INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Paper

Plectranthus Barbatus - A Major Source of Forskolin for The Treatment of Neurodegenerative Diseases

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ARTICLE INFO

Published: 28 Mar 2026
Keywords:
Forskolin, Ellambai, Alzeimer, Adenylate Cyclase
DOI:
10.5281/zenodo.19285280

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative condition that initially presents with memory loss and, in its advanced stages, leads to a diminished capacity for affected individuals to interact with their surroundings. In patients with AD, the development of ß-amyloid plaques and neurofibrillary tangles in the brain correlates with a gradual decline in cognitive abilities, accompanied by heightened neuroinflammation. Recent reports indicate reduced levels of adenylate cyclase (AC) in cerebrospinal fluid (CSF) and postmortem brain tissue samples from dementia patients. Some research has demonstrated that there are disruptions in G-protein stimulation of AC activity in the brains of individuals with AD after death. Although there is currently no effective cure for AD, ongoing research aims to identify treatments that may slow the progression of dementia symptoms and enhance the quality of life for those affected. This may involve improving non-cognitive behaviors. Numerous natural compounds derived from medicinal plants, such as baicalin, curcumin, and resveratrol, have exhibited promising effects in alleviating the symptoms of the disease. Additionally, compounds from the terpenoid family, including ginsenosides, gingkolides, and cannabinoids, have also been identified as potential anti-AD agents. Further research has even proposed the use of diterpenoids as a therapeutic strategy for neurodegenerative disorders. Among these, forskolin is the only diterpene known to activate AC in cells. . Coleus barbatus is a significant medicinal plant that originates from India. It is also found in tropical regions of East Africa, West Asia, Nepal, Bhutan, Sri Lanka, South China, and Thailand . Commonly referred to as Coleus or Indian Coleus, this plant is documented in Ayurvedic Materia Medica under the Sanskrit names Makandi and Mayani. The entire plant serves as a rich source of various phytoconstituents, including monoterpenes, diterpenes, sesquiterpenes, glycosides, and phenolic glycosides. The primary clinically significant compound isolated from the root is a labdane diterpene known as Forskolin (Colenol). This plant has been utilized in

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

treating conditions such as eczema, asthma, psoriasis, cardiovascular disorders, hypertension, skin infections, cardiac issues, piles, urinary problems, epilepsy, and insomnia, among others. It is reported to possess anti-aging, antioxidant, anti-obesity, and anti-depressant properties. Forskolin, a crucial labdane diterpenoid extracted from the plant's roots, activates the enzyme adenylate cyclase, which elevates cyclic adenosine monophosphate (cAMP) levels in cells. cAMP is a vital cell-regulating compound that leads to the inhibition of platelet activation, enhances the heart muscle's contraction force, relaxes smooth muscle, boosts insulin secretion, and improves thyroid function. There are several key takeaways. First, while AC5 and AC6 are the primary isoforms found in the heart, they perform significantly different functions, especially under stress conditions. Second, AC5, being one of the main cardiac isoforms of AC, may play a more crucial role in addressing diabetes, obesity, and longevity than in cardiac protection, which has already been established. Therefore, it is ultimately concluded that *Plectranthus Barbatus* (Makandi) is a promising and perennial herb for the treatment of Alzheimer's disease, supported by both ethnobotanical applications and validated scientific research.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with memory impairment and cognitive deficit. It is characterized by low levels of acetylcholine in the brain of AD patients. According to the cholinergic hypothesis, the inhibition of acetylcholinesterase (AChE), an enzyme that catalyzes acetylcholine hydrolysis, increases the levels of acetylcholine in the brain, thus improving cholinergic functions in AD patients. Furthermore, although the general consensus concludes that AChE inhibitors (AChEi) can alleviate AD symptoms, they neither delay nor reverse the disease progress. Most of the drugs currently available for the treatment of AD are AChEi: tacrine (**1**), donepezil (**2**), rivastigmine (**3**) and galanthamine (**4**), all of which have limited effectiveness and some kind of side effect [1]. Tacrine (**1**) and donepezil (**2**), both from synthetic origin, were the first drugs approved for the treatment of cognitive loss in AD patients by US-FDA in 1993 and 1996, respectively. Rivastigmine (**3**) was approved in 2000 (US-FDA) and was designed from the lead compound physostigmine, a natural AChEi alkaloid. Galanthamine (**4**), a natural alkaloid first obtained from *Galanthus* spp. was approved by US-FDA in 2001. Huperzine A (**5**), an alkaloid found in *Huperzia* spp., is an AChEi commercialized as a dietary supplement for memory support and it is used to treat AD symptoms in China. This alkaloid has been thoroughly studied with promising results yielded particularly from the evaluation of cognitive performance of animals as well as from studies on its efficacy, tolerance and safety. Taking into account that inhibitors **3**, **4** and **5** are related to natural products and that AChEi are an important therapeutic strategy for the treatment of AD, many research groups have focused their studies on naturally-occurring compounds from plants as potential sources of either new or more effective AChEi. These studies led to the discovery of an important number of secondary metabolites as well as plant extracts, both of which are characterized by their ability to inhibit AChE. On the other hand, the fact that a significantly relevant number of research papers have been recorded in this field during the last decades can be clearly attributed to the development of colorimetric methods which allow a rapid and facile screening of a large number of samples. Ellman's method is the most widely used for the detection of AChEi, even in complex mixtures, and for the quantification of anti-AChE inhibitory activity [2-6]. Several reviews on the newly discovered AChEi obtained from plants, fungus and marine organisms have also been published over the last years [7-10]. The majority of these AChEi belong to the alkaloid group, including indole, isoquinoline, quinolizidine, piperidine and steroidal alkaloids .On the other hand, several non-alkaloidal and potent AChEi have been obtained from natural sources, including terpenoids, flavonoids and other phenolic compounds.

