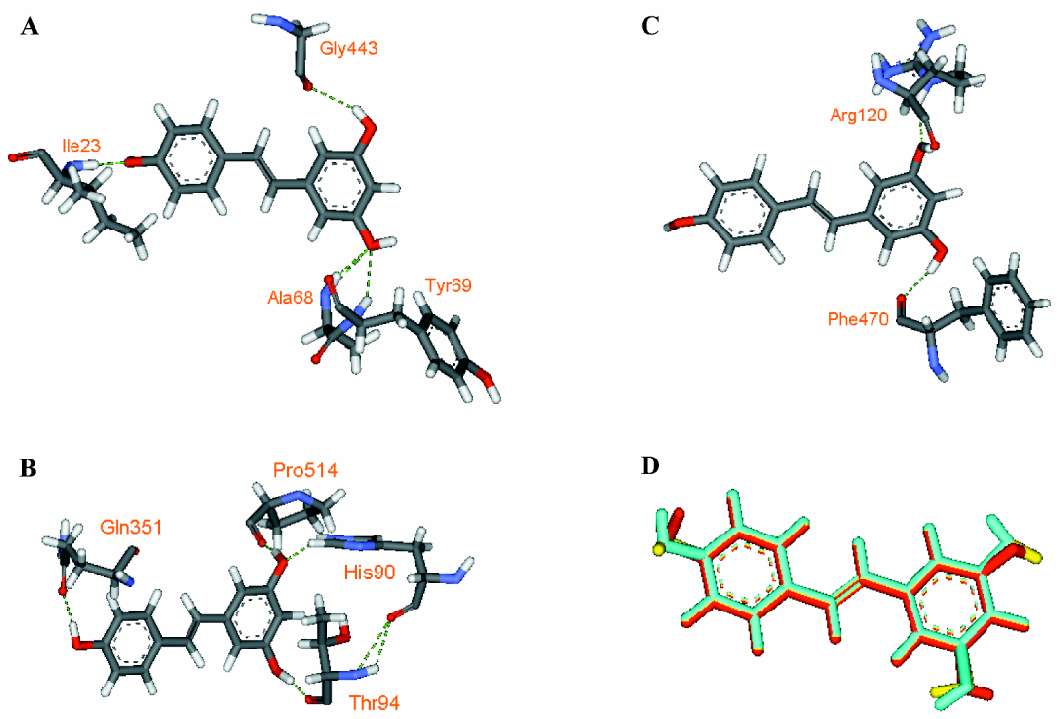


Figure 6. Close-up views of binding modes of resveratrol with MAO-A (A), COX-1 (B) and COX-2 (C) and superimposed resveratrol structures in conformations of binding with MAO-A (in yellow), COX-1 (in red) and COX-2 (in cyan) (D). The hydrogen bonds are marked in green dotted lines.

