



(REVIEW ARTICLE)



Lead Compounds for Brain Protection against Alzheimer's

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Abstract

To find a promising drug for treatment of Alzheimer's` is not that easy target. Although some medications have FDA approval for management of AD, all of them offer symptomatic benefits. This is because efforts to find the treatment are distributed among many targets in the brain which make it so difficult to find a drug that can correct all of them at once. The primary histopathologic lesions of Alzheimer's pathology are amyloid plaques, NFTs and neuronal loss with a wide genetic background which deteriorate the patient condition so rapidly. In the current article, we highlight some lead compounds that protect brain cells from undergoing this dark pathway or, which is more important, to stop deterioration and worsening of the case after starting of the disease. sex lead compounds of natural sources suggested as anti-AD drugs with brief discussion of each of them regarding its chemistry, physiochemical properties, mechanism of action, bioavailability, derivatives and method of synthesis. These natural extracts can be expected as lead compounds for design and synthesis of more effective derivatives as prophylactic treatment against Alzheimer's. The aim of our review is to help to direct efforts to treat AD toward the prophylactic choice according to research results and scientific facts.

Keywords: Alzheimer's`; Epigallocatechin-3-gallate; Dementia; Curcumin; Lead compounds; Quercetin; Beta amyloid

1. Introduction

Alzheimer's disease (AD) (fig.1) is a progressive neurodegenerative disorder that is characterized by the loss of memory and cognitive impairments ¹. Many biochemical changes within cell have been identified to induce neuronal cell death. Oxidative stress, disruption of Ca²⁺ homeostasis, inflammation, metabolic disturbances, and accumulation of unfolded/mis-folded proteins are among cellular changes that finally lead to programmed cell death in AD ². It is characterized clinically by progressive memory and orientation loss and other cognitive deficits, including impaired judgment and decision making, apraxia and language disturbances. These are typically accompanied by various neuropsychiatric symptoms (i.e., depression, apathy, anxiety, agitation, delusions, and hallucinations) ³.

The continuing expansion of life expectancy, leading to a fast-growing number of patients with AD, has led to an enormous increase in research focused on the discovery of drugs for primary, secondary or tertiary prevention of the disease. Despite all scientific efforts, at the moment there are no effective pharmacotherapeutic options for prevention and treatment of AD. To date, established treatments are only symptomatic in nature, trying to counterbalance the neurotransmitter disturbance of the disease. A further therapeutic option available for moderate to severe AD is meantime. At the same time antipsychotic and antidepressant treatments are used for the behavioral symptoms of the disease ⁴. Treatments under research include compounds that act on the pathological substrate of the disease: extracellular amyloid β (A β) plaques and intracellular neurofibrillary tangles (NFTs) ⁵.

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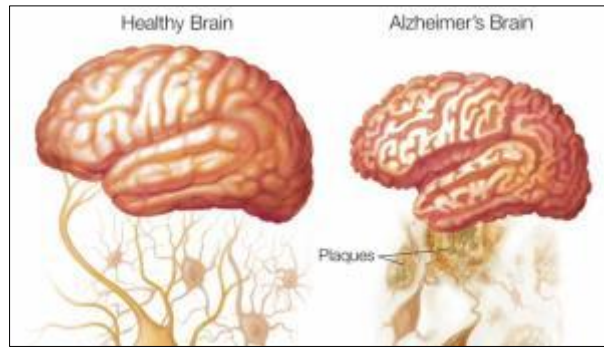


Figure 1 AD

The contributing factors to AD involve both genetic and non-genetic components. Non-genetic factors that contribute to the prevalence of AD are closely affiliated to lifestyle and other factors including diabetes, advanced age, obesity, trauma and cardiovascular diseases. The genetic factors contributing to AD are complex, heterogeneous and involve mutations and polymorphisms of several genes. Mutations of amyloid β precursor protein (APP) and presenilin (PS 1 and 2) (fig.2) cause autosomal dominant AD, which manifest as early-onset AD pathogenesis ⁶. Mutations of these three genes are associated with alterations on three different chromosomes: APP on chromosome 21, PS 1 on chromosome 14 and PS 2 on chromosome 1 ^{7,8}.

Although these mutations are present in different chromosomal locations, the altered genes trigger the same biochemical pathway notably in the altered expression of $A\beta$ peptides that lead to neuronal death and therefore AD. For instance, a common mutation in APP known as The Arctic mutation increases $A\beta$ deposition while the mutation of PS results in elevated levels of readily aggregating $A\beta_{42}$ ⁹.

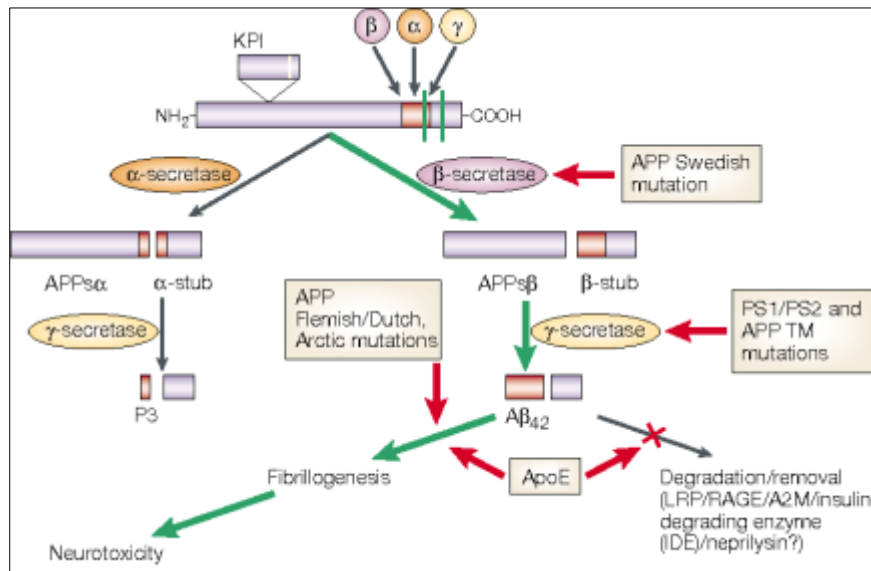


Figure 2 Effect of genetic factors

2. Amyloid Hypothesis

APP genes locate in chromosome 21 has been proposed that their mutations result in cognitive impairment ¹⁰. APP cleavage by β -secretase at extracellular domain, and by γ -secretase at the trans-membrane region, leads to formation of $A\beta$ proteins. Gamma-secretase complex consists of at least four proteins, including PS. PS, an aspartyl protease is the catalytic subunit of the enzyme and its mutation causes alterations in APP processing and increases the amount of toxic $A\beta$ ¹¹.

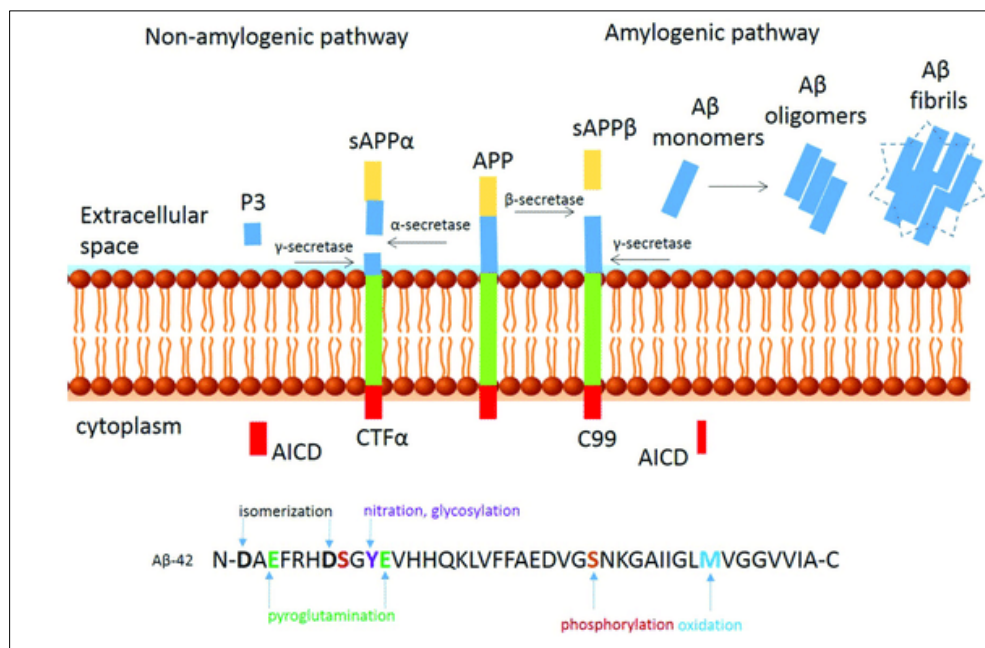


Figure 3 Alzheimer's pathology

The primary histopathologic lesions of Alzheimer's pathology are amyloid plaques, NFTs and neuronal loss. Mature plaques consist of a central amyloid core with surrounding degenerating neurons affected by the toxic effect of the Aβ. NFTs consist of hyper phosphorylated tau protein that has assumed a double helical filament conformation⁵. The Aβ derives from the APP through sequential proteolysis by β secretase β-site APP cleaving enzyme (BACE1) in the extracellular domain and γ secretase in the transmembrane region. Full-length APP undergoes sequential proteolytic processing. It is first cleaved by α secretase (nonamyloidogenic pathway) or β secretase (amyloidogenic pathway) within the luminal domain, resulting in the shedding of nearly the entire ectodomain and the generation of α or β C-terminal fragments (CTFs) (fig.3). The major neuronal β secretase, named BACE1, is a transmembrane aspartyl protease that cleaves APP within the ectodomain, generating the N-terminus of Aβ. The second proteolytic event in APP processing involves intramembranous cleavage of α and β CTFs by γ secretase. Major sites of γ-secretase cleavage correspond to positions 40 and 42 of Aβ. Amyloidogenic processing is the favored pathway of APP metabolism in neurons because of the greater abundance of BACE1, whereas the nonamyloidogenic pathway predominates in other cells¹².

3. Current symptomatic control of Alzheimer's disease

3.1. Cholinesterase inhibitors

The cholinergic hypothesis of AD concludes that cholinergic systems in the basal forebrain are affected early in the disease process, including loss of acetylcholine neurons (fig.4), loss of enzymatic function for acetylcholine synthesis and degradation, resulting in memory loss and deterioration of other cognitive and noncognitive functions such as neuropsychiatric symptoms. A strategy to enhance the cholinergic transmission by using ACEI to delay the degradation of acetylcholine between the synaptic cleft has been proposed. Three cholinesterase inhibitors (ACEI) are Food and Drug Administration (FDA) approved for the treatment of mild to moderate AD¹³.

3.2. N-methyl-D-aspartate antagonist

This drug is an uncompetitive, moderate- affinity N-methyl-D-aspartate (NMDA) antagonist believed to protect neurons from excitotoxicity¹⁴. Memantine was shown to prevent neuronal necrosis, disruption of axonal transport trafficking, DNA fragmentation and neurite retraction. Memantine unable to attenuate Aβ-induced potentiation of extracellular glutamate levels but protects neurons by attenuating tau-phosphorylation¹⁵.

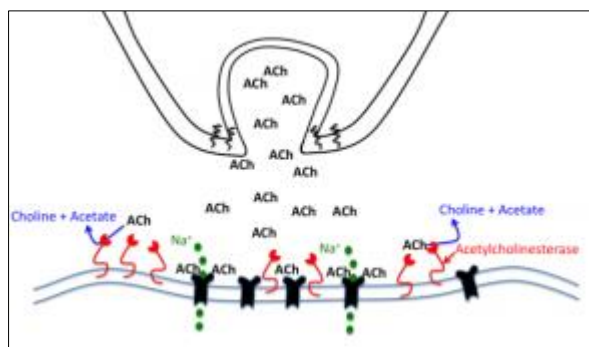


Figure 4 Acetylcholine Neurons

4. Medications Approved

Five medications have FDA approval for management of AD, all of them offer symptomatic benefits; Tacrine (**1**), Rivastigmine (**2**), Donepezil (**3**), and Galantamine (**4**) are ACEI. While Memantine (**5**) is NMDA receptor antagonist ¹⁶.

