Non-Alkaloid Cholinesterase Inhibitory Compounds

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The classes of cholinesterase inhibitors discussed here are mainly terpenoids, phenolic compounds, and coumarins, and some of these compounds have shown high potency. In order to consider which classes are most suitable, based on the benefits and drawbacks, certain structural features of each class will be of great importance. Using chalcones as an example, it is believed that besides economical and cost-effective production, small molecular size and flexibility for modifications to improve lipophilicity necessary for blood-brain barrier permeability are important to consider for a preferred potential therapeutic candidate for AD.

Keywords: Alzheimer’s disease ; cholinesterase inhibitors ; terpenoids ; phenolic compounds ; coumarins

1. Introduction

The research of novel drug candidates has shown that natural products such as plant extracts and plant-originated compounds have enormous potential to become drug leads with neuroprotective activity. Several non-alkaloid phytochemicals have been obtained from natural sources, including terpenoids, coumarins, flavonoids, and other phenolic compounds which have beneficial neuroprotective properties particularly in cholinesterase inhibition hence, they are potential drug candidates for the treatment of Alzheimer’s disease (AD). Alzheimer’s disease (AD), one of the leading causes of dementia, is an overwhelming neurodegenerative disease that particularly affects brain function, resulting in memory loss and impairment of language, emotional disturbance, personality changes, depression, behavioral problems, and judgment capacity [1][2]. Besides dementia, it is a major cause of death amongst old people. In the brains of Alzheimer’s disease (AD) patients, key neuropathological features of pathological protein deposits such as insoluble amyloid-β (Aβ peptides which form senile plaques) and hyperphosphorylated tau (which aggregates into NFTs) have been revealed [3]. It was reported that 35.6 million individuals suffered from AD in 2010, over 44 million people had dementia in 2013, and that the number will increase regularly to around 115 to 135 million individuals by 2050 [4][5]. The major physiological evidence of AD involves the degradation of cholinergic neurons and reduction in acetylcholine.

Cholinergic neurotransmission is terminated by two cholinesterases acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), which play an essential role in the hydrolysis of ACh [6]. According to the cholinergic hypothesis, memory impairment in Alzheimer’s disease is due to the deficit of cholinergic function in the brain, thereby, reducing hippocampal and cortical levels of the neurotransmitter acetylcholine (ACh) and associated enzyme choline transferase [7][8]. In the healthy brain, acetylcholinesterase (AChE) is the most important enzyme regulating the level of ACh, while butyrylcholinesterase (BChE) plays a minor role [1]. It is therefore expected that if the hydrolysis of ACh by AChE and BChE is inhibited in the brain of an AD patient, the amount of ACh in the synapse will be significantly increased and the neurotransmission mechanism will be more fluid [9]. For this reason, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors such as galantamine, donepezil, and rivastigmine are used in the management of AD, and the inhibition of the two types of cholinesterase enzymes (AChE and BuChE) as remedial for such treatment [10]. However, the high cost, non-selectivity, limited efficacy, poor bioavailability, and adverse cholinergic side effects in the periphery, such as nausea, vomiting, diarrhea, dizziness, gastro-intestinal disorders, moderate to low effectiveness, short half-life, and hepatotoxicity are the several limitations of these drugs [11]. These reasons have prompted the search for newer molecules from natural products by researchers worldwide because cholinesterase inhibitors are known to occur in plants used traditionally for failing memory and other cognitive declines associated with age [12]. For example, galantamine, physostigmine, and huperzine A have been isolated from Galanthus nivalis , Physostigma venenosum, and Huperzia serrata , respectively, and clinically used for AD symptomatic management [13].

2. Natural Non-Alkaloid Cholinesterase Inhibitors

Alzheimer's disease (AD) is the most common form of dementia mostly in old people, characterized by low acetylcholine levels and oxidative stress, involving progressive neurodegeneration with the formation of amyloid-β deposits in the brain. The number of individuals suffering from this disease and its related neuropathologies has been increasing over the years and a majority of the patients are old people. A proper strategy to overcome AD is by the inhibition of cholinesterase enzymes which helps to increase acetylcholine levels in the brain which is necessary for neurotransmission, memory, reasoning, and other cognitive activities. Though synthetic cholinesterase inhibitors, including rivastigmine, donepezil, and galantamine are usually employed as a remedy to AD, there is a growing interest in the search for new cholinesterase inhibitors from natural sources due to the drawbacks of synthetic ones, and most non-alkaloid natural anticholinesterase compounds are terpenoids, phenolic compounds, and coumarins, amongst others.