Interestingly, although literature demonstrates to be rich in the study on AChEi obtained from plants, this issue keeps on being the center of attention for research as confirmed by the increasing number of studies published every year.[7](Natural Achee Inhibitor)

Cholinergic

The importance of cholinergic function in learning and memory processes is known since the early 70's, [8] and research work about the importance of the cholinergic system in AD demonstrated several characteristics, such as the decrease in the concentration of choline acetyltransferase (ChAT), the enzyme responsible for the synthesis of acetylcholine (ACh) in the cortex and hippocampus, as well as a variable decrease of cholinergic neurons in the basal nucleus of Meynert. [9]

It is believed that inhibition of the enzyme acetylcholinesterase (AChE) increase the concentration of acetylcholine in the synapse, which would decrease or retard the progression of symptoms of AD. In cholinergic hypothesis, people suffering from AD have low levels of acetylcholine, an important neurotransmitter. Inhibitors of AChE enzyme slows metabolic degradation of acetylcholine, thereby optimizing availability of the substrate for the communication between cells. This helps to delay the progression of cognitive impairment and can be effective for some patients the initial and middle stages of the disease. [10, 11] There are now four drugs belonging to this class approved by the FDA, to know: tacrine, donepezil, rivastigmine and galantamine. Marketed inhibitors usually have detrimental effects. In this respect it is of great value to search for new inhibitors present in natural products that may have fewer side effects. The causes of the development of AD are not fully understood, but the information about certain changes in the brain tissue are characteristic of the disease. Among these changes, they can be identified: formation of extracellular amyloid plaques, which are extracellular deposits of amorphous b-amyloid protein and microtubule, formation of microtubules and intraneuronal neurofibrillary tangles. In normal brain, these configurations present in minor amounts. [12, 13, 14-15] The enzymes butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) are present in the brain and are found in neuritic plaques and neurofibrillary tangles. To the extent that inhibition of acetylcholinesterase is modified by the deposition of b-amyloid protein, this method is considered a key component for understanding the pathophysiology of AD.[16]Assays of plant extracts are widely used to test the inhibitory activity of the enzyme acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). The neurotransmitter acetylcholine is inhibited AChE first and then by BuChE. The measure of AChE activity can be obtained by an easy and rapid assay based on the method of Ellman,[17]modified by Rhee et al [18] in this procedure the reagents used are 5,5'-dithiobis [2- nitrobenzoic acid] (DTNB) and acetylthiocholine iodide (ATCI).(Medicinal plant of Brazil)