4.1. Tacrine (Cognex) (1)

Tacrine (1,2,3,4-tetrahydroacridin-9-amine) (**1**-figure 5) (Parke-Davis Pharmaceuticals, 1993) was the first FDA-approved AD drug, but is no longer used in practice. This agent inhibits acetylcholinesterase reversibly in a noncompetitive manner. Tacrine's severe side effects (hepatotoxicity) and short biological half-life (1.6 h to 3 h), however, limit its clinical use ¹⁷.

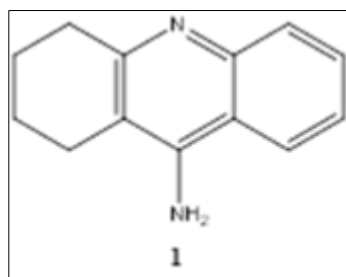


Figure 5 Chemical Structure of Tacrine

4.2. Rivastigmine (Exelon) (2)

Rivastigmine; [3-[(1S)-1-(dimethylamino)ethyl]phenyl] N-ethyl-N-methylcarbamate (**2**-figure 6) (Novartis) is also a reversible ACEI with high brain selectivity. Its use has been approved in at least 40 countries around the world. Plasmatic half-life is only 2 h, however. Rivastigmine's adverse effects are gastrointestinal, including nausea, vomiting, anorexia, and weight loss ¹⁸.

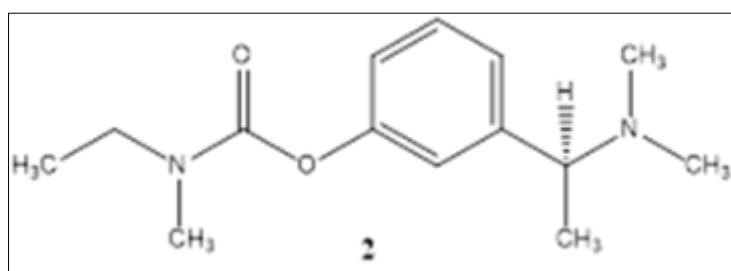


Figure 6 Chemical Structure of Rivastigmine

4.3. Donepezil (Aricept) (3)

Donepezil (1-benzylpiperidin-4-yl methyl]-5,6-dimethoxy-2,3-dihydroinden) (Eisai Inc., 1999) (**3**-figure 7) is a piperidine-based reversible ACEI which was approved by the FDA and is in use for AD treatment. It is significantly more

selective towards Acetylcholinesterase compared to butyryl cholinesterase. The plasma half-life is much longer than tacrine, approximately 70 h. Furthermore, compared to Tacrine, the hepatotoxicity is substantially lower. Side effects, which are generally mild and transient, include nausea, diarrhea, vomiting, constipation, headache, dizziness and sleep disturbance ¹⁹.

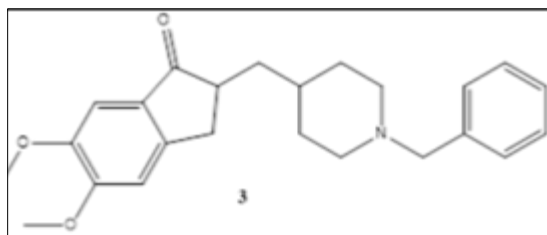


Figure 7 Chemical Structure of Donepezil

4.4. Galantamine (Reminyl) (4)

Galantamine (4a*S*,6*R*,8a*S*)- 5,6,9,10,11,12- hexahydro- 3-methoxy- 11-methyl- 4a*H*- [1] benzofuro[3a,3,2-*ef*] [2] benzazepin-6-ol (Janssen Pharmaceutica) (4-figure 8) is a selective competitive ACEI 50 times more effective against human ACEI than butyryl cholinesterase at therapeutic doses. It has also shown agonistic ability against nicotinic receptors although this action has not been fully investigated yet. The serum half-life is 4 to 6 h, which is slightly longer than tacrine but much shorter than donepezil. Dosing of 16 to 24 mg/day proved beneficial for cognitive and non-cognitive AD symptoms. Adverse effects in the dose-escalation phase include nausea, vomiting, diarrhea, and headache ²⁰.

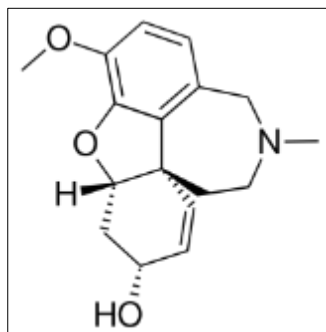


Figure 8 Chemical Structure of Galantamine

4.5. Memantine (5)

Memantine (1-amino-3,5-dimethyl-adamantane hydrochloride) (5-figure 9) is a recently FDA-approved NMDA antagonist. Its half-life is between 3 to 7 h and clinical tests show better outcome from patients compared to placebo. Furthermore, memantine was not associated with severe adverse effects. During studies on some groups of patients with moderate to severe AD showed a significant benefit in cognitive function, language, behaviors and global state from combination use of memantine and donepezil over the placebo group (memantine and placebo) ²¹.

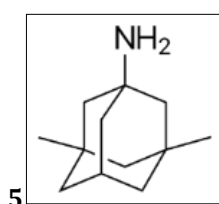


Figure 9 Chemical Structure of Memantine

5. Several problems exist in development of new therapeutics

The Main problem in development of AD therapy is that several compounds with positive results in preclinical studies fail at clinical trials because of their low penetration across blood brain barrier (BBB), which limits their targeting. In recent years, several compounds have been reported for their neuroprotective effects in cellular and/or animal models of AD. Although some of them are promising candidates for AD treatment, many of them were failed in different phases of clinical trials ²².

6. Complementary and Alternative Medicine as a source of lead compounds for AD Treatment

Drugs fail in the clinic for two main reasons; the first is that they do not work and the second is that they are not safe. As such, one of the most important steps in developing a new drug is in the level of lead identification and optimization. On the other hand, Complementary and Alternative Medicine (CAM) covers a wide range of over 100 healing approaches, philosophies and therapeutic modalities that are not provided by conventional medicine ²³. Alternative medicine has an extensive worldwide history and is commonly used by older patients. A number of different alternative medicines are used by patients having Alzheimer's disease. It is both desirable and expected for clinicians to be acquainted with these medications. While many of these medicines have been associated with interesting basic science, none has shown clear clinical benefit to date. Data available for some, such as curcumin and huperzine A, suggest that further evaluation is warranted. The proved efficacy of such compounds accompanied with their high safety profile compared to synthetic chemicals make herbs an excellent source for lead discovery and optimization especially against AD. In this research, we will represent six compounds that were extracted from natural sources and proved to be effective in protection of brain cells against AD beginning and deterioration. These compounds are excellent leads to be incorporated in the growing researches for finding the promising drug against this complex disease ²⁴.

7. Some Lead Compounds of natural Sources suggested as anti-AD drugs (Figure 10)

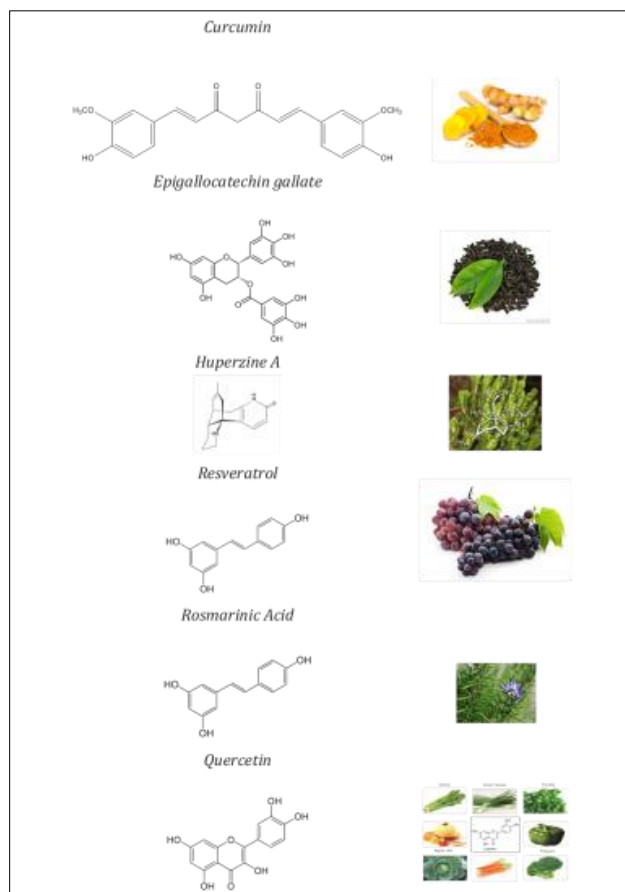


Figure 10 Lead Compounds with their natural Sources suggested as anti-AD drugs

7.1. Curcumin

Curcumin (6)-Figure 11) is the principal curcuminoid of turmeric, popular Indian spice derived from ginger family ²⁵.

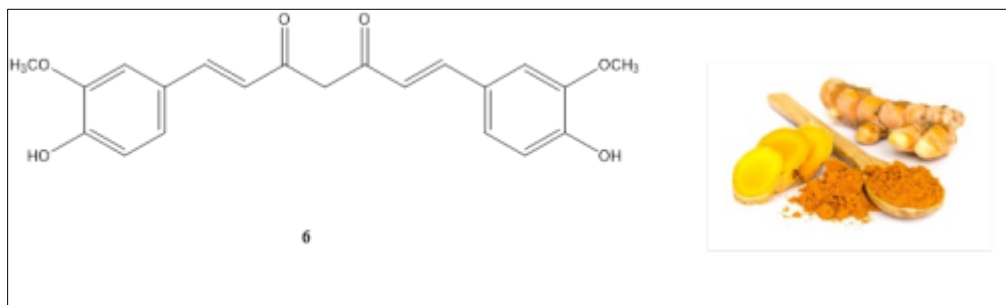


Figure 11 Curcumin and its natural source

Curcuminoids in turmeric roots are a mixture of three main bioactive components, Curcumin (**6**), Demethoxycurcumin (**7**) (**DMC**) and Bisdemethoxycurcumin (**8**) (**BDMC**) (fig. 12) where constitutes about 80%. Many of the biological activity studies were carried out on curcumin obtained from commercial sources, which could be a mixture. The three components differ in their solubility and methoxy groups, which can influence the biological activity ²⁶.

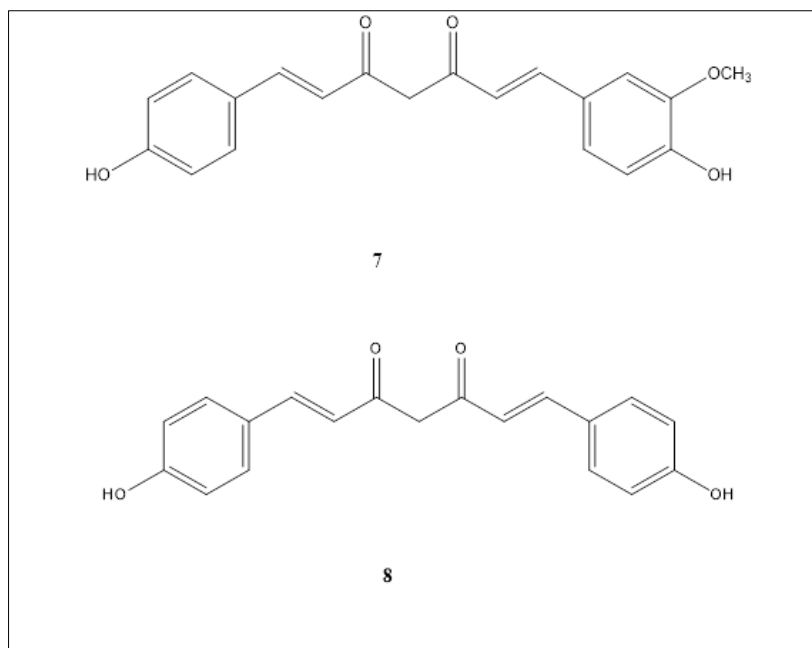


Figure 12 DMC (Demethoxycurcumin) & BDMC (Bisdemethoxycurcumin)

7.1.1. Chemistry and Physiochemical properties

Curcumin (**6**) belongs to the diaryl heptanoid class of compounds, where two aromatic rings are linked through a seven-carbon chain. The two aryl groups are symmetrically substituted with methoxy and phenolic OH groups at ortho position and the seven-carbon chain has conjugation, an Enon moiety and a 1,3-diketone group. The IUPAC nomenclature of curcumin is (1E,6E)-1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione. The active functional moieties of curcumin are two o-methoxy phenolic groups, two Enon moieties and 1,3- keto-enol moiety. The single crystal X-ray diffraction studies of curcumin indicated that in solid state the molecular structure shows three substituted planar groups connected through the double bonds ²⁷.

