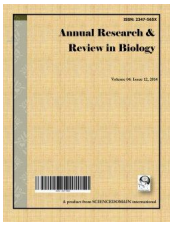

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# Synthesis and Development of BACE 1 Inhibitor for Alzheimer's Diseases from Medicinal Plants

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors BAAA and FMMTM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors RV, MV and JM managed the analyses of the study. Author MMM managed the literature searches. All authors read and approved the final manuscript.*

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## ABSTRACT

Medicinal plants have shown great promise in treating Alzheimer's disease (AD), which significantly contributes to the production of pharmaceutical and cosmetic molecules with biologically efficient moieties. Plants derived bioactive compounds have been isolated from the medicinal plants and are used in brain diseases. Accountable for brain diseases. Plant extracts have undesirable effects such as acute or chronic toxicity; this could be involved in the delay or discouraging the adoption to the

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brain cells for proper and effective treatment. β-secretase is the primary protease in the process of producing Amyloid β (Aβ), which is an amyloid precursor protein in brain cells. This review is focused on the numerous different bioactive compounds present in medicinal plants such as Flavonoids, Phenyl propanoids, Prenylated flavones, Naphthoquinone, Resveratrol, Phlorotannins and Glycoside derivatives. Even though medicinal plants and their functional derivatives were reported to be good source of alternative medicines for long sought diseases like AD; but clinical trials on human are yet to be beyond the preliminary stages. The useful applications of these compounds, as bio-markers are also being explored, to further enrich control of Alzheimer's.

*Keywords: Medicinal plant; natural products; essential oil; clinical trials; BACE 1 inhibitors; Alzheimer's disease.*

## 1. INTRODUCTION

Alzheimer's disease (AD) is an age related neurodegenerative disorder with clinical characteristic and pathological features associated with loss of neurons in certain brain areas leading to impairment of memory, cognitive dysfunction, behavioral disturbances, deficits in activities of daily living, which eventually leads to death [1-3]. In 2010, approximately 35 million people worldwide were suffering from AD and this number is believed to reach 65.7 million by 2030 [4].

AD is the most common form of dementia, is a progressive neurologic disorder of the brain that leads to irreversible loss of neurons. AD impairs cognitive and memory functions, communication, personality, behavior, and ability to function properly. The average duration of survival of AD patients after the onset of dementia is 5 to 9.3 years [1,2]. AD is a progressive inexorable loss of cognitive function associated with the presence of senile plaques in the hippocampal area of the brain. The disease is the most common form of dementing illness among middle-aged and older adults patients.

AD is a neurodegenerative disorder characterized by accumulation and deposition of amyloid β (Aβ) peptides, which are generated from the cleavage of the β-amyloid precursor protein (APP) by consecutive action of β-secretase (BACE 1) and γ-secretase[1-3]. AD is a progressive neurodegenerative disease for which there is no cure. It affects approximately five million people in the US alone. Worldwide, a new case is diagnosed every 70 seconds [4]. The most common form of dementia is AD, which now affects over 30 million people worldwide[5]. γ –secretase enzyme secreted in the brain and affect the north cleavage; while β-secretase mechanism not necessary for App cleaveage [6]. The action of β-secretase is strongly tied to the onset of AD. The development of β-secretase will offer a mechanistic approach in targeting AD. Aβ peptides are thought to play an important role in the development of AD as several mutations associated with familial forms of AD affect their production, accumulation or oligomerization [6]. The brains of Alzheimer's disease patients present extracellular deposits of Aβ peptides and intra-neuronal neurofibrillary tangles made of hyper-phosphorylated tau protein [7]. In some cases, Aβ peptides are produced by the sequential cleavage of the amyloid precursor protein (APP) by β-secretase (β-site APP cleaving enzyme or BACE 1) and γ-secretase and considerable effort have been devoted in both academia and industry to identify inhibitors of these enzymes for the treatment of AD. It has been shown to be a membrane-bound aspartyl protease. The cleavage of APP by BACE 1 occurs in the lumina and is considered to be the rate limiting step in the processing of APP to Aβ peptide [8]. Aβ dimers are the most abundant soluble Aβ oligomers present in AD brains [9] and their levels strongly correlate with the severity of cognitive impairment in AD [10]. When researchers carried out clinical trials with active compounds, these have been disappointing [11] and suggest that alternative approaches for lowering Aβ production should be explored. Since we have shown that various compounds of unrelated structure that block NF-κB (is a protein complex that controls transcription of DNA, cytokine production and cell survival) activation reduce Aβ production by preventing the β-cleavage of APP [12].

AD is a neurodegenerative disease and the most frequent and predominant cause of dementia in the elderly, provoking progressive cognitive decline, psycho-behavior disturbances, memory loss, the presence of senile plaques, neurofibrillary tangles, and a decrease in cholinergic transmission [13,14]. Although the AD pathogenesis involves two major molecular hypotheses, cholinergic and the amyloid cascade hypothesis. A strategy frequently employed in

designing BACE 1 inhibitors is replacement of the scissile amide bond of APP with non-cleavable transition state isosters such as statine, hydroxyethylene, norstatine, or hydroxyl-ethylamine (HEA), all of which should have a nanomolary affinity to BACE 1 [15-17]. Plant drugs which are being considered for the treatment of Alzheimers must cross the blood brain-barrier (BBB) and plasma membrane [18]. *In vitro* BACE 1 inhibitory activity has also been discovered in a range of natural plant products, particularly by secondary metabolites having a polyphenolic structure [19,20]. Drug therapeutic potential is preferably smaller than 700Da, rendering large/hydrophilic peptide-based inhibitors of low viability *in vivo*. Whereas, the secondary metabolites of plants and microbes which have relatively low-molecular weight and high lipophilicity may be good drugs for BACE 1 inhibitors [21], rising interests are in drugs which are convenient, safe, and economical alternatives to the main stream of plant expression systems for industrial pharmaceutical protein derivatives. This production has inspired the development of plant-derivative proteins. The major advantages of using medicinal plants compared with other systems include: similarity of plant cells to mammalian cells regarding post-translational modification (e.g., glycosylation); sustainable, agricultural-scale production; and minimal risk of contamination by mammalian pathogens [22,23].