***Coleus malabaricus* Benth.** Currently, the accepted botanical name of this medicinal plant is *Coleus malabaricus* Benth. All other names mentioned in the literature for this are treated as its synonyms. **Synonyms:** *Plectranthus malabaricus* (Benth.) R. H. Willemse, *Coleus macraei* Benth, *Coleus ovatus* Benth, *Coleus leptostachys* Benth, *Plectranthus malabaricus* var. *leptostachys* (Benth.), *Coleus walkeri* Benth . **Local Names:** The plant's local name in different languages is not included in any traditional manuscripts. Most of the names mentioned in the review are collected from the survey reports of tribal communities of different localities mentioned in various

literatures. Indian name: Ellambai. Tamil: Kurali, Periyathulasi, Malayalam: Parakkoorka, Kattuthulasi, Kattappa by the tribes of Wayanad region, Kerala. [19]

Ethnobotanical Uses: An ethnobotanical survey report on Kurumba tribes of Nilgiri district of Tamil Nadu revealed that the plant is used by the tribes under the name Periya Thulasi and is used for the treatment of asthma by applying the leaf paste on the chest or vapour of the leaf is boiled in water and inhaled like Sacred Basil (*Ocimum sanctum*, Tulsi) [20]. Ethnobotanical survey of Irula tribal settlements in forest areas of Chengal, Combai, and Coonoor of the Nilgiris showed that the tribes have been using the leaf juice orally under the local name Ellamabai for the smooth functioning of the heart and the authors reported that the tribes are also using this plant to prevent heart attack [21]. A study conducted on the folklore medicinal uses of some indigenous medicinal plants among the tribes of Nilgiri's south, Shola division of Western Ghats documented that the tribal communities of these areas use the seeds of the plant for the treatment of cough and cold under the local name Kurali [22]. The whole plant is made into a paste and applied knots for curing muscular pain [23]. Major medicinal species of *Coleus* found in India are *Coleus forskohli*, *Coleus amboinicus, Coleus malabaricus, Coleus scutellaroides* and are used for the treatment of dysentery and digestive conditions[24].

Importance of Coleus forskohlii as a medicinal plant

The medicinal properties of forskolin, the main diterpene constituent of *C. forskohlii* contributes to its emergence as a taxon of importance in modern medicine. Forskolin is used for the treatment of allergies, respiratory problems, cardiovascular diseases, glaucoma, psoriasis, hypothyroidism, weight loss, eczema, asthma, psoriasis and hypertension. Recently, it was reported as a natural remedy for urinary tract infections (UTI) by enhancing the ability of antibiotics to kill the bacteria that cause 90 % of infections in the bladder. Usually decreased intracellular cAMP level is believed to be a major factor in the development of the disease process (Rupp et al., 1986). The presence of yellowish to reddish brown cytoplasmic vesicles in cork cells of *C. forskohlii* tubers is unique character of the plant and these vesicles store secondary metabolites including forskolin [25].

Role of Forskolin in treating Alzeimer

Forskolin, a labdane diterpene is the main active ingredient in the ayurvedic herb *Coleus forskohlii* (Labatiae) that has been used in India since ancient times. Forskolin activates the enzyme adenylyl cyclase and increases intracellular levels of cAMP. cAMP is an important second messenger necessary for the proper biological response of cells to hormones and other extracellular signals. It is required for cell communication in the hypothalamus/pituitary gland axis and for the feedback control of hormones. Cyclic AMP acts by activating cAMP-sensitive pathways such as protein kinase A and Epac.

Forskolin exerts most of its biological activity by stimulation of adenylate cyclase, thereby increasing cellular concentrations of the second messenger cyclic AMP. The principle mechanism by which forskolin exerts its hypotensive activity is by stimulation of adenylate cyclase and thereby increasing cellular concentrations of the second messenger cyclic AMP (cAMP) [26]. Forskolin directly activates almost all hormone sensitive adenylate cyclases in intact cells, tissues and even solubilised preparation of adenylate cyclase [27].The unique feature of this activation is that the site of action for forskolin is the catalytic subunit of the enzyme or a closely associated

protein [26]. Of the 9 types of adenylate cyclase in humans, forskolin can activate all except type IX, which is found in spermatozoa [28]. Stimulation of adenylate cyclase is thought to be the mechanism by which forskolin relaxes a variety of smooth muscles. This action of forskolin proved the potential use of the molecule, not only as an invaluable research tool for understanding cyclic – AMP dependent physiological processes.