It has two tautomeric forms, the bis-keto form which is predominantly found in neutral and acidic conditions and in a solid phase and enolate form is found in alkaline condition (fig. 13). The ground state dipole moment of curcumin is computed to be 10.77 D, and the hydrophobicity parameter log(P) value was computed to be in the range of 2.5 to 3.6

indicating its negligible solubility in water. These parameters also support that the polarity of curcumin is such that it is soluble in lipids and proteins²⁸.

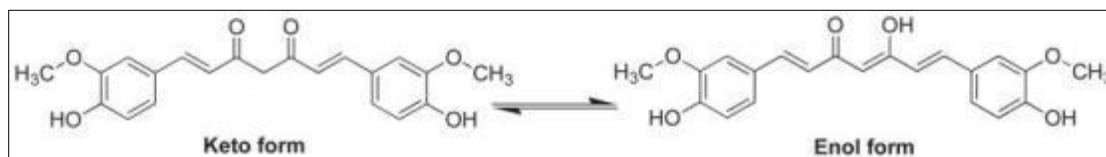


Figure 13 Tautomeric forms of curcumin

Tonnesen and Karlsen have studied the hydrolytic degradative reaction kinetics of curcumin over the range of pH 1–11 by using HPLC and found that at pH < 1, curcumin aqueous solution exhibits red color which is indicative of the protonated form. At a pH range 1–7, curcumin molecules are in the neutral state with yellow color and low water solubility, while at pH > 7.5 this color turns to red²⁹.

In the keto form of curcumin, the heptadienon linkage between the two methoxyphenol rings contains a highly activated carbon atom and the C–H bonds on this carbon are very weak due to delocalization of the unpaired electron on the adjacent oxygen atoms. Curcumin possesses three protons that are ionizable in water, as that as the enolic proton with a pKa of approximately 8.5 and two phenolic protons with pKa of 10 – 10.5 (in mixed alcoholic/water solvent). The pKa values for the dissociation of the three acidic protons in curcumin (forms **a**, **b** and **c**) have been determined to be 7.8, 8.5 and 9.0, respectively (fig. 14)³⁰.

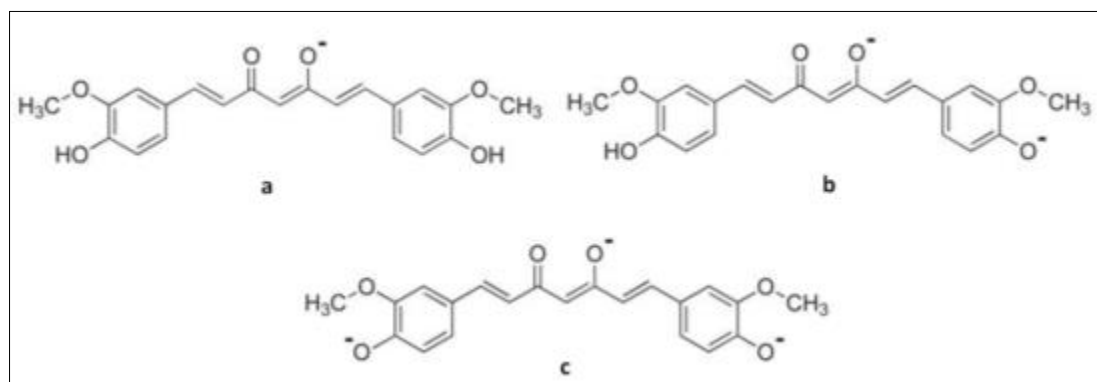


Figure 14 Three acidic protons in curcumin

Curcuminoids are polyphenolic compounds that give turmeric its yellow color and can be used as a food coloring. Many preclinical studies suggest that it may be useful for the prevention and/or treatment of several diseases, such as colorectal cancer, cystic fibrosis, inflammatory diseases, anti-tumor, and anti-metastasis and AD³¹.

In phase I clinical studies, up to 8,000 mg/day, did not result in significant side effects except mild nausea and diarrhea. However, excessive use of curcumin can damage the gut microbiota, interfering with the normal physiology and immune response³².

7.1.2. Mechanism of action and Bioavailability

Bioavailability of orally administered curcumin is relatively low and mostly metabolites of curcumin, instead of curcumin itself, are detected in plasma following oral consumption. Its conjugation with amino acids (such as isoleucine, phenylalanine, and valine) increases its α -secretase activation³³.

In its unmodified form α , β -unsaturated carbonyls in curcumin play the role of a good Michael acceptor and can undergo nucleophilic additions under biological conditions which may enhance its bioavailability. Exploiting this strategy led to limited success in terms of modulating curcumin's metabolism, resulting in ill-defined and unstable products. The inhibition of $A\beta$ formation and aggregation is arguably amongst the most rational strategies employed to treat AD since it is established that $A\beta$ is the key component to trigger AD pathogenesis (fig. 15). Out of 214 anti-oxidant compounds tested in preventing fibrils formation, curcumin demonstrated the strongest inhibitory effect ($IC_{50} = 0.25 \mu\text{g/mL}$)³⁴.

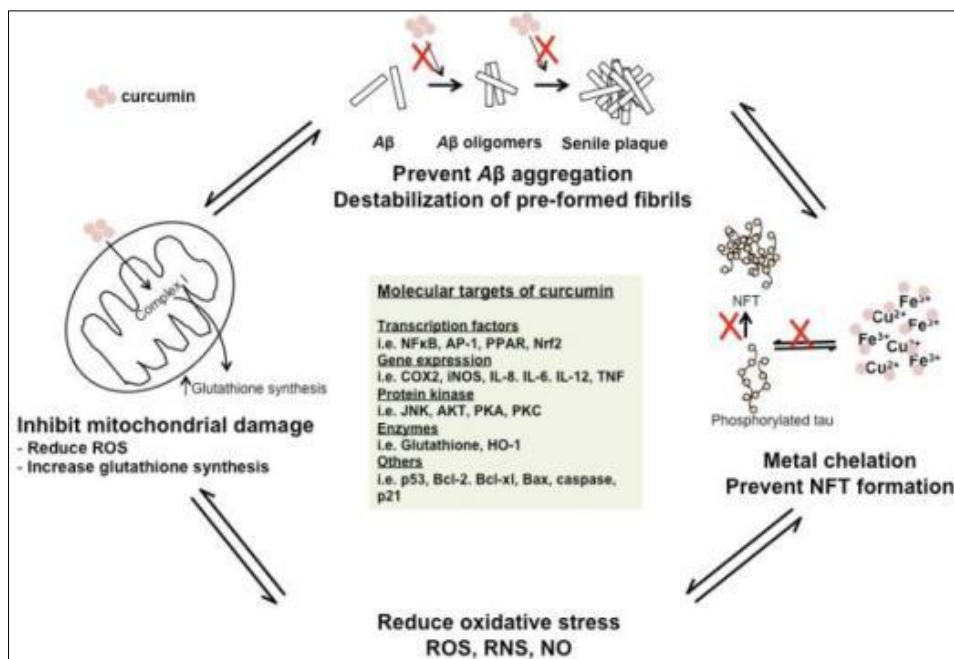


Figure 15 Curcumin against AD

7.1.3. Synthesis and Derivatives

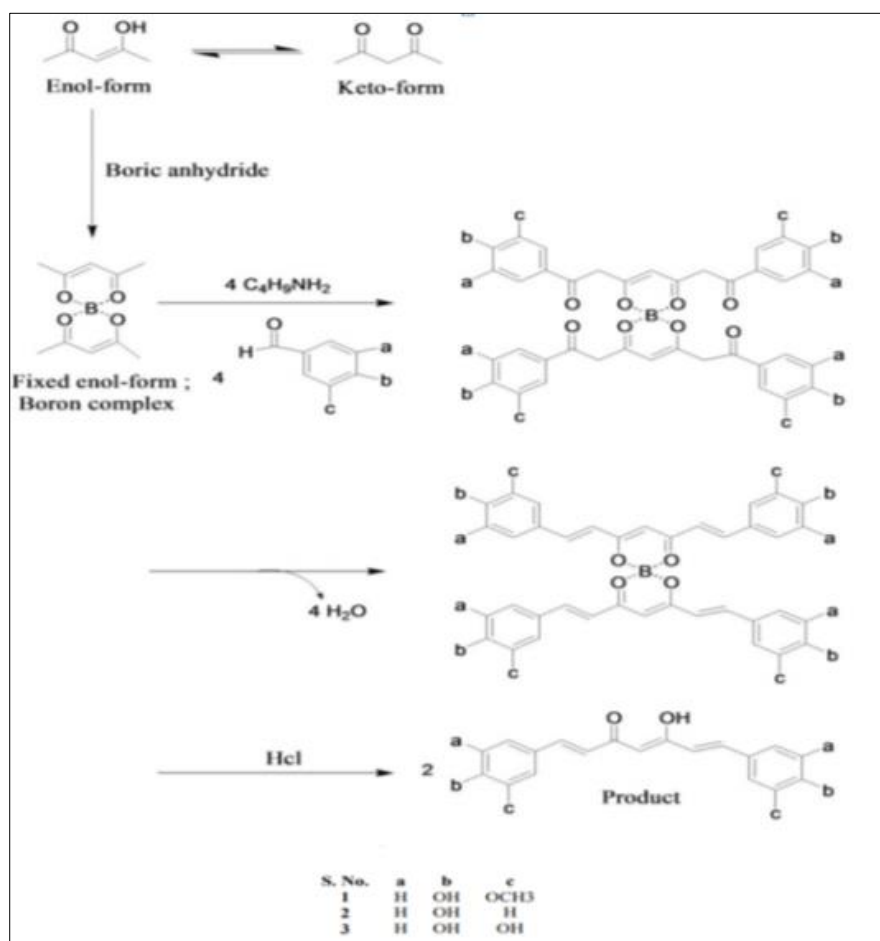


Figure 16 Scheme for the synthesis of Curcuminoid compounds

The synthesis of Curcuminoid compounds used a boric anhydride (B_2O_3) was used because it forms boron complex to avoid Knoevenagel condensation of the reactive methylene group (C-3) in acetyl acetone, thus making the lateral methyl groups to react with the aldehyde group of 4-hydroxy-3-methoxy benzaldehyde. N-butylamine ($C_4H_9NH_2$) was used as a proton extracting reagent which activates the methyl group in 2,4-pentanedione. Tributyl borate [$CH_3(CH_2)_3O$] $_3$ B was used to absorb the water that produced during the reaction. Ethyl acetate ($CH_3COOC_2H_5$) was used as a reaction solvent. Sodium sulphate (anhydrous) (Na_2SO_4) was used to remove water in organic solvent portion of the extraction (fig. 16)³⁵.

Such analogues like dimethoxy curcumin and diacetyl curcumin decreased the antioxidant activity but retained or improved the anti-tumor activity. Dimethoxy curcumin has specifically great advantage over curcumin as its metabolic stability is several folds higher than that of curcumin. Acetylated, alkylated, and glycosylated derivatives of curcumin were prepared and examined for different biological properties like antioxidant, antibacterial, antifungal, antitumor and anti-inflammatory activities. The glycosylated derivatives have been found to improve water solubility of curcumin. Although the diketone moiety is essential for the biological activity, it is suggested that the metabolic stability of curcumin can be improved by modifying the diketone moiety by derivatizing with hydrazine, semi carbazone, thiosemicarbazone, thiophene, and functionalized pyrazole moieties³⁶.

7.2. Epigallocatechin gallate

Epigallocatechin gallate (**EGCG**) (**9**- fig 17) is the most abundant catechin in green tea leaves (*Camellia sinensis*). Carob flour, a cocoa-like substance derived from the ground pods of the carob plant or *Ceratonia siliqua* has also a high content of **EGCG**. Apples, blackberries, strawberries, nuts, peaches, avocados, plums, onions and raspberries have lower amounts of **EGCG**³⁷.