With the increase in life expectancy associated with a modern lifestyle, neuronal degenerative diseases are currently increasing rapidly. In this paper, we have mentioned that plant natural products are soluble Aβ oligomers and more specifically Aβ dimers isolated from AD brains that can induce tau hyper phosphorylation and neuritic degeneration [24]. As a result, the discussed known compounds, revealing a potentially novel natural products that could be investigated on a large scale and could ultimately find biological application as new drugs against BACE 1 (Fig. 1) since there are lots of studies regarding BACE 1 mechanisms carried out since a decade ago, we have review the lastest literature (2008-2017) (Fig. 2). The section on medicinal plant includes too much of an elaborate information which is already explained by many similar reviews. The focus of this review can be more on the phytoconstituents and its association with β-secretase in AD. While selecting the potential phytoconstituents a holistic approach will be very well accepted both scientifically written to the toxic nature of certain compounds as well as the synergistic effects contributed by the combinatorial therapies. It would be good to lead the discussion in this direction.

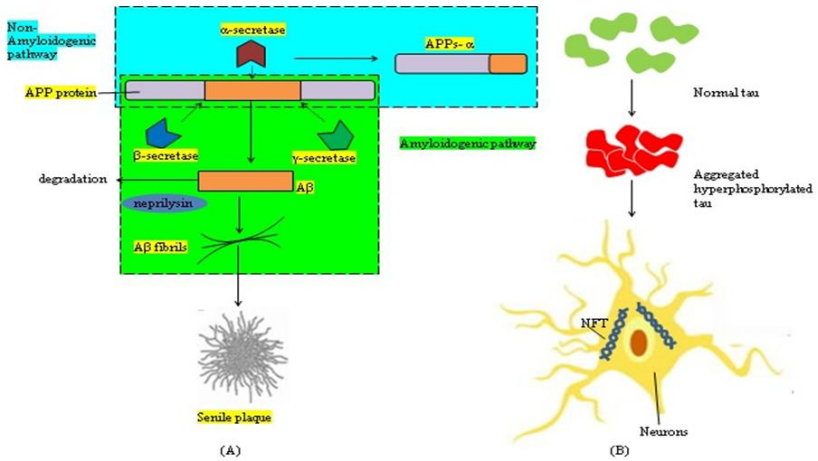


**Fig. 1. Development of pathological characteristics of Alzheimer disease: a) In non-amyloidoigenic pathway, α secretase cleaves APP within the APP protein within the Aβ but doesn't generate any Aβ, while in the amylodoigenic pathway the β- and γ-secretase cleaves the APP resulting in production and deposition of Aβ, which consequently forms senile plaque (SP). (B) Aggregation of hyperphosphorylated tau in AD neurons results in the formation of neurofibrillary tangle (NFTs), reducing the ability of tau to bind microtubules and resulting in cytoskeletal degeneration and neuronal death. The figure was adapted from Jun et al.[100] and Thinakaran and Koo[101]**

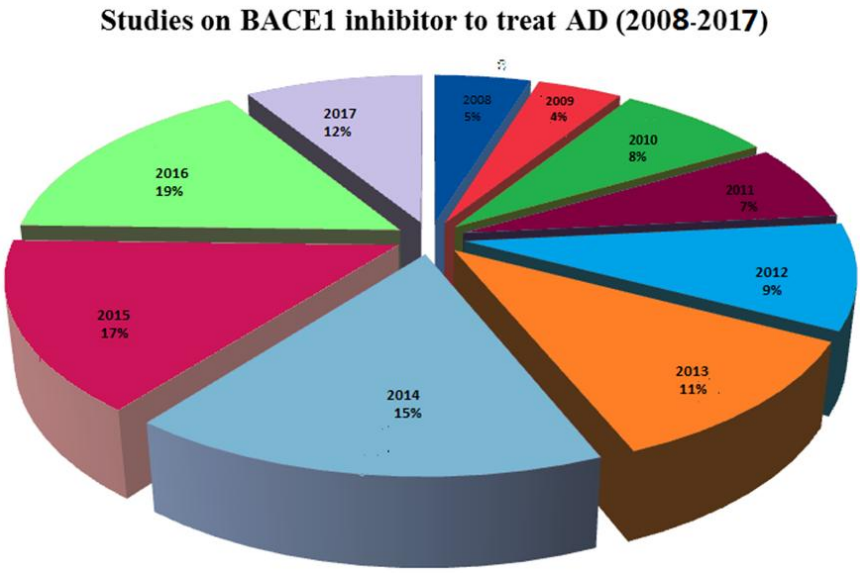


**Fig. 2. Studies on BACE1 inhibitor to treat AD (2008-2017). The pie chart shows that the studies on mechanism to treat AD has started to increased rapidly on 2010 onwards. This shows that lots of efforts have been done to understand the mechanism of BACE1 inhibitor in order to treat AD patients**

## 2. NATURAL PLANT PRODUCTS

Plants have been utilized as medicines for thousands of years for curing various ailments and diseases [25]. These medicines were initially used in the form of crude drugs such as tinctures, teas, poultices, powders, and other herbal formulations [25,26]. In recent history, the use of plants as medicines has evolved from the isolation of active compounds, beginning with the isolation of morphine from opium in the early 19th century [25-27] followed by other AD drugs such as phenyl propanoids, flavonoids, naphthoquinones, resveratols, phlorotannins and glycosides. Isolation and characterization of pharmacologically active compounds from medicinal plants continue to this day (Table 1). More recently drug discovery techniques have been applied to the standardization of herbal medicines to elucidate analytical marker compounds [28]. Among these are alkaloids, glycosides, galactomannan gum, poly-saccharides, peptidoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids and inorganic ions used as markers [29]. In contrast, BACE 1 knocked-out mice which lacked Aβ production [30]. These results indicate that BACE 1 inhibitors should reduce Aβ levels, which may counter the progress of AD pathogenesis. Development of BACE 1 inhibitors are generating tremendous interests as potential therapeutic agents for AD [31].