3. Discussion

Several terpenoids from natural sources have been reported as cholinesterase inhibi-tors [14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42]. The compounds 1– 11, are of the Abietane-type diterpene skeletons isolated from Salvia austriaca , Salvia glutinosa , Caryopteris mongolica, and Perovskia atriplicifolia [14][15][16]. Between compounds 2– 7 , there is an -OH group on the side chain, except for compound 5 which has a methoxy (CH 3O-) group on the side chain and has the highest AChE inhibition activity. The high activity could be due to the presence of this methoxy group. In the same way, compound 2 has good activity and possesses a methoxy group on ring C and has an IC 50 of 27.9 ± 5.2 μM compared to compound 5 with an IC 50 of 20.8 ± 7.1 μM. Compounds 8 to 11 are miltirone derivatives though with little structural differences, there is no significant difference in their cholinesterase inhibition activity. Compounds 12– 19 are tanshinone derivatives [16]. Compounds 16 and 17 are the most active with percentage inhibitions of 6.19 ± 3.91% and 5.55 ± 3.03%, respectively at 10 μg/mL. This could be attributed to the conjugated double bond system in ring A which is particular to these two compounds. Compound 20, a monoterpene glycoside nuciferoside, shows very high activity with an IC 50 value of 3.20 ± 0.22 μM [17]. Compounds 21– 36 are cycloartanes triterpenoids isolated from Cimicifuga dahurica and Nelumbo nucifera [17][18]. Amongst them, compound 25 is the most active with a percentage inhibition of 15.8 ± 4.3% and 14.0 ± 2.6% on AChE and BChE, respectively, at 100 μM. This could possibly be attributed to the absence of the double bond in ring B of this compound. Compounds 37– 42 are lupane type triterpenoids isolated from Garcinia hombroniana and Xylia xylocarpa and they show relatively low activities [19][20]. The oleanane triterpenoids 43, 44, and 45 isolated from Xylia xylocarpa and Rhynchospora corymbose show low activities [19][21]. The sterols 46 and 47 from Rhynchospora corymbose show low activities as well as the monoterpenes 48, 49, and 50 from Pimpinella anisoides [21][22]. Sesquiterpene lactones from 51–64 isolated from Inula spp. , Cynara cornigera , and Amberboa ramosa show good anticholinesterase activities [23][24][25]. Compounds 58– 61 are amberbin C, amberin, amberbin A, and amberbin B, and have high anticholinesterase activity [24]. Amongst them, those possessing sugar moieties, amberin (IC 50 17.5 ± 0.01 μM and 2.7 ± 0.02 μM for AChE and BChE, respectively) and amberin B (IC 50 0.91 ± 0.015 μM and 2.5 ± 0.15 μM for AChE and BChE, respectively) are the most active and the structural difference between them is the interchange of the positions of an acetyl group and sugar moiety. The agarofuran derivatives 62–73 isolated from Euonymus japonicus and Maytenus disticha have low activities [25][26]. The taraxaranes 74, 75, and 76, oleananes 77, 78, and 79, as well as the ursane tritepenoids 80 and 81, have relatively low activities except for compound 74 with IC 50 values of 13.5 ± 0.95 μM and 10.6 ± 0.54 μM on AChE and BChE inhibitions [20][27][28]. Its relatively high activity could be attributed to the presence of the caffeoyl group at position 3. It can be concluded that amongst the terpenoids, sesquiterpenes are the most active compounds, especially sesquiterpene lactones.