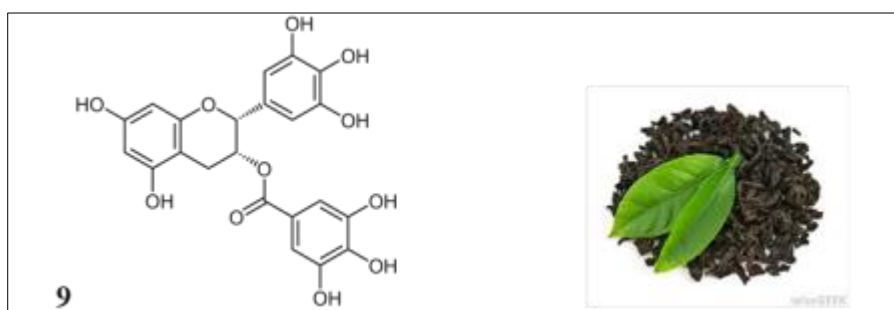


Figure 17 Epigallocatechin gallate & its natural source

EGCG is a potent antioxidant flavonoid and has been the subject of many studies in cancer, atherosclerosis, and neurodegenerative diseases, such as AD, it shows anti-amyloid activity with its antioxidant activity which make it effective in treat amyloid disorders³⁸⁻⁴⁰.

7.2.1. Chemistry and Physiochemical properties

The IUPAC name of EGCG is 3,4,5-Trihydroxybenzoic acid (2*R*,3*R*)-3,4-dihydro-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-2*H*-1-benzopyran-3-yl ester, it consists of (-)-epicatechin (**EC**, **a**), (-)-epigallocatechin (**EGC**, **b**), (-)-epicatechin-3-gallate (**ECG**, **c**), and (-)-epigallocatechin-3-gallate (**EGCG**, **d**, **9**) (fig.18)⁴¹.

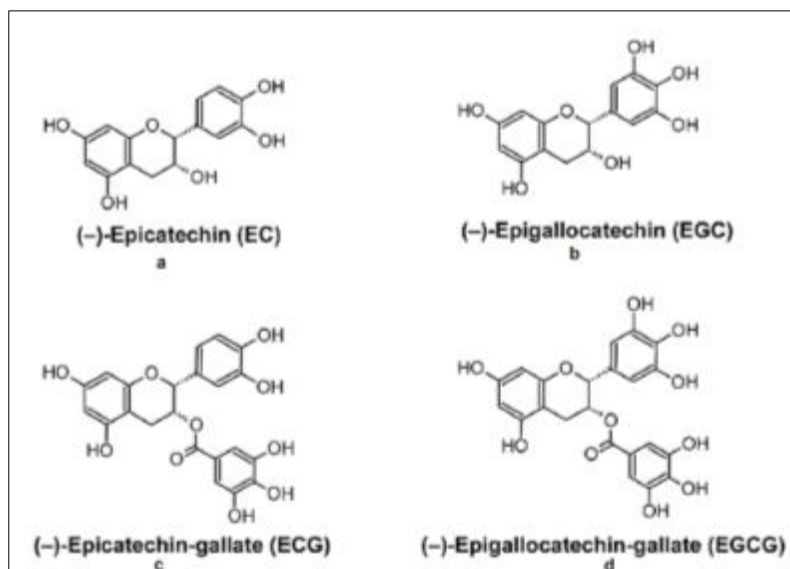


Figure 18 Compounds of EGCG

7.2.2. Mechanism of action and Bioavailability

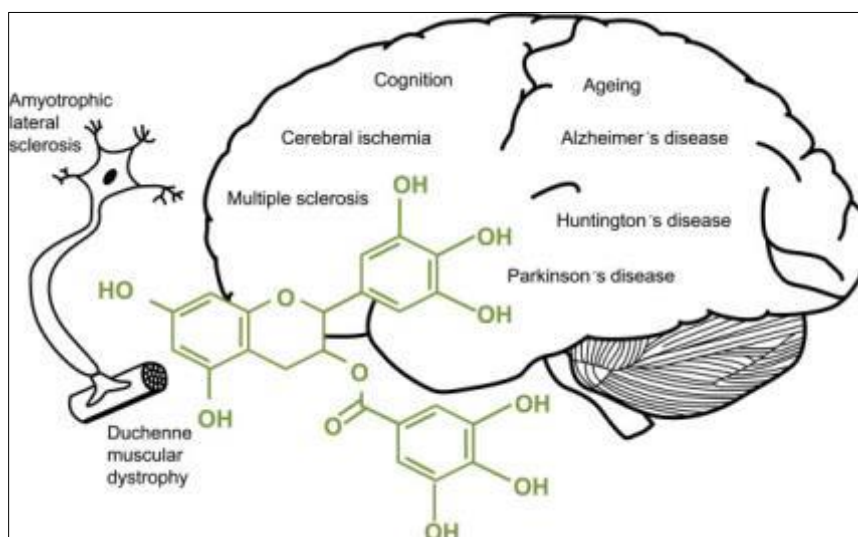


Figure 19 Neurological conditions positively affected by epigallocatechin-3-gallate

Absorption of EGCG from the small intestine is largely by passive diffusion; however, at high concentrations, the small intestinal and colonic tissues become saturated⁴². After oral absorption, tea catechins undergo extensive methylation, glucuronidation, and sulfation. The elimination half-life of EGCG is about 3 h. It has been shown that EGCG nano lipids oral bioavailability was two folds more than free EGCG and they show a better β -secretase enhancing effect. Orally administered EGCG (10 mg/kg) could reduce AChE activity and glutathione peroxidase activity⁴³. Out of these compounds, (-)-EGCG is the most abundant and has shown potent pharmacological activities after intravenous administration of catechins in rats, it was seen that the half-lives of EGCG, ECG, and EC were 191, 362, and 45 min, respectively⁴⁴. When pure EGCG was given, a shorter half-life was observed, suggesting the effect of other components in the extract on the plasma concentration and elimination of EGCG⁴⁵. It has been observed that (-)-EGCG is poorly absorbed in rats and humans due to its unstable nature in neutral and alkaline media⁴⁶. Under the basic environment the phenolic groups of (-)-EGCG lead to the formation of phenoxide anion, which is more reactive toward the electrophilic agents (free radicals) in the body. The formed semiquinone radical results in dimerization. However, (-)-EGCG is more stable at low pH. As pH of the intestine and body fluid is neutral or slightly alkaline, the bioavailability of (-)-EGCG is greatly reduced in vivo⁴⁷.

However, NO does not only exert protective effects in the central nervous system (CNS) but also mediates tissue damage because of its reaction with O_2^- yielding NO_3^- , an ion Neuronal tissue is more prone to oxidative damage than other tissues because of (1) its high content of unsaturated fatty acids that are sensitive targets for free radical attack leading to peroxidation and (2) the brain's high oxygen consumption (20% of total) despite its relatively small (2% of human body) weight^{48,49}.

EGCG does not only exert protective effects in the central nervous system (CNS) but also mediates tissue damage because of its reaction with O_2^- yielding NO_3^- the ion that can nitrosylate tyrosine or cysteine residues in proteins⁵⁰. The hydroxyl and trihydroxy (gallate) groups of **EGCG** appear important for scavenging physiologically relevant ROS/RNS (fig.19)⁵¹.

7.2.3. Synthesis and Derivatives

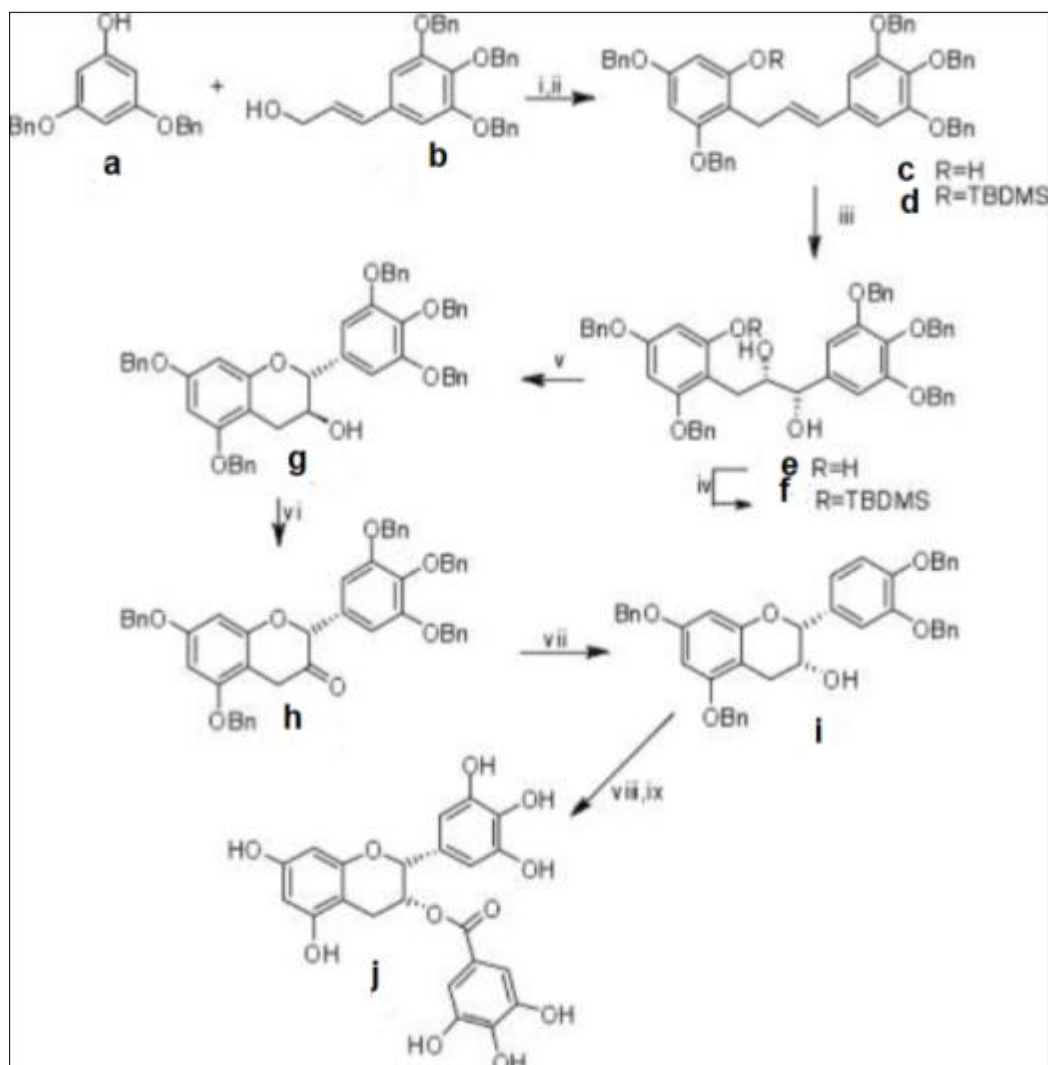


Figure 20 Synthesis of ECGC, reagent and condition: i) $H_2SO_4(SiO_2)/CH_2Cl_2/rt$; ii) TBDMSCl/imidazole/DMF,rt; iii) AD-mix- $\alpha/CH_3SO_2NH_2/H_2O/t-BuOH, 00\ C$; iv) TBAF/THF, rt; v) $CH(OEt)_3/PPTS/CH_2Cl_2$, rt; vi) Dess Martin periodinane/ CH_2Cl_2 , rt vii) L-selectride/HTF, $-780C$ rt; viii) 3,4,5-tris (benzyloxy) benzoyl chloride/DMAP/ CH_2Cl_2 , rt; ix) $H_2/Pd(OH)_2/MeOH/THF$, rt

The **EGCG** (-)-epigallocatechin-3-gallate (**j**, **9**) and its enantiomer (+)-*ent*-epigallocatechin-3-gallate. The (*E*)-1,3-diarylpropene (**c**) was synthesized by coupling of *O*-benzyl protected phloroglucinol (**a**) and (*E*)-cinnamyl alcohol (**b**). Asymmetric dihydroxylation of the TBDMS protected diarylpropene (**d**) using AD-mix- α afforded the (1*S*,2*S*)-*syn*-diol (**e**) which was deprotected to give phenol (**f**), and the latter subsequently cyclized to afford (+)-penta-*O*-benzylgallocatechin (**g**). This was converted into (-)-penta-*O*-benzylepigallocatechin (**i**) by Dess-Martin oxidation into the 3-ketoflavan (**h**) and subsequent stereoselective reduction of the latter. The compound **EGCG** (**j**, **9**) was then

accessible via a simple acylation using 3,4,5-tri-*O*-benzylbenzoyl chloride, followed by deprotection via reductive de-*O*-benzylation. (+)-*ent*-Epigallocatechin-3-gallate was available via simply replacing AD-mix- α with AD-mix- β in the asymmetric dihydroxylation step (fig.20) ⁵².