Despite the evident success of drug discovery from medicinal plants, future endeavours face many challenges. Pharmacognosists, phytochemists, and other natural product scientists will need to continuously improve the quality and quantity of compounds that enter the drug development phase to keep pace with other drug discovery efforts [32]. The process of drug discovery has been estimated to take an average of 10 years and upwards [33] and cost more than 800 million dollars [34]. Much of this time and money is spent on the numerous leads that are discarded during the drug discovery process. In fact, it has been estimated that only one in 5000 lead compounds will successfully advance through clinical trials and be approved for use. Lead optimization and identification (involving medicinal and combinatorial chemistry), lead development (including pharmacology, toxicology, pharmacokinetics, ADME [absorption, distribution, metabolism, and excretion], and drug delivery), and clinical trials all take considerable length of time. Drug discovery from medicinal plants has traditionally been lengthier and more complicated than other drug discovery methods. As such, many pharmaceutical companies have to eliminate or scale down their natural product research [28,32,35].

**Table 1. Potential plants to treat AD. Studies on the extracted compounds and their effects**

| Plant name | Part(s) of plant used | Compound(s) extracted | Effect(s) of compound(s) | Exp. study* | Ref. |
|---|---|---|---|---|---|
| *Sophora flavescens* | Chloroform extract of root | Lavandulyl flavanones | - Inhibit the activity of BACE 1 in a dose-dependant manner | a | 66 |
| *Fructus gardeniae* | Methanol extract of whole plant | Geniposide | - Inhibit acetylcholinesterase activity<br>- Ameliorate scopolamine-induced memory impairment in amnesic mice | a,b | 102 |
| *Paeonia lactiflora* | Ethanol extract of seeds | Resveratrol oligomer | - Exhibit a significant inhibitory effect on baculovirus-expressed BACE 1 | a | 86 |
| *Psoralea corylifolia* | Methanol extract of seeds | Isoflavones | - Exhibit a significant inhibitory effect on baculovirus-expressed BACE 1 | a | 20 |
| *Cordia sebestena* | Ethanol extract of fruit | Sebestenoids | - Exhibit moderate inhibition of the aspartic protease BACE 1 | a | 53 |
| *Perilla frutescens* var. *acuta* | Methanol extract of leave | Luteolin and rosmarinic acid | - Inhibit the activity of BACE 1 in a dose-dependant manner | a | 19 |
| *Smilax china* L. | Methanol extract of rhizomes (Smilax Rhizoma) | *Trans/cis*-resveratrol mixture, oxyresveratrol, veraphenol, and *cis*-scirpusin A | - Inhibit the activity of BACE 1 in a dose-dependant manner | a | 88 |
| *Sanguisorba officinalis* L. | Methanol extract of roots (Sanguisorbae Radix) | 1,2,3-trigalloyl-4,6-hexahydroxydiphenoyl-β-d-glucopyranoside and 1,2,3,4,6-pentagalloyl-β-d-glucopyranoside | - Inhibit the activity of BACE 1 in a dose-dependant manner | a | 103 |

** a: In vitro (cell lines) study; b: In vivo (animal) study*

## 2.1 Challenges of Drug Discovery

Natural product chemistry is a multi-disciplinary field that combines Chemistry, Botany, Biochemistry, Environmental Science, Medicine, etc. With the development of science and technology, this field has gained increasing importance. History tells us that mankind was interested in naturally occurring substances. In ancient cultures, plant extracts were utilized as healing substances and tribal hunters, still use plant extracts as healing substances. The majority of natural products are isolated from plant origin. It is mainly due to the ease of the isolation process. Natural products are usually given a trivial name derived from the plant origin. Recent developments in biology have given some hints about the properties of these compounds.

1. Many natural products have a regulatory role
2. Some act as chemical policemen against pests
3. Some function as chemical communicators (or) messengers and
4. Some behave as chemicals for protection.

**a. Natural product functions:** The naturally occurring substances are broadly classified into two types: 1. Endogenous and Exogenous substances and 2. Primary metabolites and

Secondary metabolites. Endogenous substances occur as a result of a normal functioning of an organism, for example, amino acids, proteins, carbohydrates, steroids and hormones etc., belong to this category. Exogenous substances come from outside the organism. For example, drugs, environmental pollutants etc, are in this class. They are otherwise termed 'Xenobiotics'.

**b. Primary and Secondary metabolites:** Plant cells produce far more chemical compounds than is necessary for their basic functions, i.e. biochemical pathways for survival and propagation. Basic or primary metabolism refers to all biochemical processes for the normal anabolic and catabolic pathways, which result in assimilation, respiration, transport, and differentiation. Basic and "primary" metabolism is shared by all cells, while "secondary metabolism" generates diverse and seemingly less essential or non-essential by-products called "secondary products" and showed the colours, flavours, and smells. These produces are sources of fine chemicals, such as drugs, insecticides, dyes, flavours, and fragrances, and phytomedicines found in medicinal plants [36].

While primary metabolism consists of biochemical pathways that are in general common to all cells, secondary metabolism consists of a large number of diverse processes that are specific to certain cell types. Plant pigments, alkaloids, isoprenoids, terpenes, and waxes are some example of secondary products [29,34]. Many secondary products have been rather ambiguous, and initially they were thought to be just waste materials. However, considering their non-motile nature and the lack of sophisticated immune systems that we have, plants had to develop their own defence system against pathogens and predators, and systems to lure motile creatures for fertilization and dissemination. Indeed, many of the secondary products are bactericidal, repellent (by bad tastes, etc), or even poisonous to pests and herbivores [35].

Secondary plant products have been directly used as food and herbs. Now-a-days, they are used either directly or after chemical modification. Plant secondary metabolites represent a tremendous resource for scientific and clinical researches and new drug development. Over all, their pharmacological value not only remains undiminished until today, but is increasing due to constant discoveries of their potential roles in healthcare and as lead chemicals for new drug development. The need to find new small molecules that have good BACE 1 inhibitory activities is ever growing, as this enzyme is a key player in the onset of AD. Since, a wide array of anti-amyloid and neuroprotective therapeutic approaches are under investigation on the basis of the hypothesis that Aβ peptide plays a pivotal role in disease onset and progression. Development of β-secretase inhibitors and targeting the fibrillary aggregates of Aβ peptide are strategies which are being explored and shows promise for acute improvement in AD [36]. By a recent estimate, 60% of all currently approved antibiotics and over 50% of all anti-cancer agents are derived from microorganisms or plant products [37]. Galantamine is produced by daffodils (*Narcissus* sp.) and several other plants within the order Amaryllidaceae [38]. Rivastigmine, developed by Novartis, is a simplified analogue of physostigmine, which is produced by the West African perennial climbing plant *Physostigma venenosum* [39]. Natural products have been pre-selected to interact with specific biological targets that often share structural and mechanistic features with macromolecules relevant to maintaining proper human health or to the development of the disease state [40].