Phenolic compounds from natural sources have shown anticholinesterase activity in several studies [34][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78][79][80][81][82][83][84]. Compounds 1– 19 are flavone derivatives with a double bond in ring C and a carbonyl at position 4 [34][43][44][45][46][47][48][49][50][51][52][53]. There is no observable regular pattern of variation in activity. However, compounds with no hydroxyl group on position 3 show seemingly high cholinesterase inhibition activity, for example, compounds 4 and 5. However, compounds 16– 19 do not have a hydroxyl group at position 3 but their activities are low and could be accounted for by the occurrence of methoxy groups on the other rings. There is an observable decrease in cholinesterase inhibition in flavones with methoxy substituents, for example, compounds 13 and 14, and compounds 7 and 8. This observation is not true for compounds 14 and 15 as 14 has a methoxy group on ring B but is more active than 15 without a methoxy group. This could be due to the absence of a substituent on ring B of compound 15. Between cirsilineol (18) and isothymusin (19), an additional hydroxy group on ring A causes a decrease in cholinesterase inhibition. For the flavonoid glycosides, compounds 20– 33 [43][45][46][49][50][54][55], those with a sugar moiety at position 7, have higher activities than the others, for example, 27, 28, and 29 isolated from Achillea millefolium . If the sugar has substituents, as is the case of 32 and 33, the activity is further reduced. Compounds 34 to 38, isolated from Dodonaea viscosa , have isoprenyl substituents but, however, show no significant

difference in their activities [51]. Rather, their activities are lower than their corresponding compounds without isoprenyl substituents. Compounds 39– 41 have acetyl groups and their BChE inhibitory activity decreases with an increase in the number of acetyl groups [21]. The phenolic acid compounds 42– 45, and compound 44 ferulic acid methyl ester have a good percentage of cholinesterase inhibition [17][18][57]. The presence of sugar substituents causes a decrease in cholinesterase inhibition as seen in compounds 46– 48 [17][58], while an additional phenolic group causes an increase in cholinesterase inhibition as seen in compounds 49– 64 [16][18][47][52][59][60][61][62]. Amongst the biphenyl compounds, 58, 59, 60, and 61 isolated from Myristica cinnamomea have high activity, and in these compounds, the carbonyl function is adjacent to one of the phenyl groups (phenyl carbonyl). Isoflavones compounds 65– 79 isolated from Iris pseudopumila , Maclura pomifera , and Belamcandae chinensis rhizoma have low activities [52][54][59][63]. Amongst them, methoxy substituents cause no significant change in cholinesterase inhibition while the presence of sugar molecules causes a decrease in this activity. For those with prenyl groups (75– 79) isolated from Maclura pomifera , there was no observable effect due to the presence of the prenyls, but an -OH group on ring B caused an increase in activity between compounds 75 and 76. Catechin and its derivatives 79 to 84 isolated from Eugenia dysenterica and Orostachys japonicus had no good activity and no significant difference despite structural differences except between compound 82 and 83 where the additional benzoic acid substituent increased AChE and BChE inhibition activities [40][44][57]. This observation was similar for the flavanones 85 to 89, though the addition of sugar molecules caused an increase in AChE and BChE inhibitions in compound 90 compared to compound 85 [50][51][56][64]. The xanthones compound 95– 101 isolated from Garcinia mangostana and Belamcandae chinensis rhizoma showed moderate to good AChE and BChE inhibition activities [19][66][67]. Evidently, an increase in the hydroxyl groups causes an increase in the cholinesterase inhibitory activity of these xanthones, while no significant difference in cholinesterase inhibition is observed for the prenyl groups. For the chalcones 102 to 105 isolated from Humulus lupulus , the activity decreases from compound 102 to 105 with a decrease in the number of hydroxyl (-OH) substituents [56]. Aurones 106– 109 isolated from Morus alba have low activities though 109 had BChE inhibition with an IC 50 of 7.22 ± 0.22 µM [68]. Amongst the tannin compounds 110 to 115, isolated from Cornus officinalis , Phyllanthus niruri , and Calceolaria talcana , compound 114 (Isocorilagin) is the most active with an IC 50 of 0.49 µM and 4.20 µM on AChE and BChE inhibition, respectively [28][32][36][69][70]. This could be because it is less bulky, having only three benzoyl groups as compared to compounds 112 and 113 with five benzoyl groups and 110 and 111 with four benzoyl groups. The triflavanone Garcineflavanone A and biflavonol Garcineflavonol A isolated from Garcinia atroviridis both showed good percentage inhibition of cholinesterase. M. charantia extract showed many inhibitory activities, however, ligballinol a lignan found in extract showed relatively high activity. According to previous studies, not many lignans have been reported to exhibit cholinesterase inhibitory activity [85].

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