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Review Article

HERBAL MEDICINE: A PROMISING APPROACH FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disease manifesting in cognitive decline, impairment of memory, and behavioural deterioration. Alzheimer's is a relatively common type of dementia. The pathological basis for the progression of Alzheimer's disease is beta-amyloid protein accumulation, phosphorylation of tau protein, abnormal glial cell function, inflammation, neurotransmitter imbalance, along with oxidative stress in brain tissue. Current available therapies are targeted at amelioration of symptoms alone and focus on a limited spectrum of pathophysiological processes. It is evident that it is essential to develop a multi-target therapeutic option in managing Alzheimer's disease, in view of the broad range of factors in disease progression and sever consequences for sufferers. Herbal medicines are seen as a potential resource in the treatment of Alzheimer's disease, in view of their historical use in traditional medicine as neuroprotectants. Herbal medicines have been evaluated in animal studies designed to determine their capacity to prevent neurodegenerative disease and ameliorate memory defects. This review elaborates on the studies conducted on several medicinal plants that have been investigated for their potential in the prevention and treatment of memory defects in animal models.

INTRODUCTION

Alzheimer's disease (AD) is an irreversible neurodegenerative disease caused by damage to neuronal cells, leading to cognitive impairment, and changes in personality and behaviour. It is the most common cause of dementia worldwide. The global population's aging is contributing to an increase in the prevalence of Alzheimer's disease [1]. AD is a cause of significant morbidity with a huge economic impact on the healthcare system of individual countries. Various types of dementia including dementia due to AD affect at least 50 million individuals around the world. It is anticipated that the prevalence of AD could exceed 152 million by 2050 worldwide. AD stands in sixth place for cause of death in the United States; currently, more

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than 5 million Americans live with AD. In 2020, Alzheimer's and other types of dementia were estimated to cost the United States about $305 billion. This cost could rise to $1.1 trillion by 2050 [2]. The prevalence of AD in Malaysia was estimated to be 0.126% of the population in 2020 and is expected to increase to 0.454% by 2050. It is estimated that there are currently about 50,000 people living with AD in Malaysia [3]. It is likely that increasing awareness of AD among the population could lead to earlier identification of the disease and subsequently an increase in these estimations.

Pathogenesis of AD

The primary pathological markers of AD are the presence of neuritic plaques and neurofibrillary tangles in the affected brain tissue. Plaques are sequentially related to the accumulation of the amyloid-beta peptide (Aβ) in the brain tissue, and to the cytoskeletal changes that arise from the hyper phosphorylation of tau protein in neurons. The pathophysiological mechanism of AD development mostly affects the medial temporal lobe and associated neocortical structures [4]. The cleavage of amyloid precursor protein (APP) by proteases identified as β and γ secretases generate a group of Aβ peptide fragments, which forms the main constituent of amyloid plaques. The difference between the rate of production and clearance of Aβ causes the formation of Aβ plaques during AD's early pathogenesis. Aβ accumulation triggers a cascade of neurofibrillary tangle formation, synaptotoxicity, mitochondrial dysfunction, and neuroinflammation due to activated microglial cells and eventually neuronal death [5] (Figure 1).

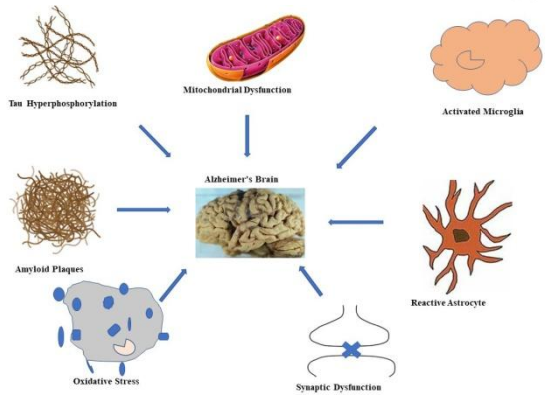

Figure 1: The pathophysiology of Alzheimer's disease i``s associated with diverse processes in affected neurons including mitochondrial dysfunction, inflammation resulting an aberrant activation of astrocytes and microglial cells, inflammation contributes to oxidative stress in affected tissues. Protein changes include hyperphosphorylation of tau protein and the formation of β-amyloid plaques. All these effects will impact cell viability, neuronal function, neural communication, and neurotransmitter release at synapses.