Nature cures too many human ailments [41]. Modern pharmacology is founded on drugs derived from natural sources and the fundamental biological insights gleaned from studies on their mechanism of action. The commonly prescribed AD drugs are in US [Donepezil (Aricept), Rivastigmine (Exelon). Memantine (Namenda) and Galantamine (Razadyne) too, are derived from natural sources (*Narcissus* sp.) and several other plants within the order Amarylidaceae (Fig3). Extracts of these plants were widely used in Europe as a traditional medicine before the development of galantamine by Janssen Pharmaceutica as a medication to treat Alzheimers [38, 42]. Despite these years of research, only a small fraction of the Earth's total biodiversity has been examined. Ultimately, the modern drug discovery timeline of hit to clinic in two years is incompatible with the traditional iterative cycle of natural products lead discovery. Once optimized and integrated into our discovery platform, this assay has the potential to break the iterative cycle of natural products lead discovery and accelerate the

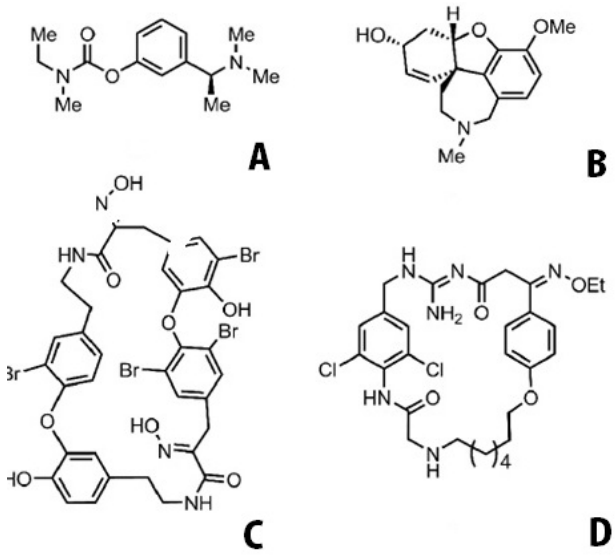


**Fig. 3. Common Alzheimer's drugs are available in world markets. a. Rivastigmine; b. Galantamine; c. Bastadin 9; d. BMS (Bristol-Myers Squibb) compound**

identification of potential novel drug leads from plant sources for AD. Therefore, investigations with agents that reduce amyloid production (or) limit aggregation, (or) increase removal might block the cascade of events comprising AD pathogenesis. Modern pharmacology is founded on drugs derived from natural sources and the fundamental biological insights gleaned for their mechanism of action.

## 3. CLINICAL TRIALS - STATEMENT OF PROBLEMS

BACE 1 inhibitors are under intensive study and a large number of peptidomimetic inhibitors have been reported and developed [43-44]. BACE 1 is located in neuronal and glial cells in the brain. Several strong synthetic BACE 1 inhibitors are synthesized and under development [31,45], although the majority have serious clinical problems, such as safety margin or BBB permeability. The peptidomimetic inhibitors seem to have difficultly crossing the BBB. On the other hand, quinines in general are very small compounds which are relatively advantageous for crossing the BBB. Indeed, recent studies revealed that quinines like plumbagin [46], thymoquinone [47] and coenzyme Q10 [48] are able to traverse the BBB *in vivo*. Fundamentally this iterative process is necessary to link a specific chemical structure in the mixture to the observed biological activity. The initial biological testing using crude mixtures must be followed by chromatography to separate the constituents and subsequent biological testing. Only through the repeated cycles of purification and testing can the activity be linked to any particular compound in the mixture. Several strategies have been developed to accelerate this process. The most popular is automated purification of crude extracts to generate pre-purified libraries before chemical screening, although this can also be time-consuming. In the Amyloid Cascade Hypothesis [49] of AD progression, cleavage of amyloid precursor protein (APP) by BACE 1 begins a cascade leading to formation of soluble polypeptide oligomers that trigger neurodegeneration [50]. The operational simplicity of this counter screen suggests it should be incorporated early in any screening campaign involving natural plant products.

Cognitive identified drug evaluation scales and psychometric tests of the AD should be properly carried out and their applications must also consider the daily life activities and compartmental disorders. In case of animal experiments on rats, mice, rabbits and monkeys etc remain classical, the use of aged animals do not give much information and are more expensive than on young animals [50]. Alzheimer clinical trials are a set of procedures on the part of medical research and novel drug development that are conducted to allow safety and efficacy of data to be collected for health interventions. These trials can take place only after satisfactory

information has been gathered on the quality of the non-clinical aspects of safety, and after approval from the health authority (ethics committee) is granted in the country where the trial is taking place [43]. Phase I clinical trials are small scale safety tests. Approximately 10-25 healthy volunteers given different doses (depends upon body weight) of the Alzheimer plant drug for several months under study. (i) Scientists should identify the plant derived drugs, how it can be absorbed or eliminated, how it reacts in a healthy human body, and what kinds of side effects it causes. The scientists should have a good idea on how the new drugs will affect healthy humans in phase I clinical trials which are similar to those involving laboratory mammals such as rats and monkeys etc. If the potential drugs outweigh the side effects that turn up in phase I trials, the FDA allows it to proceed to phase II. In this phase (II) it must be carried out with extreme rigor in the methodology, and especially with an evaluation of pertinent clinical benefits in the cognitive and non-cognitive fields. Phase II clinical trials are longer, Scientists recruit 25-100 volunteers. Phase II trials typically last about two years [45]. While they focus on effectiveness and dosage, the scientists also continue to monitor the side effects of the plant derived drugs. If the new drug appears to be effective at a practical dose without side effects the FDA considers too toxic, it is then approved for phase III trials. Phase III clinical trials mark the final stage of pre-approval drug testing. Scientists are fairly confident that a known dose helps treat the intended condition and that the new drug is reasonably safe. Phase III trials last two to four years and typically involve several thousand individuals at medical centers around the country (Fig4).