However, the use of **EGCG** is often hindered by problems such as its poor water solubility, rapid metabolism, and ready degradation in aqueous solutions. To obtain more potent analogues and overcome this problem, a great deal of research has been performed. Examples include permethyl **EGCG**, peracetyl **EGCG**, perbenzylated **EGCG**, EGCG-octa-*O*-TBDMS, **EGCG**-3SH, **EGCG** monoester derivatives, and **EGCG** glycosides, which are more active than **EGCG** or have been found to inhibit **EGCG** oxidation. As illustrated in the literature, the glycosylated derivatives of catechins exhibited similar antioxidant properties, increased solubility in water and stronger tyrosinase inhibitory effects. Thus, the trans-glycosylated derivatives of **EGCG** are important for their utility as food additives and cosmetics. Recently, preparation of glycoconjugates of small molecule drugs has become an attractive strategy in order to overcome problems of water solubility and stability in aqueous solution and reduce side effects, nanocarriers is promising for their ability to enhance EGCG effect ⁴³.

Both epigallocatechin gallate-5-*O*- α -D-glucopyranoside and epigallocatechin gallate-4',4''-*O*- α -D-glucopyranoside, two EGCG glycosides have been synthesized by enzymatic reactions, are derivatives of EGCG α -D-glucopyranoside that exhibit similar antioxidant effects and are more water soluble than EGCG. The corresponding β -D-glucopyranosides of EGCG are not reported in the previous literature. The chemical modification by glycosylation is still not known for EGCG, and the chemical modification of compounds can be controlled with respect to biosynthesis and should further broaden the potential industrial applications. Therefore, the chemical modification of EGCG may be an effective strategy for synthesizing useful epigallocatechin gallate glycosides ⁵³.

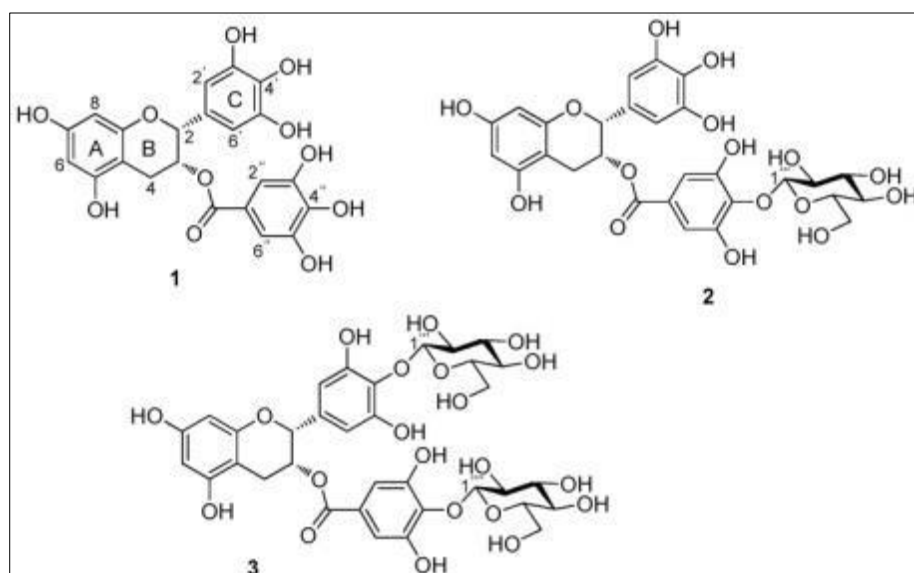


Figure 21 Derivatives of EGCG

EGCG glycosides are synthesized by a chemical strategy, in which a D-glucopyranosyl residue is attached to the 4''-hydroxyl group of the D-ring (**EGCG-G1**, **2**) or both the 4'- and 4''-hydroxyl groups of **EGCG** (**EGCG-G2**, **3**). EGCG, (**1**-fig 21) is the most abundant catechin (accounting for approximately 50% of total catechins) and has been reported to have stronger physiological activities than others and can be expected as a lead compound for synthesis of more effective new promising drugs for treatment of Alzheimer ⁵⁴.

7.3. Huperzine A

Huperzine (**10**-fig 22) is a naturally occurring sesquiterpene alkaloid. In the 1980s the alkaloids huperzine was isolated from *Qian Ceng Ta herbal* and since then the plant has become well known worldwide as a traditional Chinese medicinal plant ⁵⁵.

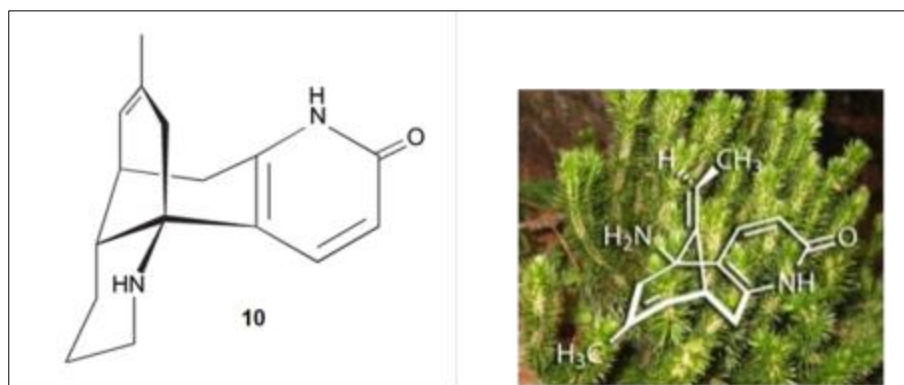


Figure 22 Huperzine A & its natural source

The potency and duration of Huperzine **A** depended on ACE inhibition similar or superior to the pharmaceutical drugs tacrine, donepezil, rivastigmine and galantamine, with fewer toxic effects ⁵⁶. Huperzine **A** has recently been approved for use in China as a palliative therapy for AD, and is currently used in USA as a supplement for preventing further memory degeneration. Huperzine **B** demonstrates lower anti-ACE activity than Huperzine **A**, but has a longer duration of action and exhibits a higher therapeutic index, and like Huperzine **A**, shows a relative lack of toxicity. It is used as a dietary supplement for improving memory and has been also used in China for the treatment of fever and swelling ⁵⁷.

Clinical trials showed minimal adverse cholinergic effects of Huperzine **A** such as dizziness, nausea, gastroenteric symptoms, headaches, and depressed heart rate. These minimal cholinergic side effects would be an advantage of Huperzine **A** compared to other ACEIs for the treatment of AD ⁵⁸.

7.3.1. Chemistry and Physicochemical properties

In China, huperzine **A** (fig. 23) is the first-choice drug in the treatment of AD. Therefore, Huperzine **A**, and to a lesser extent Huperzine **B**, have attracted recent pharmaceutical interest. The IUPAC name is **(11E)-5-amino-11-ethylidene-7-methyl-5,6,9,10-tetrahydro-5,9-methanocycloocta[b]pyridin-2(1H)-one**. Published syntheses produce racemic mixtures of (+, -)-huperzine which exhibit less potent inhibition of ACE than does the plant extracted (-)-Huperzine **A** isomer ⁵⁹.

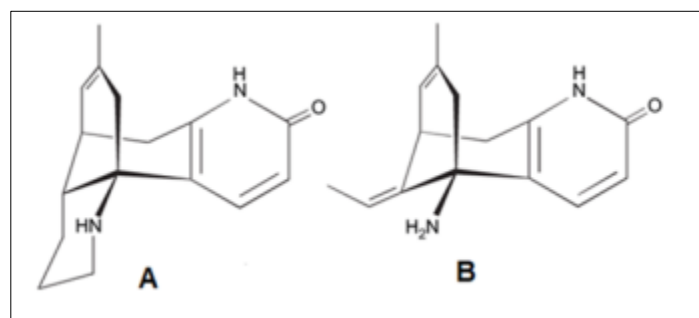


Figure 23 Isomer of Huperzine

7.3.2. Mechanism of action and Bioavailability

Huperzine **A** has been found to be an inhibitor of the enzyme acetylcholinesterase. This is the same mechanism of action of pharmaceutical drugs such as galantamine and donepezil used to treat AD. It is displaying a good pharmacokinetic profile with rapid absorption, wide distribution in body and low to moderate rate of elimination. Encapsulated and microsphere formulations of Huperzine **A** were designed to control the release of Huperzine **A** and thereby increase its efficacy ⁶⁰. Huperzine **A** is a strong ACEI. New tacrine-Huperzine **A** hybrids (Huperzines) are potent ACEI and significantly attenuate A β -induced oxidative injury ⁶¹.

7.3.3. Synthesis and Derivatives

In order to avoid the low-yielding step of elimination of the aldol product, the palladium-catalyzed bicycloannulation of β -keto ester **i** was reported by Kozikowski's group using tetramethylguanidine as base and 2-methylene-1,3-

propanediol diacetate as bis-electrophile in the presence of tetrakis (triphenylphosphine)-palladium (fig. 24). The resulting methylene-bridged compound **ii** was in 92 % yield. The double-bond migration was pursued with triflic acid, affording endocyclic olefine **iv** in 90 % yield. Since the double-bond migration could be performed in the last step, an isomer **iii** was obtained ⁶².

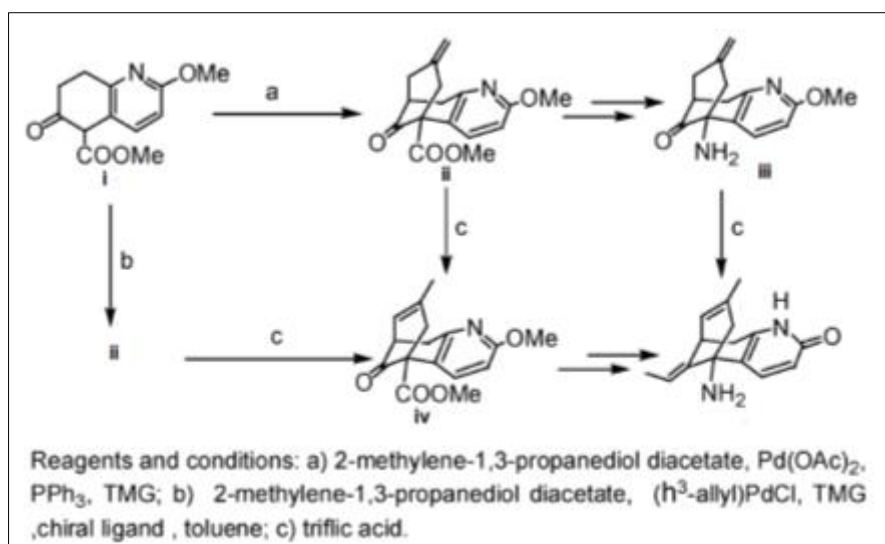


Figure 24 The overall yield of Huperzine A was 40 % from β -keto ester 3

Analogs and derivatives of Huperzine A were prepared and tested for their inhibitory activities of AChE. Unfortunately, neither the structurally simplified analogs nor the derivatives from the natural Huperzine A exhibited the anti-AChE potency as Huperzine A itself except 10-methyl Huperzine A and a few of the Schiff bases of (-)-Huperzine A ⁶³.

The combination known as ZT-1 is a Schiff base of Huperzine A and 5-chloro-2-hydroxy-3-methoxybenzaldehyde. As a prodrug, it is hydrolyzed nonenzymatically into the active compound Huperzine A. In vitro, the AChE inhibitory activities of ZT-1 and Huperzine A are in the same range. In vivo, a marked dose-dependent inhibition of AChE in brain by ZT-1 was observed in rats, and it was similar to Huperzine A. A study in monkeys showed that ZT-1 reversed the memory deficits induced by scopolamine in young adult and aged monkeys. Phase I clinical studies demonstrated that it was safe and well tolerated. The oral bioavailability of ZT-1 was better than Huperzine A. Phase II clinical trials for efficacy assessment in mild and moderate AD patients is now underway in Europe. Thus, Huperzine A could be considered as the lead compound for successful drugs as anti-AD candidates ⁶⁴.

7.4. Resveratrol

Resveratrol (**11**-fig 25) belongs to a class of polyphenolic compounds called Stilbenes. Stilbenes are produced by several plants after exposure to stress, injury, fungal infection, or UV radiation. It is one of the main flavonoids can be found in the skin of grapes and other fruits and nuts ⁶⁵.