The tau protein stabilizes microtubules in the neurons under normal physiological conditions. The microtubules system supports structural changes, axonal transportation, neuronal growth and regulates synaptic function. The dysfunction of tau protein primarily arises from a loss of microtubule binding, thereby leading to many downstream events, like impairment in mitochondrial transport and function, synaptic deficits, defective axonal transportation, increased oxidative stress and enhanced stress granule formation, manifesting as clinical neurofunctional degeneration [6].

Oxidative stress (OS) occurs when the production of reactive oxygen species (ROS) and the level of antioxidants is significantly disturbed, resulting in cell damage. ROS interact with nucleic acids, proteins, and lipids. OS is an essential factor in AD pathogenesis, as the redox balance mechanisms within neuronal cells under conditions of inflammation are affected. Mitochondria are vulnerable to OS, which may directly disrupt their respiratory functions (energy production, decreased antioxidant enzymes, and loss of membrane potential), leading to a further increase in ROS levels that contribute to cell death, caspase activation, and finally apoptosis [7].

Acetylcholine (Ach) is a neurotransmitter essential for processing memory and learning. It's abundance and functionality are decreased in the brains AD patients (15). Evidence points to both cholinergic and glutamatergic neuronal involvement in the pathogenesis of AD [8].

It is conjectured that Aβ is perhaps the primary factor in the pathogenesis of all the described AD processes, and hence future research in therapeutics should perhaps focus on this facet of the disease.

The Potential for Medicinal Plants to Help Manage Alzheimer's Disease

The practice of traditional medicine dates to prehistory, when the treatment of diseases was achieved entirely through natural remedies obtained from the biological world. Progress in science has led to the identification of the active components in many of these natural treatments and developments in synthetic chemistry have supported the design of targeted drugs. Even with the capacity to precisely synthesize mono molecules with predictable properties, the practice of traditional medicine continues to follow the ancient principles and uses crude biologic extracts for treating medical conditions [9]. The impetus for continuing to use these traditional methods often stems from the cost of novel therapeutics, their lack of availability or the lack of efficacy. Overcoming cultural barriers can also be an impediment to applying novel interventions, this has been seen all too clearly in the recent pandemic. Historical, anecdotal evidence points to natural

therapies, including those from derived medicinal plants, having been found helpful in treating AD, dementia, amnesia, and other neurological diseases. Herbal medicines were popularly used by physicians and herbalists in the Egyptian, Indian, and Chinese civilizations.[10] Modern research approaches with evidence-based analysis are increasingly being focused on the evaluation of herbal medicine or identifying the active components of these traditional therapeutics. Plants produce a huge spectrum of simple and complex metabolites, by focusing on those with centuries of demonstrated therapeutic effectiveness, it may be possible to develop more defined and effective therapies with perhaps fewer side effects compared to empirically designed synthetic medications [11] (Figure 2).

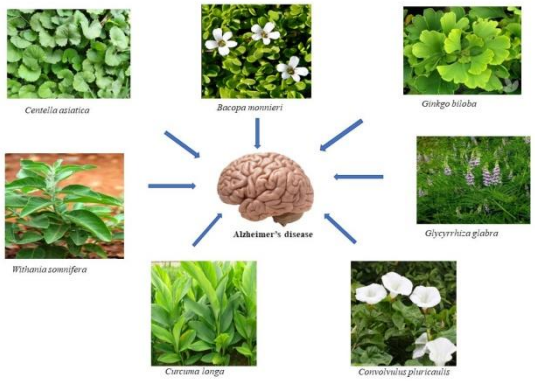

Figure 2: This review focuses on diverse plant species found in Southeast Asia which have been investigated for their potential in the treatment of Alzheimer's disease: *Centella asiatica, Bacopa monnieri, Ginkgo biloba, Withania somnifera, Curcuma longa, Convolvulus pluricaulis* and *Glycyrrhiza glabra.*