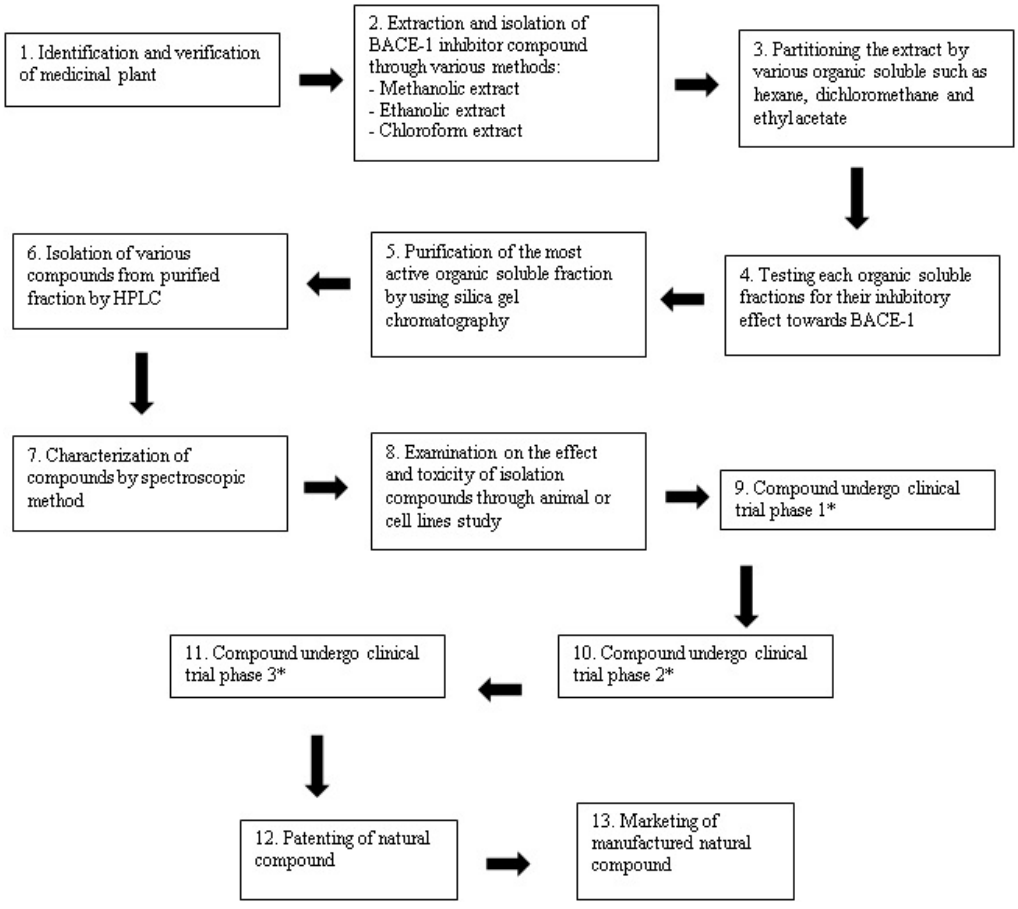


**Fig. 4. Schematic diagram on how a natural compound was extracted and isolated from a known medicinal plant, undergo clinical trials*, patenting and marketing upon approval by FDA**

**The way of conducting clinical trials was discussed earlier in the text*

## 4. PHENYL PROPANOID DERIVATIVES

Phenyl propanoids are one of a number of active compounds of AD derived from cinnamic acid, which is formed from phenylalanine by the action of phenylalanine ammonia-lyase (PAL), the branch point enzyme between primary and secondary metabolism and have been reported to display a wide range of biological activities. Feng and Shoichet have demonstrated that many compounds that are frequently found in enzyme assays are promiscuous inhibitors that aggregate with enzymes in a non-stoichiometric fashion [51], which disrupts protein folding [52]. The Alzheimer's drug inhibitors were isolated from the fruit of *Cordia sebestena* (Hawaiian plant). The bioactive compounds of four secondary metabolites were isolated from the ethanol extract and their structure defined [53]. Active extracts showed BACE 1 activity against the aspartic protease, which is a central blocker in the etiology of AD. A Column fractions extract has showed that the new active phenyl propanoids, such as sebesteniods A-D can inhibit BACE 1 formation (Fig. 5), when the BACE 1 assay combined with additive is also disrupting the crucial protein aggregation [54]. While this activity was dose-dependent, it was also strongly influenced by the addition of detergents suggesting a non-specific inhibition. In the Amyloid cascade hypothesis [49] the disease progression of AD, cleavage of amyloid precursor protein (APP) by BACE 1 begins as a cascade leading to formation of soluble polypeptide oligomers that trigger neuro-degeneration [50]. Sebestenoids C and D were the most potent with $IC_{50}$ values of 20 and 22 μM, respectively. In comparison, the smaller compounds such as sebestenoids A and sebestenoids B were less active at 32 and 116 μM, respectively. In addition, sebestenoids C and D were investigated using a surrogate system. These compounds were assayed against the serine protease chymotrypsin in a standard chemiluminescent assay [55] with and without the addition of detergent. The $IC_{50}$ values of sebestenoids C and D were strongly inhibit BACE 1. These findings suggest that phenyl propanoid derivatives of sebestenoids A, B, C and D are a potential agents for AD.

## 5. FLAVONOID DERIVATIVES

The flavonoids represent an important group of pigments that occurs in the plant kingdom. The flavones, one of the flavonoids, possess BACE 1 inhibit activity. Flavonoids have low toxicity and are found in a variety of plants such as fruits, vegetables and flowers. Specific sources include citrus, garlic, and tea etc. Indeed, recent studies revealed that flavonoids are able to traverse the BBB *in vivo* [56]. In addition, these flavonoids have a wide safety margin [57]. The natural flavonoids inhibited BACE 1 enzyme activity in both a cell free system and neuronal cells. In this study, the flavonoid derivatives have significantly reduced the levels of Aβ1-40 and Aβ1-42 in neurons. Natural flavonoids are well known anti-oxidants. Since, numerous studies have reported the protective effects of natural polyphenols, including flavonols and flavones, against various substances, such as Aβ. It is hypothesized that natural flavonoids may counter the progress of dementia pathogenesis through the activities of its constituent flavonoids [58-59]. Moreover, many compounds, including natural plant extracts and flavonoids, have been analyzed for their ability to decrease Aβ-induced neuronal cell death [60]. It was revealed that natural flavonoids, including flavonols and flavones, reduced Aβ induced neuronal cell death [61,62]. These flavonoids have a strong anti-oxidative activity and inhibit Aβ oligomerization [63]. Previously, it was reported that the natural flavonol myricetin showed a neuroprotective effect against Aβ induced neuronal cell injury [64] (Fig. 6).