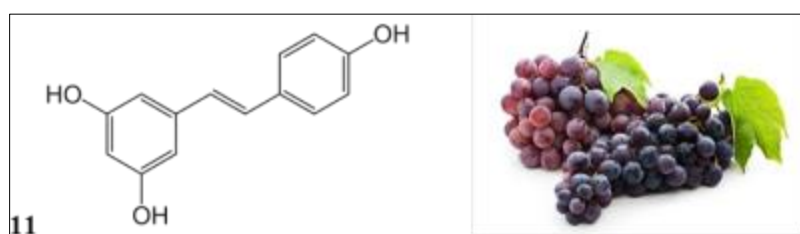


Figure 25 Resveratrol & its natural source

Several studies reported anti-cancer, anti-inflammatory, cardiovascular benefits, lowering blood glucose, and neuroprotective effects ^{66,67}. In short term study of repeated dose of Resveratrol, no severe adverse effect was reported. Only 12.5% of the participants experienced frontal headache ⁶⁸.

7.4.1. Chemistry and Physiochemical properties

Its basic structure consists of two phenolic rings bonded together by a double styrene bond, which forms the 3,5,4'-Trihydroxystilbene. This double bond is responsible for the isometric cis- and trans-forms of resveratrol (fig. 26). It is worth mentioning that the trans-isomer is the most stable from the steric point of view ⁶⁹.

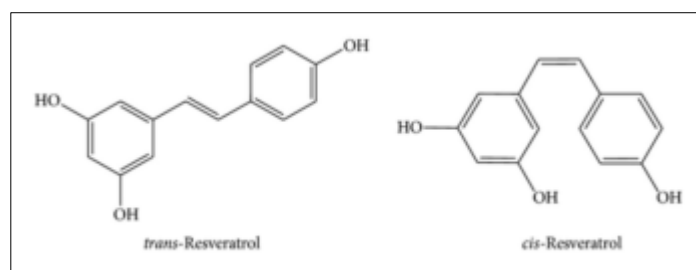


Figure 26 Chemical structures of trans-resveratrol and cis-resveratrol

Cis- and trans-isomers coexist in plants. However, cis-resveratrol has never been found in grape extract. The trans-isomer appears to be the more predominant and stable natural form. Cis-isomerization can occur when the trans-isomer is exposed to solar or artificial light or ultraviolet radiation at a wavelength of 254 or 366 nm ⁴⁸.

7.4.2. Mechanism of action and Bioavailability

One feature of AD is the accumulation of β -amyloid peptide into senile (amyloid) plaques outside neurons in the hippocampus and cortex of AD patients ⁴⁹. Senile plaques are toxic to cells, resulting in progressive neuronal dysfunction and death. Resveratrol was found to facilitate the clearance of β -amyloid peptide and promote cell survival in primary neurons in culture and neuronal cell lines ⁷⁰. Resveratrol is well-absorbed from gastrointestinal lumen but it has low bioavailability due to its rapid metabolism and elimination. Its loaded lipid core nano capsules increased concentration in brain tissue, compared to free resveratrol ⁷¹.

7.4.3. Synthesis & derivatives

The stilbene nucleus is based on a 14-carbon skeleton composed of two phenyl rings linked by an ethylene bridge. Stilbenes are derived from the general phenyl propanoic pathway, starting from phenylalanine. Stilbene synthase uses three malonyl-CoA and one *p* coumaroyl-CoA as substrates and synthesize a linear tetraketide intermediate, which is then cyclized via an aldol condensation, followed by an additional decarboxylation to afford resveratrol (fig. 27) ⁷².

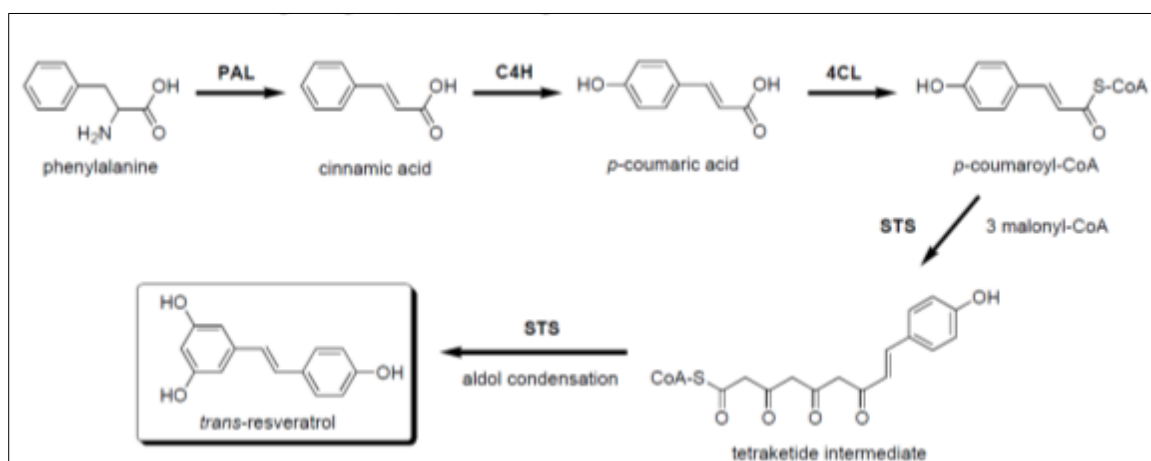


Figure 27 Biosynthesis of resveratrol. PAL, phenylalanine ammonia lyase; C4H, cinnamate 4-hydroxylase; 4CL, hydroxycinnamoyl CoA ligases; STS, stilbene synthase

Then further modifications, generate various resveratrol derivatives (fig. 28) including glycosylation, methylation, oligomerization, isomerization, and isoprenylation. One major resveratrol derivative is resveratrol-3-O- β -glucoside, also called piceid (fig. 29) ⁷³.

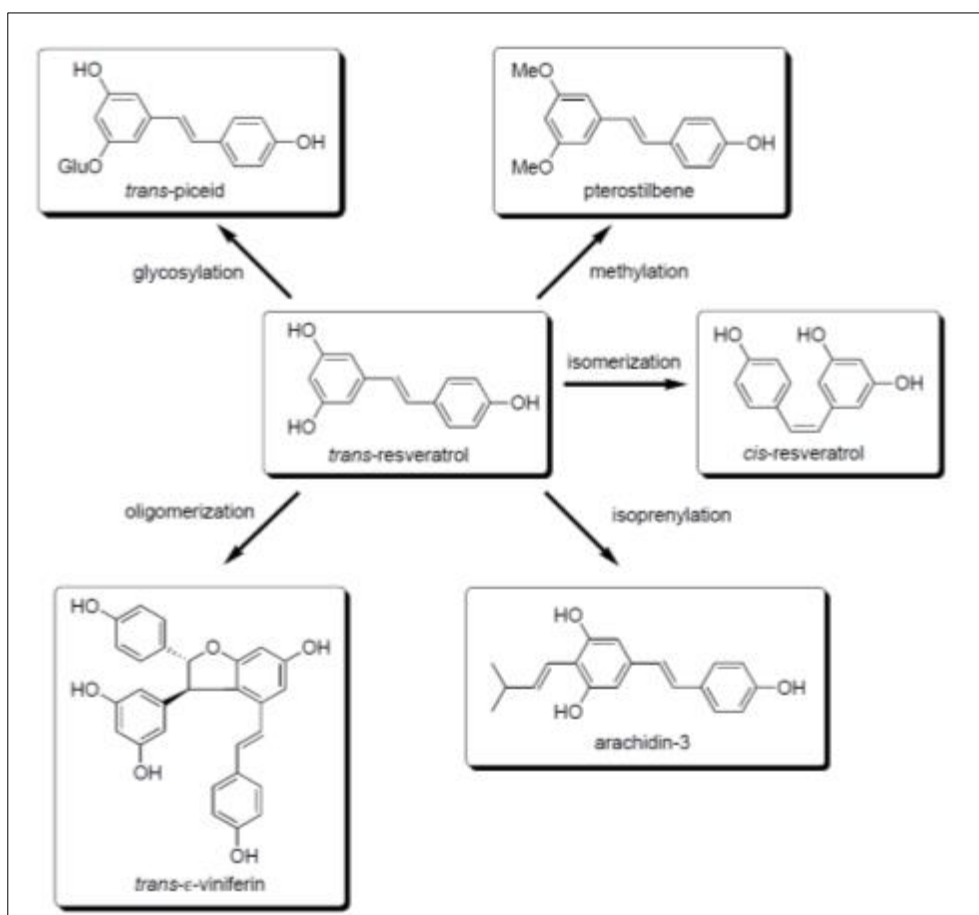


Figure 28 Common modifications of resveratrol

		R ¹	R ²	R ³	R ⁴	R ⁵	
	1	resveratrol	H	H	OH	H	OH
	2	isorhapontigenin	H	OMe	OH	H	OH
	3	oxyresveratrol	OH	H	OH	H	OH
	4	piceatanol	H	OH	OH	H	OH
	5	rhapontigenin	H	OH	OMe	H	OH
	6	gnetol	OH	H	H	OH	OH
	7	piceid	H	H	OH	H	OGlu
	8	pinosylvin	H	H	H	H	OH
	9	astringin	H	OH	OH	H	OGlu
	10	rhapontin	H	OH	OMe	H	OGlu

Figure 29 Chemical structures of resveratrol and its natural monomeric derivatives

7.5. Rosmarinic Acid

Rosmarinic acid (**12**-fig 30) is a polyphenol antioxidant carboxylic acid existed in many *Lamiaceae* herbs used commonly as culinary herbs, such as lemon balm, rosemary, oregano, sage, thyme and peppermint ⁷⁴.

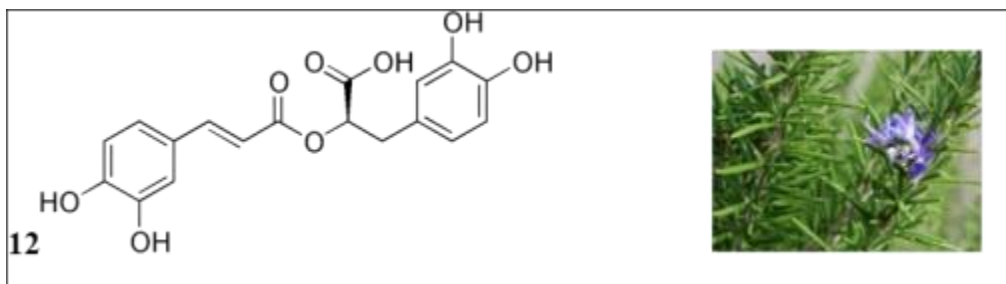


Figure 30 Rosmarinic Acid & its natural source

It possesses many biological activities including neuroprotective effects as well as antioxidant, anti-inflammatory, anticancer, antiviral and antibacterial. No severe side effect has been reported and has been (0.25-4 mg/kg, i.p.) significantly prevented A β -induced memory impairments ^{75,76}.

7.5.1. Chemistry and Physicochemical properties

Rosmarinic acid is considered one of the most important polyphenols. It is an ester of 3, 4-dihydroxyphenylacetic and its derivatives are synthesized from phenylalanine through the esterification of caffeic acid and from tyrosine through 3,4- dihydroxyphenylacetic acid. The IUPAC name is (α -o- caffeoyl- 3, 4 - dihydroxyphenylacetic acid) ⁶⁶.

7.5.2. Mechanism of action and Bioavailability

Clinically, Rosmarinic acid attenuates T cell receptor-mediated signaling, attenuates allergic diseases like allergic rhinitis and asthma, and 2,4-dinitrofluorobenzene-induced atopic dermatitis-like symptoms, protects from neurotoxicity, and slows the development of Alzheimer's disease. These attributes have increased the demand for the biotechnological production and application of Rosmarinic acid and its derivatives (fig. 31) ⁷⁷.

7.5.3. Synthesis and derivatives

Rosmarinic acid is biosynthesized (fig.31) from the amino acids L-phenylalanine and L-tyrosine by eight enzymes that include phenylalanine ammonia lyase and cinnamic acid 4-hydroxylase. It can also be chemically produced by the esterification of caffeic acid and 3,4-dihydroxyphenylacetic acid ⁷⁸.