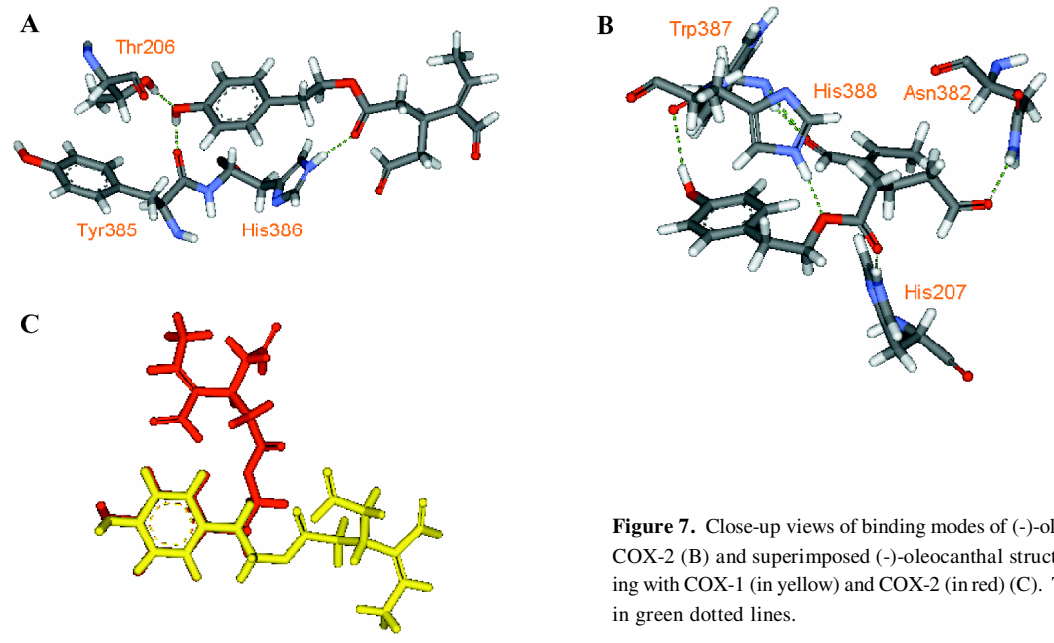


Figure 7. Close-up views of binding modes of (-)-oleocanthal with COX-1 (A) and COX-2 (B) and superimposed (-)-oleocanthal structures in conformations of binding with COX-1 (in yellow) and COX-2 (in red) (C). The hydrogen bonds are marked in green dotted lines.

Conclusion

Thanks to the continuing efforts of medicinal chemists and pharmacologists in the past decade, more and more natural agents that can hit multiple targets implicated in AD (eg, Aβ, τ protein, AChE, BChE, MAO, COX, α-, and β-secretases, ROS and transition metals) were identified. As most of these agents are bioavailable and can penetrate blood-brain bar-

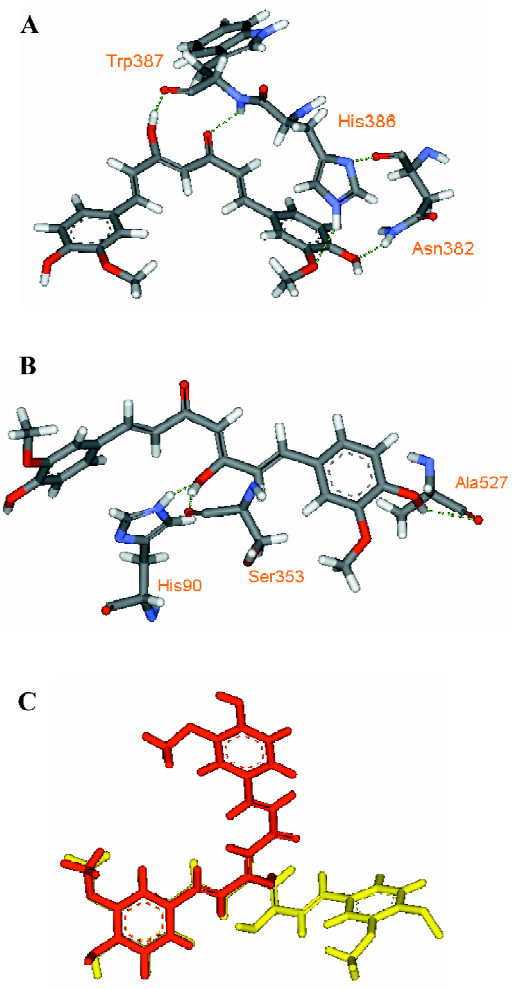


Figure 8. Close-up views of binding modes of curcumin with COX-1 (A) and COX-2 (B) and superimposed curcumin structures in conformations of binding with COX-1 (in yellow) and COX-2 (in red) (C). The hydrogen bonds are marked in green dotted lines.

rier (BBB) (at least in animal models)[35,36,76–79], they are likely responsible for the AD-preventing effects of the source plants, as revealed by epidemiological investigations and preliminary clinical trials. Thus, these agents are good starting points for finding novel anti-AD drugs. Through examining the structures of these agents, it was revealed that phenolics with certain flexibility are preferred by the naturally occurring multipotent anti-AD agents, which has important implications for screening and design of novel multipotent anti-AD drugs.

Considering the fact that current knowledge about natural products is very limited, we think that the presently identified natural multifunctional agents are the tip of the iceberg. With the increase of information on natural medicines, more and more pleiotropic anti-AD compounds will be discovered from medicinal plants in China and/or other geographical regions.

The present analysis also has significance to find drugs for other neurodegenerative diseases, such as prion diseases, Parkinson's disease, and amyotrophic lateral sclerosis, because these diseases are also characterized by progressive neuronal loss and involve similar multiple pathogenetic factors (eg, protein aggregation, transition metals and excessive ROS)[5,6,76,80] and different types of soluble amyloid oligomers bear a common structure[81].

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