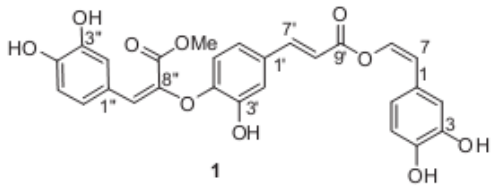


**Fig. 5. Phenyl propanoid derivatives**

**a. Prenylated flavones:** Successful β-secretase inhibitors were isolated from the stem bark of *Morus lhou,* it's considered as a rich source of prenylated flavones and a ubiquitous traditional herbal medicine. Prenylated flavones have been permitted as a natural ingredient of functional foods in many countries. Derived extracts of this plant have been reported to exhibit a broad spectrum of pharmaceutical effects including neuroprotection, hypoglycemic, hypertension, antimicrobial as well as anti-inflammatory properties with inhibition to the enzymatic oxidation of tyrosine to melanin [65]. Particularly, methanol derivatives of *Morus lhou* stem bark exhibited significant BACE 1 inhibitory activity with $IC_{50}$ (78.4 μg/ml). This extracts had showed

the following compounds such as norartocarpetin, Kuwanon C, Morusin, Kuwanon A, cyclomorusin, morusinol, neocyclomorusin, and mormin using spectroscopic 2D- NMR [65,66] (Fig. 7). Each compound has showed significant BACE 1 reversible inhibition in a dose-dependent manner. The Kuwanon C compound was increased in concentration; the enzyme activity rapidly diminished and resulted in lowering of the slope of the lines (procedure for enzyme kinetics). Whereas, the corresponding parent norartocarpetin had much less BACE 1 inhibition, increasing the hydrophilicity of the pendant prenyl groups by hydroxylation led to a decrease in potency. The compound of Morusin, cyclomorusin, morusinol, neocyclomorusin, and mormin bearing alkyl substitution therein showed lower BACE 1 inhibition (recombinant human BACE 1). Above results were declared best BACE 1 inhibitor possessed both a free resorcinol group and at least one prenyl motif at C3 position in the ring.

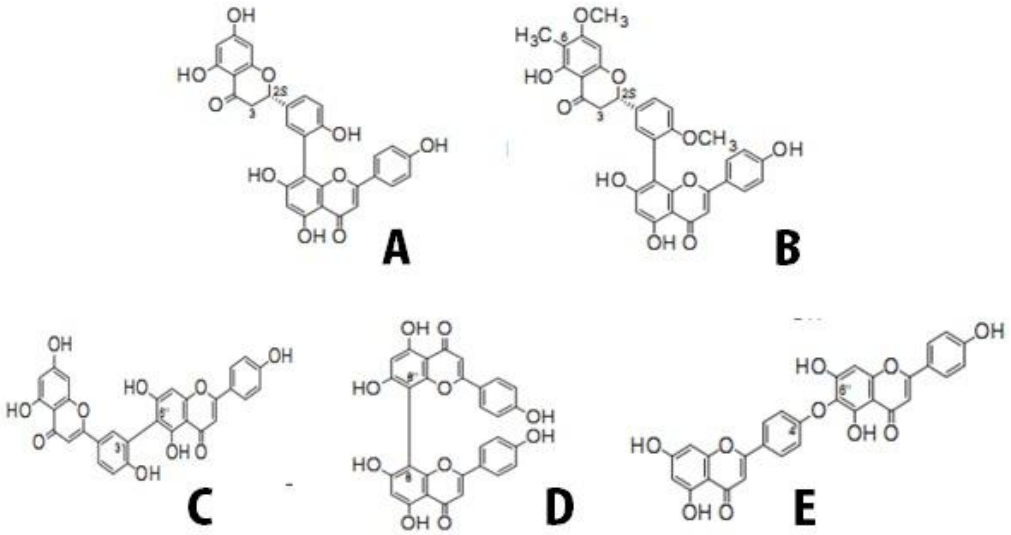


**Fig. 6. Flavonoid derivatives. a. 2,3-dihydroamentoflavone; b. 2,3-dihydro-be-methylglinkgetin; c. Robustaflavone; d. Cupressuflavone; e. Hinokiflavone**

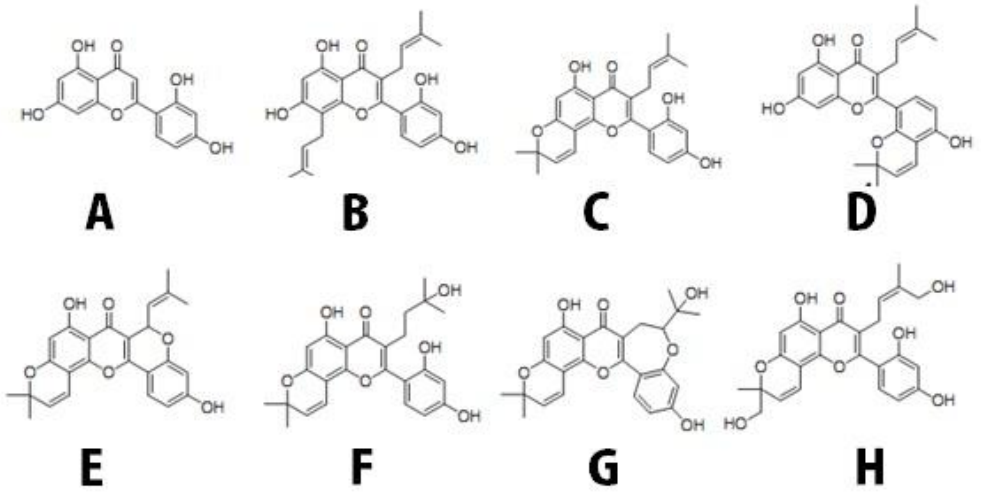


**Fig. 7. Prenylated flavones. a. Norartocarpetin; b. Kuwanon C; c. Morusin; d. Kuwanon A; e. Cyclomorusin; f. Morusinol; g. Neocyclomorusin; h. Mormin**