The lack of an effective treatment for AD and observations that biologically active phytochemicals in medicinal plants have neuro-protective effects have generated a resurgence of interest in the application of herbal extracts as an alternative treatment for AD. A significant number of phytoconstituents and extracted chemicals from a broad spectrum of medicinal plants interact with neurotransmitter receptors or affect the environment of neurones. Such actions could impact neurone behaviour and could potentially be applied to treating individual neurological illnesses[12]. The scientific foundation for the use of extracts from various medicinal plants in treating diseases in both humans and animal has been well documented over the centuries. The generic antioxidant and anti-inflammatory properties of some herbal medications, along with their cholinesterase inhibitory effects, support the possibility that they could be of value in the treatment of AD [13]. This review focuses on the following medicinal plants: Centella *asiatica, Bacopa monnieri, Ginkgo biloba, Withania somnifera, Curcuma longa, Convolvulus pluricaulis and Glycyrrhiza glabra*. These species were chosen because they are found commonly in the region of study and their spectrum of attributed actions are most likely to translate into an amelioration of the pathophysiological processes identified in AD.

Centella asiatica

Centella asiatica (*C.asiatica*) is a herb that has been used in traditional medicine for atleast three hundred years. Practitioners of traditional medicine have used *C. asiatica* in the treatment of various diseases in China, India, Africa, the Philippines, Sri Lanka, Malaysia, and Madagascar. In the 19th century, *C. asiatica* was included in the Indian Pharmacopoeia. *C. asiatica* belongs to the Apiaceae family and grows widely from East and Southern Africa to East, South and Southeast Asian countries [14]. *C. asiatica* is also known as Indian pennywort in English, Gotu kola in Sri Lanka, Brahmi in Hindi, Mandukaparni in Ayurveda, Buak bok in Thailand, Kaki kuda in Indonesia, Yuhong-yuhong in the Philippines, and Pegaga in Malaysia [15]. *C. asiatica* is a stoloniferous, perennial herb that attains a height of up to 15cm. The stem is glabrous (smooth), and the leaves are orbicular-reniform. The flowers are fascicled umbels, each umbel consisting of 3-4 white to purple flowers; the fruits are oblong and globular in shape. The seeds have pendulous embryos, with a characteristic odour, and bittersweet taste [16].

C. asiatica contains a broad spectrum of phytochemicals that may be anticipated to provide a range of beneficial effects. *C. asiatica* has many classes of phytonutrients, such as triterpenes, carotenoids, glycosides, flavonoids, alkaloids, volatile oils, and fatty oils. The primary chemical constituents that are believed to carry the medicinal properties of the plant are the terpenoid compounds: asiatoside, asiatic acid, madecassic acid, asiaticoside, brahminoside, brahmoside, centelloside, brahmic acid, centellinic acid, isobrahmic acid, betulinic acid and stigmasterol[17].

Gray et al. reported that a C. asiatica Water extract (CAW) reduces the Aβ plaque burden in the hippocampus and improved the mitochondrial function in the brains of 5XFAD mice, a murine model of AD, and also found that CAW enhanced the arborization and spine density of the neurons in Aβ-induced neuronal dystrophy models [18,19]. Further studies on CAW were carried out by Matthews et al. and it was observed that CAW increased nuclear factor-erythroid factor 2-related factor 2 (Nrf2) transcription factor expression in the hippocampus, while reducing plaque-associated superoxide dismutase-1, an indicator of oxidative stress, in the hippocampus and cortex of 5XFAD mice model [20]. The neuroprotective effect of *C. asiatica* in ameliorating the cognitive dysfunctions was evidenced by the reduced transfer latency in the modified elevated plus maze (mEPM). This test measures cognitive ability,

specifically long-term spatial memory. A high correct score in the T-maze spontaneous alternation, and more exploration time in the novel object recognition (NOR) test was observed among rats subjected to these behavioural studies [21]. The administration of *C. asiatica* could prevent the histopathological changes, significantly increase the levels of protein phosphatase 2 (PP2A) and decrease glycogen synthase kinase-3 beta (GSK-3β) in the hippocampus of the $AlCl_3$ and D-galactose induced AD-like rat model [22]. A recent study suggested that the active components asiatic acid and madecassic acid present in *C. asiatica* could be responsible for the acetylcholinesterase (AChE) inhibitory action and could be used as a marker to guide further studies on *C. asiatica* as a potential natural product for the treatment of AD [23]. Focusing on the beneficial effects of *C. asiatica* on AD would be likely to result in a tangible product for human application.