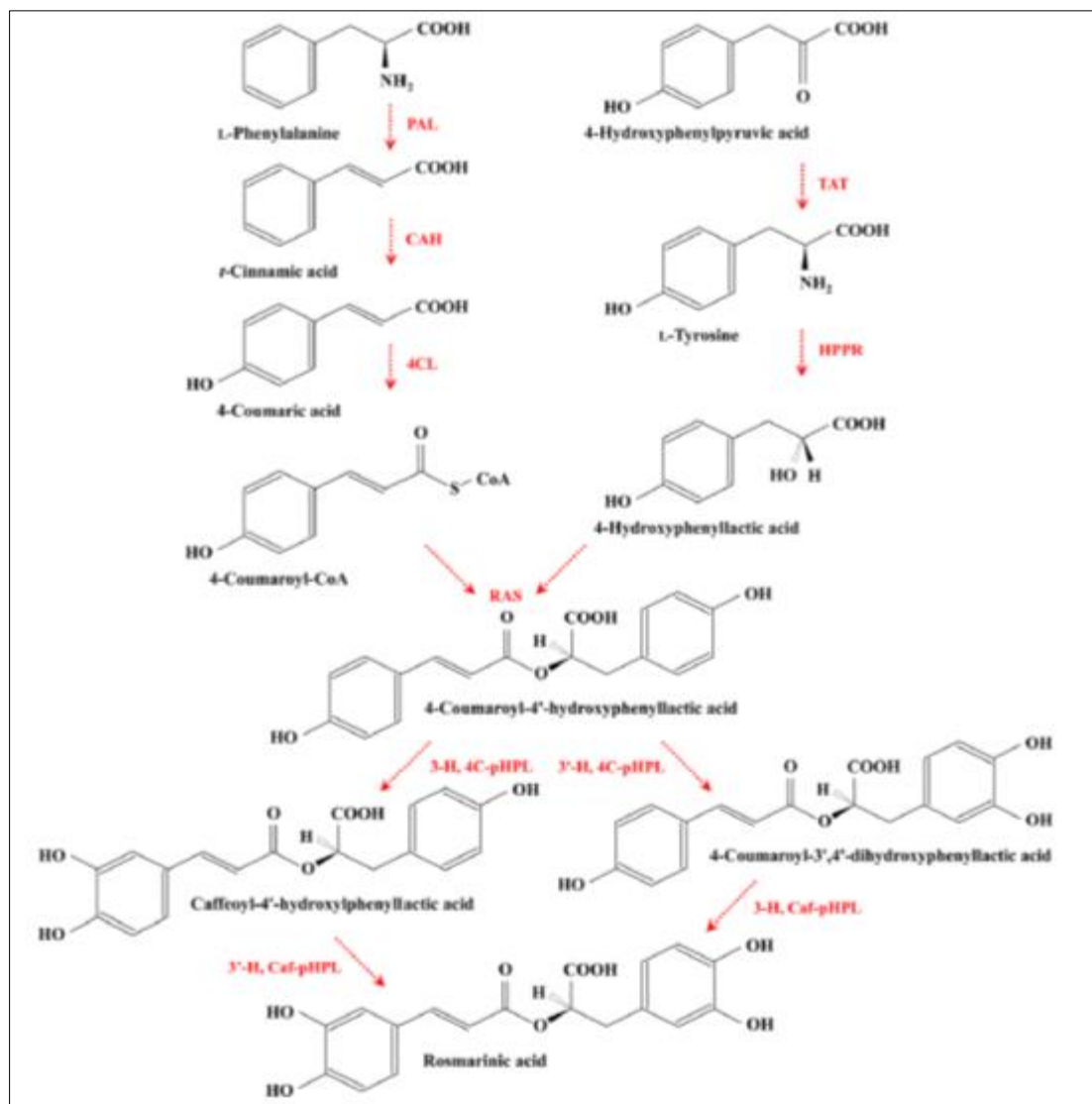


Figure 31 Summary of the biosynthetic pathways for Rosmarinic Acid in *Coleus blumei*

The involved enzymes are abbreviated: PAL phenylalanine ammonia lyase; CAH cinnamic acid 4-hydroxylase; 4CL 4-coumaric acid CoA-ligase; TAT tyrosine aminotransferase; HPPR hydroxyphenylpyruvate reductase; RAS rosmarinic acid synthase, hydroxycinnamoyl-CoA:hydroxyphenyllactate hydroxycinnamoyltransferase; 3-H and 3'-H, 4C-pHPL 4-coumaroyl-4'-hydroxyphenyllactate 3/3'-hydroxylases; 3-H and 3'-H, Caf-pHPL caffeoyl-4'-hydroxyphenyllactate 3/3'-hydroxylase.

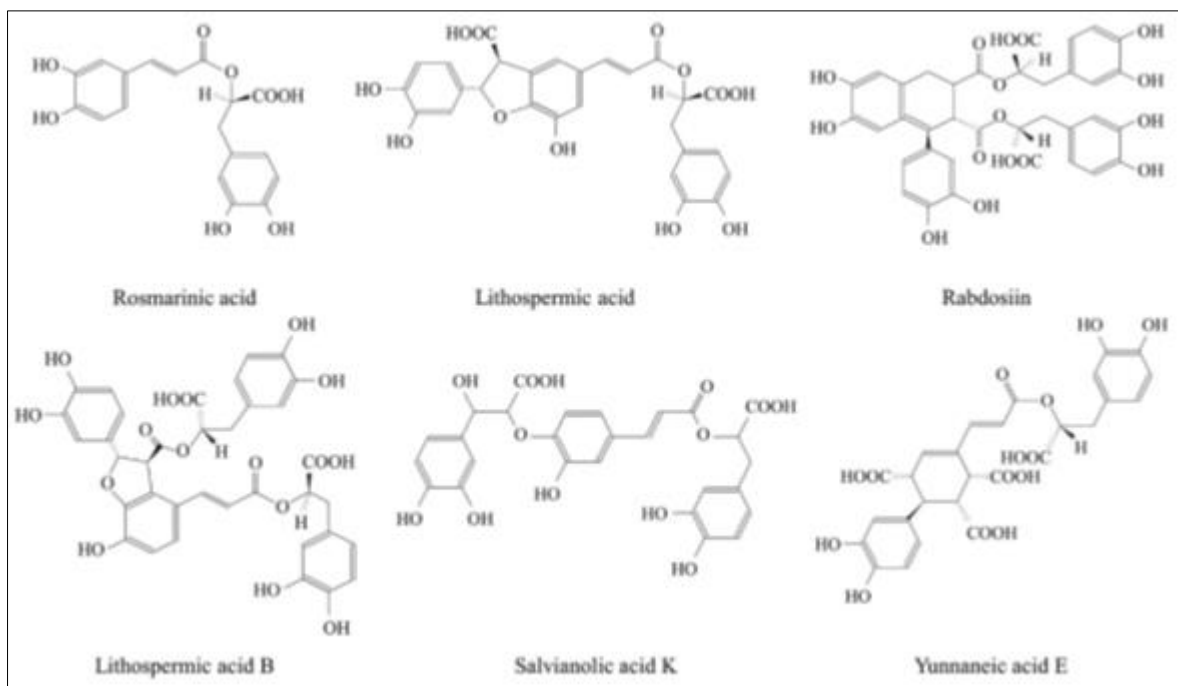


Figure 32 Derivatives of Rosmarinic acid

Rosmarinic acid and its numerous derivatives containing one or two Rosmarinic acid with other aromatic moieties are well known and include lithospermic acid, yunnaneic acid, salvianolic acid, and Meltric acid. Rosmarinic acid and its numerous derivatives containing one or two Rosmarinic acid with other aromatic moieties are well known and include lithospermic acid, yunnaneic acid, salvianolic acid, and melitric acid (fig. 32) ⁷⁹.

7.6. Quercetin

Quercetin (**13**- fig 33) is a polyphenolic flavonoid found in a wide variety of foods including capers, apples, onions, berries, green and black tea. This flavanol-type flavonoid acts as a bioactive compound, mainly by scavenging ROS and showing antioxidant properties. Quercetin, part of a subclass of flavonoids called flavanols, has received considerable attention because of its overwhelming presence in foods ⁸⁰. There are several subclasses of flavonoids: flavanols, flavanones, flavones, isoflavones, anthocyanidins, and flavanols. The divisions in flavonoid subclasses are based on structural properties. The plants, and thus foods they are found in differ, as well. The flavanols are found in red grapes, flavanones are in citrus foods, flavones are in green leafy spices, isoflavones are found in soy foods, anthocyanidins are in berries, and flavanols are found in almost all foods ^{81,82}.

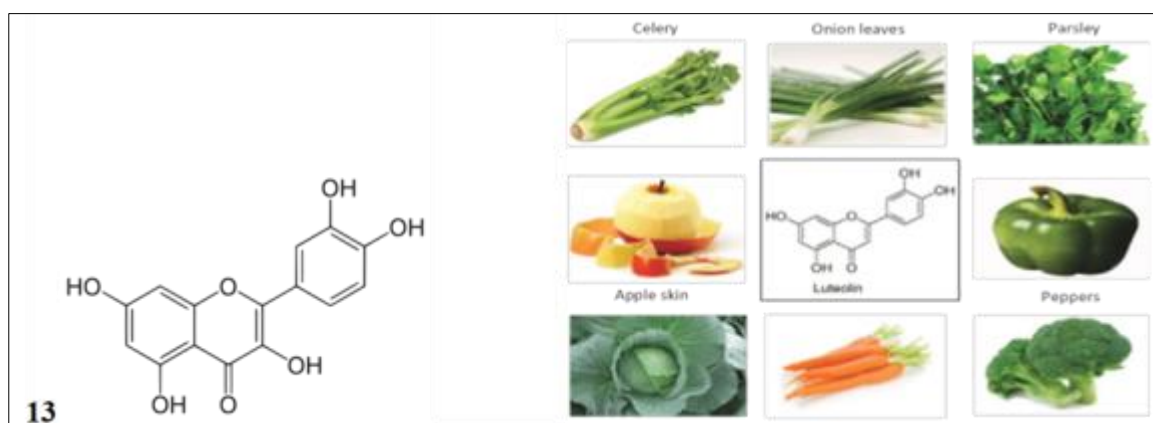


Figure 33 Quercetin & its natural source

It exerts several pharmacological effects, such as anti-amyloidogenic and it shows anti Alzheimer effect (AD), and this activity is due to its inhibitory against acetylcholinesterase⁸², anti-cancer, antiviral and anti-inflammatory activities⁸³. In human studies, Quercetin (doses up to 1,000 mg/day) had no adverse effects on blood parameters of liver and kidney function, hematology, or serum electrolytes⁸⁴.

7.6.1. Chemistry & physicochemical properties

The basic flavonoid structure consists of two phenyl groups joined by a three-carbon bridge. Flavonoids are divided into two main classes, those in which the three-carbon bridge is "open" and those in which the three-carbon bridge is involved in a heterocyclic ring, referred to as ring C⁸⁴ (fig.34). Variations in ring C and the various substitution patterns available for rings A and B allow for a variety of flavonoid structures⁸⁵.

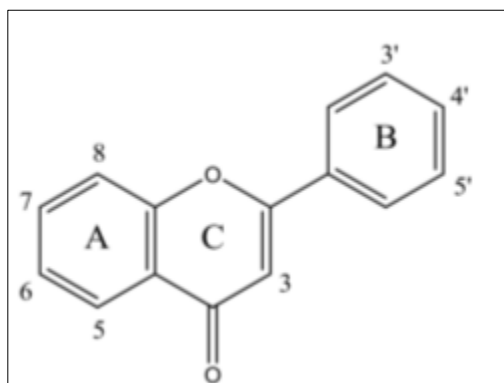


Figure 34 Core structure of quercetin

Many of the subclasses of flavonoids vary by the functional group placed on ring C. Flavanol and anthocyanidins are the only two subclasses that do not have a 4-oxo group, but they do contain a 3-hydroxyl group along with the flavanols. Quercetin has five hydroxyl groups locating at positions 3, 5, 7, 3' and 4' (fig. 35). Generally, methylation of the hydroxyl group tends to improve the efficacy of the compound due to the increased lipophilicity. The flavones, isoflavones, and flavanols have a 2-3 double bond on ring C, and anthocyanidins have a 1-2 and 3-4 double bond. The C ring on the subclasses is joined to ring B on carbon 2, except for isoflavones which are joined at carbon 3. These various substitution patterns not only define the subclasses, but also affect their absorption and their ability to act as antioxidants⁸¹.