**b. Biflavonoids:** Amentoflavone-type biflavonoids exhibited neuroprotective effects on oxidative stress-induced amyloid β peptides witch induced cell death in neuronal cells [67]. The above findings were declared that amentoflavone type biflavonoids have significant BACE 1 inhibitory activity and could be multiple targets for the development of novel therapeutic strategies for Alzheimer's disease. Biflavonoids are well known as constituents of gymnospermous plants and are flavonoid dimmers connected by C-C or C-O-C bonds. The $CHCl_3$ extracts of *Cephalotaxus harringtonia* showed BACE 1 inhibitor activity. On the other hand, these plants were found to exhibit anti-inflammatory [68], anti-malarial activities [69] and are anti-influenza [70-71]. Indeed, the flavonoids have able to transverse the BBB *in vivo* (Fig. 8).

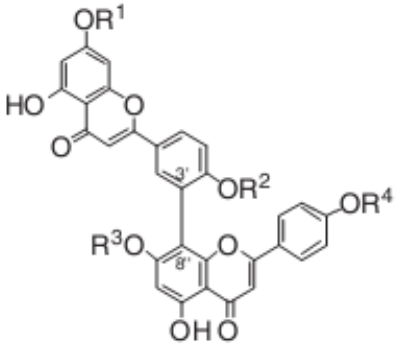


**Fig. 8. Biflavonoids**

## 6. NAPHTHOQUINONE DERIVATIVES (NQ)

Naphthoquinone is a fat-soluble vitamin. It is an organic compound that has the formula $C_{10}H_6O_2$. It can be viewed as derivatives of naphthalene through the replacement of two hydrogen atoms by two ketone groups. It is a yellow crystalline substance that is related to quinone, procurable by oxidizing naphthalene with chromic acid. 1,4-naphthoquinone structure is common in numerous natural products associated with antifungal, antibacterial, antiviral and antitumor activity (Fig. 9). Its derivatives are found in various medicinal plant parts such as leaves, flowers, roots, barks and woods and have interesting activities in physiology and pharmacology [72]. 1, 4- Naphthoquinones are widely spread in nature and their interest lies in their broad-range biological action through naphthoquinones being redox active organic cofactors and important species in biological systems [73]. Quinones account for one of the largest families of antitumor agents [74]. The basic knowledge in quinine studies has been used to design new anticancer drugs, improving selectively and providing a more rational therapeutic application for them [75]. The 1-4 NQ scaffold has been identified as a new class of Hsp90 inhibitors [76] which could be useful for the treatment of alzheimer disease [77] and numerous neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease, in which protein aggregation is a common etiology [78,79]. Different naphthoquinone derivative ring structures have shown to activate the nuclear receptor peroxisome proliferator- activated receptor gamma [80], strategy which could be promise ng in the treatment of several neurological pathologies [81]. In this regard, the α secretase activity increases with enhanced membrane fluidity [82] and processing of APP by β secretase might be explained by alterations in cell membrane fluidity [83]. The activity of BACE is sensitive to oxidative stress [84]. There is convincing evidence that oxidative stress regulates the BACE activity, resulting in Aβ accumulation [85]. Therefore, BACE inhibition by 1,4 –NQ could contribute to an improvement of the cell membrane fluidity. The active 1,4 NQ by inhibiting the BACE activity, could make the predominant metabolism of APP towards the α-secretase pathway, thus increasing the release of αAPPs.[10]

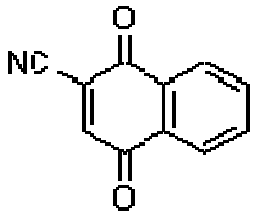


**Fig. 9. 1,4 Naphthoquinone derivatives**

**a. Resveratrol derivatives:** Resveratrol is the active compound and the potential biomarker for the treatment of Alzheimers disease. It is created by certain plants as a defense mechanism. It has quite a few health benefits in store for us. Resveratrol may also help negate the effects of a calorie-laden diet. This compound has cancer fighting characteristics that makes resveratrol so popular. Resveratrol also protects our blood vessels, and prevents the harmful effects of free radicals. It may even be beneficial to those with AD, as it is known to protect both the heart and

the brain from harmful oxidized fat. Resveratrol oligomer was isolated from the seed extract of *Paeonia lactiflora,* as the active principle responsible for the inhibition of beta-site APP cleaving enzyme 1 (BACE 1) by *in vitro* screening [86] (Fig. 10).

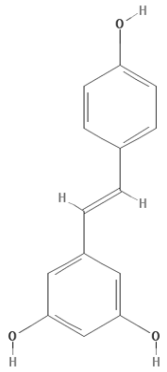

**Fig. 10. Resveratrol structure**

Vitisin A and vitisin B are resveratrol tetramers of BACE 1 biomarkers which could be employed as promising candidates for the design of new potential BACE 1 inhibitors. On the other hand, vitisin A and vitisin B were recently reported to attenuate β-amyloid induced oxidative stress in PC12 cell lines [87]. Even though, the BACE 1 inhibitory effect of resveratrol oligomers has not been fully investigated by *in vivo* experiments, resveratrol and related stilbene monomers such as oxyresveratrol, veraphenol, and cis-scirpusin have also been reported to inhibit BACE 1 *in vitro* [88]. However, it was not clear whether the BACE 1 inhibitory effect of vitisin A and vitisin B was associated with the anti-oxidative effect.

## 7. PHLOROTANNINS DERIVATIVES

During the past two decades, numerous novel compounds isolated from seaweeds have been demonstrated to possess biological activities such as antitumor, antioxidant, antibacterial, anticoagulant, and anti-inflammatory activities [89]. As shown in this review, there are significant numbers of very interesting molecules that have come from marine plant sources, among these are phlorotannins one of the important compounds. Phlorotannin derivatives (Fig. 11) from *Ecklonia cava* has been present in its limited origin (only Korea and Japan) but also due to the presence of unique phlorotannin derivatives in *Ecklonia cava*. Based on the literature, it could be suggested that phlorotannins derived from *Ecklonia cava* compounds have potential for application as antioxidants, in functional food, cosmetics, and pharmaceutical industries. Meanwhile, additional studies on the mechanisms and *in vivo* studies are highly warranted to achieve a better understanding of important antioxidant properties of the isolated phlorotannins from *Ecklonia cava.* It could be suggested that phlorotaninns could be more potential candidates for the development of unique natural antioxidants for future industrial applications as functional foods, cosmetics and pharmaceuticals [90].