Bacopa monnieri

Bacopa monnieri (*B. monnieri*) belongs to the Scrophuliaceae plant family, and is found in India, Nepal, Sri Lanka, China, Taiwan, Vietnam, and Florida in the United States of America. *B. monnieri* is a small succulent, creeping herb with short, oblong leaves, and roots at stem nodes. The stem is 10-30 cm long and 1-2 mm thick, with soft, glabrous ascending branches [24]. The leaves are 0.6-2.5cm long and 3-8mm broad, and the flowers are blue or white with purple veins, axillary and solitary on long pedicels. The plant has no distinct odour, but the taste is slightly bitter. B. monnieri is used to improve memory, to treat mental illness and to treat epilepsy. The B. monnieri active constituents include alkaloids such as brahmine, herpestine, nicotine, saponin monierin, hersaponin and four saponin bacogenins A1 to A4 [25].

Investigations conducted by Dhanasekaran et al. on homogenates from the brains of mice, showed that B. monnieri extract reduced the lipoxygenase activity in the brain tissue by inhibiting the hydrogen peroxide-induced lipid peroxidation [26]. Various studies have established the effect of B. monnieri on Aβ protein-induced cell death in primary cortical tissue culture. When neurons in lab culture are treated with Aβ protein, they exhibited a 2-fold rise in acetyl cholinesterase (AChE) activity, resulting in a loss in cholinergic function. However, those neurons treated with Aβ protein in combination with B. monnieri extract had a near-normal level of AChE, and normal cholinergic activity. Furthermore, the authors also reported that B. monnieri improved cell viability by reducing ROS in the cells and had an antioxidant activity of its own. This study demonstrated the multiple anti-AD mechanisms may be initiated by B. monnieri and so it may be more effective in preventing progression of the disease [27].

The neuroprotective effects of a *B. monnieri* extract has been observed in experiments where the neurons survived the Aβ-induced cell death by suppression of cellular AChE activity. *B. monnieri*-treated neurons exhibited lower ROS levels, suggesting that BM restrained intracellular oxidative stress [28]. More research on molecular mechanisms and the usefulness of *B. monnieri* as an alternative medicine to prevent and cure AD is needed.

Ginkgo biloba

Ginkgo biloba is a gymnosperm dioecious tree. The leaves have a characteristic fan shape and are seasonal. The seeds are yellow, on a long stalk surrounded by a fruit-like, fleshy arillus. The roasted seeds are edible. G. biloba has been used for over 600 years in traditional Chinese medicine to treat diseases such as asthma, renal dysfunction, bladder conditions, bronchitis and as an anti-inflammatory agent. The main active components of G. biloba are flavonoids, represented by various classes of benzo-c-pyrone derivatives [29].

Various studies have reported positive effects of G. biloba on AD. Recent studies have shown that G. biloba protects against Aβ-induced neurotoxicity by the obstructing Aβ-induced events, such as glucose uptake, ROS accumulation, activation of serine/ threonine protein kinases, mitochondrial dysfunction, cJun N-terminal kinase, and extracellular signal-regulated kinase (ERK) 1/2 pathways, and apoptosis [30, 31]. Research have reported that G. biloba inhibits the production of Aβ in the brain by lowering the levels of free cholesterol in the circulation, as AβPP processing and amyloid genesis are putatively affected by the free circulation and intracellular cholesterol levels [32, 33]. There has been very little research on the effect of *G. biloba* on AD, but its effects on other neurological conditions are well documented, thus additional research is needed to prove its beneficial effects on AD.

Withania somnifera

Withania somnifera (*W. somnifera*) is a small woody shrub that belongs to the Solanaceae family. It is called *'Ashwagandha'* in Sanskrit and *'Asgand'* in Urdu. It grows mainly in the Canary Islands, the Mediterranean, and tropical regions of South Asia, some Middle East countries, China and Africa [34]. The plant has been used in Ayurveda therapy for its medicinal properties since ancient times. It is an adaptogen with hypoglycemic and hypolipidemic effects and has been shown to be helpful in enhancing learning and memory. *W. somnifera* has demonstrable anti-inflammatory, anti-platelet aggregatory, anxiolytic, anti-convulsive and neuroprotective actions [35]. The major phytochemicals present in the plant include alkaloids, flavonoids steroidal lactones, steroids, salts and nitrogen containing compounds.