Mechanism action

The reported method of action of forskolin is activation of adenylate cyclase (AC), which increases cyclic adenosine monophosphate (cAMP) levels, an important signal carrier for cell communication. Indeed, increasing cAMP levels was reported to improve long-term memory, provide neuroprotection, and improve cognition. Therefore, forskolin may be a good candidate for studies investigating Alzheimer disease (AD) treatment.. Decreased AC levels have recently been reported in CSF and postmortem brain tissue samples from patients suffering from dementia (6). Previous studies have shown that there are disruptions of G-protein stimulation of AC activity in AD postmortem brains. It has also been reported that the AC signal transduction pathway is affected in AD leading to the suggestion that increasing cAMP levels could benefit AD patients. Moreover, stimulation of AC activity in AD was also correlated with histopathological changes in patients. It binds to AC with high affinity, thereby contributing to the increment of cAMP levels in cells. It was reported that forskolin activates all mammalian AC by interacting with cytoplasmic domains (C1 and C2) at the catalytic core. The acidification of lysosomes by treating microglia with forskolin also contributed to amyloid fibril degradation [30].

DISCUSSION

Medicinal coleus (Coleus forskohlii) is a significant therapeutic crop known for its roots containing forskolin. This plant has been classified as an endangered species due to the ongoing harvesting of its root tubers, which are consumed as a condiment, as well as its vulnerability to various diseases such as root rot and wilt. Coleus belongs to the mint family and is indigenous to India, thriving in the subtropical temperate climates of India, Nepal, Thailand, and Sri Lanka. It is widely recognized as an ornamental plant and is utilized as a sedative in regions such as Africa, Arabia, and Brazil. The isolation of the labdane diterpene forskolin (coleonol) has emerged as a crucial research tool for investigating the functions of the enzyme adenylate cyclase and cyclic-AMP in cellular physiology.

The plant has been traditionally used by the Irula tribes, referred to as Ellamabai, to promote the smooth functioning of the heart. Reports indicate that these tribes also utilize this plant to avert heart attacks. Additionally, the Badagar community of Nilgiri origin employs this plant to address anxiety and mental disorders. The tribes of Wayanad have a historical practice of using this plant for cardiovascular issues, known locally as Kattappa.

The diterpenoid extracted from the roots of the plant activates the enzyme adenylate cyclase, which elevates cyclic adenosine monophosphate (cAMP) levels in cells. This compound is crucial for cell regulation and leads to the inhibition of platelet activation, an increase in the contraction force of heart muscle, relaxation of smooth muscle, enhanced insulin secretion, and improved thyroid function. Forskolin is the sole diterpene compound known to activate AC in cells; thus, it presents a promising candidate for Alzheimer's disease (AD) treatment. The second messenger cAMP has been implicated in the intricate mechanisms that govern memory and is found to

be disrupted in the brains of AD patients. Furthermore, the activation of the cAMP/PKA (protein kinase A) pathway has been suggested as a means to ameliorate age-related cognitive deficits, as evidenced by studies on hippocampal function. In the past decade, research has concentrated on AC activators as potential therapeutic targets for neurodegenerative diseases. Forskolin has shown significant antidepressant effects in a rat forced swimming model and has been effective in preventing induced seizures in mice. Additionally, it may act as an indirect inhibitor of the transcription factor NF-kB. In fact, the cAMP generated following AC activation by forskolin inhibits NF-kB, which not only mitigates inflammation in the brain but also directly aids in reducing the production of Ab peptides. Another investigation indicated that rolipram could enhance cognitive performance in normal rats by activating AC.

CONCLUSION

Research indicates that Forskolin exhibits effective anti-inflammatory properties on macrophages and microglia in animal models of rheumatoid arthritis by reducing TNF production and activating AC. This implies a potential impact of Forskolin in neurodegenerative disorders, as microglia are considered the primary immune cells in the brain, playing a crucial role in the removal of amyloid beta plaques.

ACKNOWLEDGMENT

I sincierly thanks to Principal and management of sanjo college of pharmaceutical studies for their support and encouragement to make this study possible.

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HOW TO CITE: Sivakumar B, Plectranthus Barbatus - A Major Source of Forskolin for The Treatment of Neurodegenerative Diseases, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 3, 3816-3823, https://doi.org/10.5281/zenodo.19285280