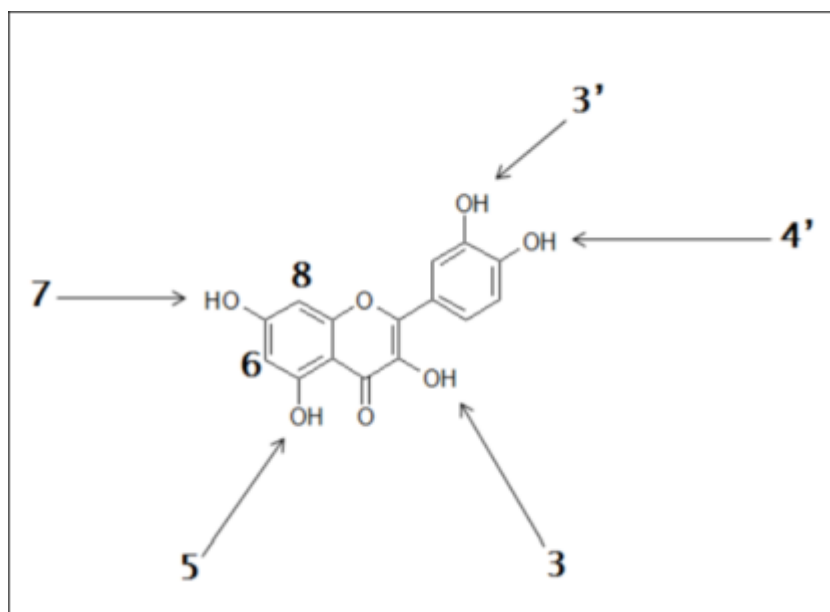


Figure 35 Five Hydroxyl Groups in Quercetin

7.6.2. Mechanism of action and Bioavailability

One characteristic feature of Quercetin is that the elimination of its metabolites from plasma is quite slow, with reported half-lives ranging from 11 to 28 h, which makes Quercetin accumulation in body in daily uptake. Quercetin (10 μM) showed anti-amyloidogenic effects by inhibiting the formation of A β fibrils. Lower doses of Quercetin (5-20 μM) significantly attenuated A β -induced apoptosis in hippocampal cultures; however, it induced cytotoxicity at high doses (40 μM)³⁷.

When the flavanol quercetin (3,5,7,3',4'-pentahydroxyflavone) (fig.36) reacts with a free radical, it donates a proton and becomes a radical itself, but the resulting unpaired electron is delocalized by resonance, making the quercetin radical too low in energy to be reactive⁸⁶.

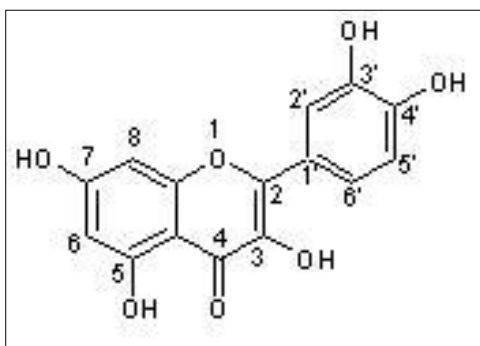


Figure 36 Quercetin structure numbering

Three structural groups aid in quercetin's ability to maintain its stability and act as an antioxidant when reacting with free radicals: the B ring *o*-dihydroxyl groups, the 4-oxo group in conjugation with the 2,3-alkene, and the 3- and 5-hydroxyl groups. The functional groups can donate electrons to the rings, which increase the number of resonance forms available in addition to those created by the benzene structure⁸⁶. Many flavonoids are bound to sugars in their natural state, the *O*-glycoside form, where glycosylation can occur at any hydroxyl group to yield a sugar. The most common quercetin glycosides have a sugar group at the 3-position, such as quercetin-3-*O*- β -glucoside (fig. 37). It is these glycosylated structures that are most common in nature, not the aglycone, or parent compound⁸⁷.

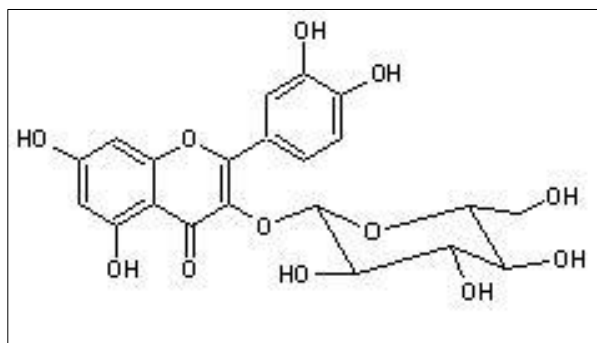


Figure 37 Quercetin-3-*O*- β -glucoside Synthesis

The biosynthesis of phytochemicals, like flavonoids, is a defensive response of plants to their environment. Flavonoids often function as protection from ultraviolet sunlight and lipid peroxidation. Mohle et al. (1985) demonstrated that when cell cultures were subjected to UV-B radiation, the predominant flavonoid synthesized was quercetin-3-*O*- β -glucuronide. They proposed that the biosynthesis of flavonoids is regulated by ultraviolet light and their accumulation acts as a defense. Most studies assessing the antioxidant properties of quercetin utilize the aglycone form; however, analysis of plasma after quercetin consumption indicates that quercetin metabolites, like glucuronide (quercetin-3-*O*- β -D-glucuronide), are the primary compounds circulating in the blood. The metabolites are also what are primarily found in plants. The aglycone is used in studies because there are few quercetin metabolites commercially available. The chemical synthesis of the metabolites, however, is possible (fig. 38)⁸⁸.

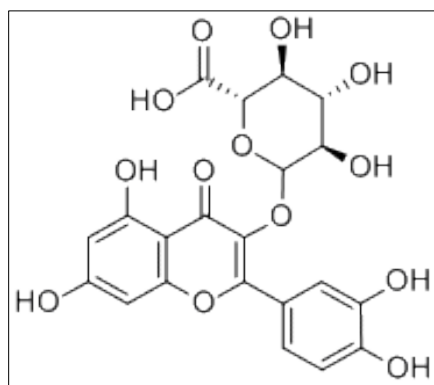


Figure 38 Quercetin-3-O- β -D-glucuronide

7.6.3. Synthesis and Derivatives

Quercetin analogues were synthesized from 2-hydroxyacetophenone and 4-substituted benzaldehydes in two steps. The first step involves Synthesis of chalcone by Claisen Schmidt reaction, followed by treatment with H_2O_2 (fig. 39) ⁸⁹.

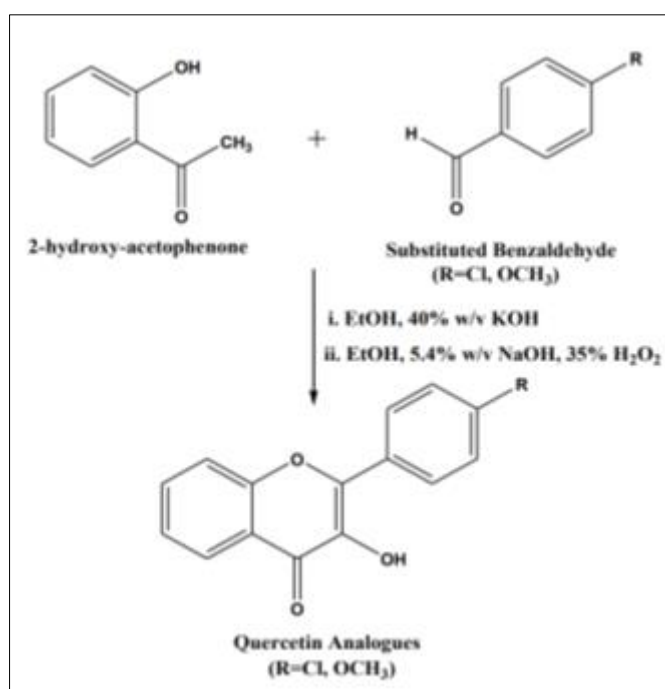


Figure 39 Synthesis of Quercetin analogues

The second step, the regioselective synthesis of tetra-O-acyl derivatives with the free OH group in position 5 of I was achieved with a high yield by the reaction with ten equivalents of acyl chloride. By careful control of the reaction conditions, it is possible to stop the acylation at the 3, 3', 4', 7-tetra-O-acyl stage. We report here on direct acylation of I with II in the presence of N, N-diisopropylethylamine (DIPEA) under controlled conditions and on careful separation of individual regiostereoisomers by chromatography. A series of 3-chloro-2,2-dimethylpropanoyl derivatives of quercetin (IIIa–III g) was prepared by adapted acylation of quercetin with 3-chloro-2,2-dimethylpropanoyl chloride. A simple protocol formed the basis for the relatively easy preparation of variously substituted O-acylated I. It was established that the omission of protection/deprotection steps followed by careful chromatographic purification is a time-saving procedure (fig. 40). The approach used for the preparation of these quercetin derivatives may readily be applied to other acylated flavonoids. Chloronaphthoquinone derivative III h was found to be the most appropriate candidate for a bi-functional drug, combining high anti-oxidant activity with efficient inhibition of aldose reductase (fig. 41) ⁹⁰.

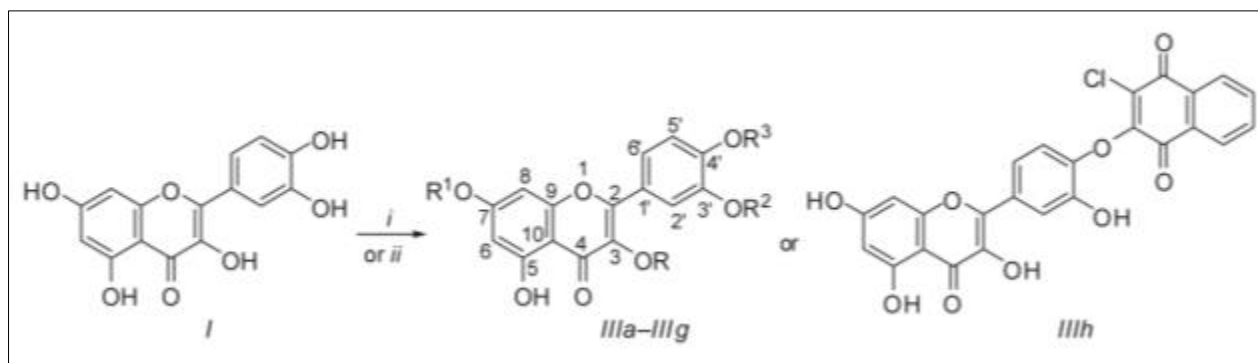


Figure 40 Synthesis of quercetin derivatives. Reaction conditions for preparation of O-acyl derivatives IIIa–III g: i) 3-chloro-2,2-dimethylpropanoyl chloride (II), acetone, DIPEA, 5 ° C, 2 h, then 25 ° C, 2 h; for preparation of III h: 2,3-dichloronaphthoquinone, pentan-2-one/toluene, DIPEA, 100 ° C, 12 h

Compound	Substituent			
	R	R ¹	R ²	R ³
<i>IIIa</i>	H	H	X	H
<i>IIIb</i>	H	X	X	X
<i>IIIc</i>	H	X	H	H
<i>III d</i>	H	H	H	X
<i>IIIe</i>	X	X	X	X
<i>III f</i>	X	H	X	X
<i>III g</i>	X	X	X	H
<i>III h</i>	H	H	H	Y

Figure 41 Synthesis and characterization of quercetin analogues: X = 3-chloro-2,2-dimethylpropanoyl, Y = 2-chloro-1,4-naphthoquinon-3-yl

8. Conclusion

Although few drugs approved by FDA to control Alzheimer's` symptoms, there is no medication until today can be used as prophylactic treatment. The goal for this review is not to represent new drugs that can control the scattered symptoms of Alzheimer's` but to protect brain cells from undergoing this dark pathway or, which is more important, to stop deterioration and worsening of the case after starting of the disease.

A number of different alternative medicines are used by patients having Alzheimer's` disease. While many of them have been associated with interesting basic science, small number has shown clear clinical benefit to date. Data available for some of them suggest that further evaluation is needed. The represented compounds; curcumin, EGCG, Huperzine A, Resveratrol, Rosmarinic acid and Quercetin, all can be expected as lead compounds for design and synthesis of more effective derivatives as prophylactic treatment against Alzheimer's`.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest

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