However, the pharmacological effects are mainly described to the withanolide steroid lactones [36].

W. somnifera and withanolide extracts eased memory loss and hippocampal neurodegeneration in rats by inducing the production of the antioxidant glutathione (GSH) in hippocampal cells after exposure to hypobaric hypoxia. These protective mechanisms were facilitated by the Nrf-2 transcriptional pathway and induction of nitric oxide production in a corticosterone-dependent manner [37].

Gupta and Kaur established that an extract of W. somnifera ameliorated the deficits in cognitive and motor coordination associated with systemic inflammation in rats by regulating the expression of proteins involved in the survival of neuronal cells and synaptic plasticity [38].

A W. somnifera extract could reverse pathogenesis of AD by facilitating the efflux of Aβ from the brain into the blood by activating hepatic low-density lipoprotein receptor-related protein in the liver (LRP1) [39]. Treatment with a W. somnifera extract improved the cognitive deficits that were induced by the sub-chronic exposure to propoxur, an insecticide in rats through regulation of the AChE activity [40]. Furthermore, a *W. somnifera* extract improved cognitive decline caused by oxidative damage in the streptozotocin-induced rat model [41]. Studies conducted on healthy human participants have confirmed that administration of an aqueous extract of W. somnifera through ingestion improved cognitive and psychomotor performance [42]. Consecutive oral administrations of the W. somnifera extracts for 30 days reversed behavioural memory deficits in rats which were subjected to behavioural tests such as the radial arm task. Studies also observed that there was a decrease in the levels of Aβ in the cerebral cortex and hippocampus in APP/PS1 AD model transgenic mice following W. somnifera extract administration [43]. A recent study found that an aqueous extract of W. somnifera enhanced the cholinergic activity of neurones by increasing the acetylcholine content and choline acetyltransferase activity in rats, which supports the cognition-enhancing and memory-sustaining effects of W. somnifera [44]. W. Somnifera research has shown that it is a promising herb for usage as an alternative therapy for AD; nevertheless, more clinical trials on safety and dosage are required.

Curcuma longa

Curcuma longa belongs to the Zingiberaceae family. The plant grows up to 4-5 ft tall and has yellow-coloured flowers. The roots of the plant have been widely used for medicinal and food preparation and extracts have anti-septic properties. The root is an underground stem that is thick and fleshy. The roots are boiled, dried, and ground to make the distinctive bright yellow spice, turmeric [45]. Turmeric is used in the preparation of curries and other spicy dishes in India, Asia and the Middle East. *C. longa* was first used as a food and its remarkable medicinal properties were discovered later. In Ayurveda, *C. longa* was used as an anti-inflammatory agent for the relief of pain and inflammation [46].

Several studies have found that *C. longa* extract may have a potential role in preventing AD progression. It was observed to inhibit the formation of amyloid-beta (Aβ) fibrils and inhibit tau phosphorylation in rabbits fed with *C. longa* in a diet [47]. Moreover, experiments with transgenic murine AD models have indicated that when *C. longa* was added as a dried root supplement it reduced protein oxidation and inflammatory cytokine release in the brain, thus preventing memory deficits, cognitive decline and suppressed the behavioural deficits [48].

The chronic administration of a *C. longa* extracts significantly decreased the levels of TNF-α, with a concurrent decrease in the levels of oxidative stress in rat hippocampal tissues [49]. A recent study proved that administration of low doses of *C. longa* extract reduced Aβ level up to 40% in a rodent AD model compared to the control drug. At a low dose, *C. longa* brought about a 43% decrease in the Aβ plaque burden in the brains of a murine AD model [50]. Further research on the applications of the extracts of this plant will be worthwhile in view of the proven anti-inflammatory actions.