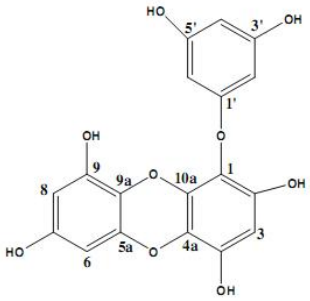

**Fig. 11. Phlorotannins derivatives**

Currently, marine plants are intriguing materials as nutraceuticals and pharmaceuticals given their numerous biological and phytochemical benefits [91]. *Ecklonia cava and Elsenia bicyclis,* one of those phlorotannin-rich natural resources, which is the common perennial brown algae (marine plant). In particular, phlorotannins, isolated mainly from the *Ecklonia* and *Eisenia* species, are responsible for a variety of bioactivities, including antitumor [92], anti-plasmin inhibitor [93], nitrite-scavenging [94], algicidal, anti-skin aging [95]. Major phlorotannin derivatives of the ethyl acetate (EtOAc) fraction with the highest activity were eckol, eckstolonol, dieckol, and triphlorethol-A, and their *Ki* (binding affinity, μM) values for [$^3$H]-flumazenil binding were 1.070, 1.491, 3.072, and 4.419 μM, respectively. Hypnotic effects of *Euklonia cava* Kjellman (ECK) extracts and the EtOAc fraction were fully inhibited by flumazenil, a specific GABA type A-benzodiazepine receptor antagonist [96].

## 8. GLYCOSIDE DERIVATIVES

BACE is a drug target for the treatment of Alzheimer's disease. Unlike other marketed anti-AD drugs, such as acetylcholine esterase and NMDA (N-methyl-D-aspartate) inhibitors, BACE inhibitors promised to be a class of disease disrupting, rather than symptom relieving

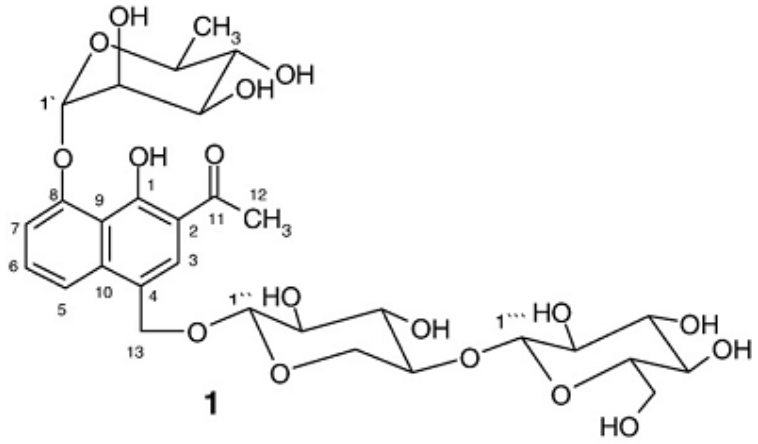


**Fig. 12. Glycoside derivatives (Aloveroside A)**

agents.[6] Nine chrome glucosides with bioassay guided fractions were determined. On the basis of spectral analysis, their structures were identified as aloveroside A, elgnica dimer A, elgnica dimer B, p-coumaroyl aloenin and aloenin [97,98] (Fig. 12). The ability of the compounds to inhibit BACE 1 cleavage of APP was assessed using a fluorescent resonance energy transfer (FRET) peptide cleavage assay. Briefly, assays were performed in triplicate in 96-well plates with a 100 µl of 50 mM sodium acetate buffer, containing 4 µM substrate, 2µg/ml recombinant human BACE 1 and different concentrations of inhibitors. In addtion, new β-cyclogeraniol diglycoside, along with four discussed components, cycloartenol, ρ-hydroxy benzoic acid, vanilloloside, 5'-O-methyladenoside were first isolated from the n-BuOH fraction of *Nelumbo nucifera* stamens. The five compounds were evaluated via the acetylcholinesterase, butyrulcholinesterase, and β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE 1) inhibition assays. The five isolated compounds lacked BACE 1 inhibition up to 100 µM. N. nicifera stemens derived compounds could potentially exert their primary anti-Alzheimer effects as acetylcholinesterase inhibitors rather than BACE 1 inhibitors [99-103].

## 9. CONCLUSIONS

Over the last two decades though, there has been a reduced emphasis on natural products as a source of pharmaceutical leads. Medicinal plants have complex constituents, and many of them have been used in traditional folk medicine throughout the world. Resources of those plants have many active compounds that have been isolated and characterized with significant biological and pharmacological activities. We discussed compounds that attenuate and reverse Aβ25-35 fibril formation *in vitro* indicating that this action might be related to their free-radical scavenger activity and might suppress neurotoxicity. These novel drugs are to prevent amyloid-related brain damages since they have shown significant inhibitory ability of BACE activity. Although the majority of the drugs discussed in this paper have not yet been tested in animals or on humans, each of these areas will continue to develop because this class of drugs has demonstrated its value in symptomatic therapy. This class of drugs will continue to be developed because it is a proven symptomatic therapy with a recognized target. Drugs in the class have a proven track of central nervous system permeability, known profile of side effects, and demonstrated efficacy. It is logical to consider further development of novel agents in this class. Challenges to development include potency, safety, and side effects as well as comparison to current β-secretase inhibitors, many of which are generic. Many compounds developed to date have no data on their effects on humans or in animals. Thus, safety, efficacy, and toxicity have not been established to possess disease – modifying properties. The risk of developing newer β-secretase inhibitors is that they will need to be more effective than donepezil (Aricept), rivastigmine (Exelon), Memantine (Nemenda) and galantamine to garner approval since these drugs are FDA approved. Further research in this class will need to focus on whether β-secretase inhibitors directly affect the pathophysiology of AD.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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