Convolvulus pluricaulis

Convolvulus pluricaulis (*C.Pluricaulis*) belongs to the Convolvulaceae family, and has been reported as a memory and intellect booster. C. pluricaulis contains various potentially active phytoconstituents such as alkaloids, flavonoids, coumarins, and polyphenols. This plant is known to contain kaempferol, delphinidine, β-sitosterol, hydroxy-cinnamic acid, N-hexacosanol, taraxerol and taraxerone as the major phytoconstituents [51].

Studies by Kaushok et al. showed that an aqueous extract of C. pluricaulis inhibited the activity of AChE within the cortex and hippocampus of male Wistar rats that were intoxicated with scopolamine. The study also revealed evidence of increased antioxidant activity as by demonstrated by elevated levels of glutathione reductase, superoxide dismutase and reduced glutathione in the cortex and hippocampus [52]. These reports were supported by the results of another study, in which the oral administration of an aqueous extract of C. pluricaulis (150 mg/kg) to scopolamine-induced rats caused a marked reduction in the mRNA levels of tau protein. As such the reduction in the tau protein expression is responsible for causing amelioration in the Aβ-induced deficits experienced in AD [53]. Recent experiments proved that an ethanolic extract of this plant also

significantly improved the learning abilities and memory retention in rats through decreased AChE activity in hippocampal CA1 and CA3 regions which is associated with the memory function and learning abilities [54, 55].

Glycyrrhiza glabra

Glycyrrhiza glabra (*G.glabra*) is also known as the liquorice plant and belongs to the Fabaceae family. It is cultivated in southern Europe and Asia. Traditionally, liquorice has been used since ancient times for its medicinal properties in the Middle East, China, India, and Japan. Its use has been recorded in the treatment of various medical conditions including viral diseases, ulcers, and neuropsychiatric disorders [56].

G. glabra was found to reduce neurotoxicity through different mechanisms including a reduction in the Bcl-2-associated X protein and caspase 3 inflammatory markers and ROS levels in neurotoxicity induced by exposure of cortical neural cells to Aβ in vitro [57]. In a study on the cultured rat pheochromocytoma cell line PC12, a water extract of G. glabra decreased the neurotoxic effects of Aβ protein [58]. Similar results were seen in a recent study in which the administration of *G. glabra* extract increased learning and memory functions assessed by the mEPM and passive avoidance test murine models of AD [59]. Another study found that constituents present in an aqueous root extract of *G. glabra* had neuronal dendritic growth stimulating properties suggesting a potential role in promoting neuronal repair [60].

CONCLUSION

AD is a neurodegenerative disease, for which currently there are medications which mitigate symptoms but do not stop progression of the disease. Experiments with extracts from several different medicinal plants which have been used in traditional medicines from various countries have shown positive results in the prevention and treatment of animal models of AD. Other studies have described their potential benefits, with elaboration on their mechanism of action in preventing the progression of AD. Cumulative data confirms that medicinal plants have great potential in the development of alternative medicines for the improvement of cognition and memory loss experienced in AD (Figure 3). Current research must increasingly focus on the active compounds identified in crude extracts to enhance precision therapy and to identify compounds which have different but synergistic targets and actions. Among the plants discussed in this review, *C. asiatica* perhaps has the greatest potential for identifying novel therapeutics, because it has been most extensively studied for its beneficial effects in animal models of AD.

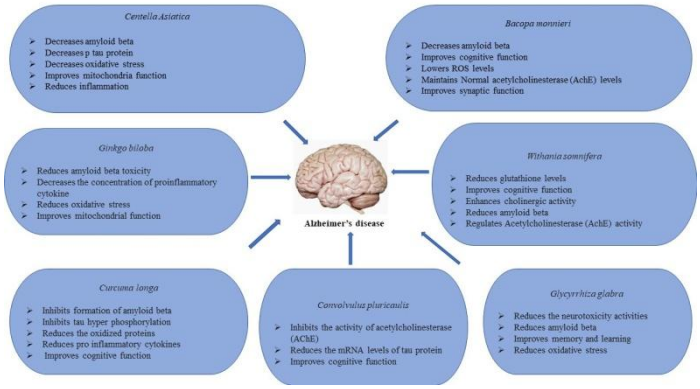

Figure 3: The different plant species evaluated in this review have all been found to help mitigate different aspects of the Alzheimer's disease process.

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FIGURE LEGENDS

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