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Review Article

NEUROPROTECTIVE EFFECT OF VARIOUS PHYTOCHEMICALS AND ITS POTENTIAL APPLICATION OF THREE MEDICINAL PLANTS IN NEURODEGENERATIVE DISEASES

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ABSTRACT

In the traditional medicines, numerous plants have been used to treat cognitive disorders. Natural products play an essential role in the prevention and therapy of various neurodegenerative diseases and neuronal dysfunction. Conventional as well newer molecules have been tried against these diseases. Different studies suggest that natural products such as polyphenolic and alkaloid compounds that isolated from plants potentially delayed the neurodegeneration and also improve memory and cognitive functions. In this review, we briefly deal with three medicinal herbs (Psidium guajava, Citrulus lanatus and Cucumis sativus) focusing on their anti-oxidativeactive phytochemical substances like phenols, alkaloids, flavonoids, fatty acids, saponins, terpenes etc, can be applied in the prevention of numerous neurodegenerative diseases, Ethno pharmacological studies have provided information to identify potential new drugs from plant sources. It was observed in this review that a number of herbal medicines used in ayurvedic practices contain multiple compounds and phytochemicals that may have a neuroprotective effect which may prove beneficial in different neuropsychiatric and neurodegenerative disorders.

KEYWORDS: *Citrulus lanatus, Cucumis sativus, Neurodegeneration, Polyphenolic, Psidium guajava.*

INTRODUCTION

In the neurodegenerative diseases, central nervous system (CNS) is lost leading to either functional loss or sensory dysfunction. Nowadays, these diseases which are associated with different multifactorial etiologies have created massive medical, social and financial problems. The pathological signs of neurodegenerative diseases are included Alzheimer's disease (AD), Parkinson's disease (PD) and Multiple sclerosis (MS) [1, 2]. It is known that brain pathology in the form of cerebrovascular and neurodegenerative disease is a leading cause of death all over the world, with an incidence of about 2/1000 and an 8% total death rate [3]. Pathologic processes, including inflammation, oxidative stress, apoptosis, mitochondrial dysfunction and genetic factors lead to neuronal degeneration in PD [4]. laboratory analysis of patients brain have shown that elevated lipid peroxidation may destroy cholinergic neurons in AD [5] and dopaminergic neurons in PD [6].

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There are different antioxidants in the brain like superoxide dismutase (SOD) as an enzymatic antioxidant [7] and thiol containing molecule such as glutathione (GSH) as non enzymatic antioxidant [8]. CNS which contains high levels of polyunsaturated fatty acids is more sensitive to peroxidation reactions. But CNS is particularly not enriched in antioxidant defenses. The human brain has high levels of ascorbate in general and iron in certain regions. Actually, the antioxidant activity of the brain is lower than other tissues. So, neural cells are more susceptible than other tissue to oxidative damage [9]. Irreversible memory impairment, cognitive and behavioral disturbances are prevalent AD symptoms [10]. Moreover, these neurodegenerative diseases are a source of high individual and family suffering mainly because of the lack of efficient therapeutic alternatives. This motivates research efforts to identify the mechanisms of neuronal death and to discover new compounds to control them.

The past decade has also witnessed an intense interest in herbal medicines in which phytochemical constituents can have long-term health promoting or medicinal qualities. In contrast, many medicinal plants exert specific medicinal actions without serving a nutritional role in the human diet and may be used in response to specific health problems over short- or long-term intervals. Phytochemicals present in vegetables and fruits are believed to reduce the risk of several major diseases including cardiovascular diseases, cancers as well as neurodegenerative disorders. Therefore, people who consume

higher vegetables and fruits may be at reduced risk for some of diseases caused by neuronal dysfunction [11, 12].

Herbal medicine has long been used to treat neural symptoms. Although the precise mechanisms of action of herbal drugs have yet to be determined, some of them have been shown to exert antioxidant effects in a variety of peripheral systems. Now, as increasing evidence indicates that neuroglia-derived oxidative stress is believed to be a central source for generation of post cerebral ischemic injury. Various experimental models of cerebral ischemic reperfusion injury showed significant neuroprotection when treated with antioxidants [13]. Herbal medicine and its constituents are proving to be a potent neuroprotector against various brain pathologies. This review will highlight the importance of phytochemicals on neuroprotective function and other related disorders, in particular their therapeutic potential.

Nootropics:

Nootropics is a term used by proponents of smart drugs to describe medical drugs and nutritional supplements that have a positive effect on brain function; "nootropic" is derived from Greek and means acting on the mind. A number of pharmaceutical compounds are in the market which has been used for their neuroprotective property. Drugs to improve neurofunction generally work by altering the balance of particular chemicals (neurotransmitters) in the brain. Some acts by selective enhancement of cerebral blood flow, cerebral oxygen usage metabolic rate and cerebral glucose metabolic rate in chronic impaired human brain function *i.e.*, multi-infarct (stroke) dementia, senile dementia of the Alzheimer type and pseudo dementia, ischaemic cerebral (poor brain blood flow) infarcts. Numbers of medicines are derived from the medicinal plants and have shown memory enhancing properties by virtue of their bioactive phytochemical constituents. One of the mechanisms suggested to dementia is decreased cholinergic activity in the brain. Therefore, cholinergic drugs (of plant origin) like: Muscarinic agonists (e.g. arecoline, pilocarpine etc.), nicotinic agonists (e.g. nicotine) and cholinesterase inhibitors (e.g. huperzine) can be employed for improving memory [14]. Some other classes of drugs used in dementia are: Stimulants or nootropics (e.g. piracetam, amphetamine), putative cerebral vasodilators (e.g. ergot alkaloids, papavarine), calcium channel blocker (e.g. nimodipine).

Neuroprotective Herbs:

Traditional practices of medicine, numerous plants have been used to treat cognitive disorders, including neurodegenerative diseases such as Alzheimer's disease (AD) and other memory related disorders. Herbal products contain complicated mixtures of organic chemicals, which may include fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, tannins, terpenes and so forth. Proponents of herbal medicines describe a plant's therapeutic value as coming from the synergistic effects of the various components of the plants, in contrast to the individual chemicals of conventional medicines isolated by pharmacologists; therefore it is believed that traditional medicines are effective, with few or no side-effects. Roughly one-quarter to one-half of current pharmaceuticals originally were procured from plants. Identification and characterization of new medicinal plants to cure neurodegenerative diseases and brain injuries resulting from stroke is the major and increasing scientific interest in recent years. There are more than 120 traditional medicines that are being used for the therapy of Central Nervous System (CNS) disorders in Asian countries [15].

In the Indian system of medicine the following medicinal plants have shownpromising activity in neuropsychopharmacology: *Allium sativum, Bacopa monnierae, Centella asiatica, Celastrus paniculatus, Nicotiana tabaccum, Withania somnifera, Ricinus communis, Salvia officinalis, Ginkgo biloba, Huperiza serrata, Angelica sinensis, Uncaria tomentosa, Hypericum perforatum, Physostigma venosum, Acorus calmus, Curcuma longa, Terminalia chebula, Crocus sativus, Enhydra fluctuans, Valeriana wallichii, Glycyrrhiza glabra* etc. Neuroprotective agents refer to substances that are capable of preserving brain function and structure by reducing and preventing oxidative stress, mitochondrial dysfunction, inflammation, various forms of neurotoxicity (eg. excitotoxicity) and protein deficiencies. Specific examples of things that can cause neurodegeneration include: traumatic brain injuries, drug abuse, pharmaceutical medications, schizophrenia, strokes, and dementia but the most common cause of neurodegeneration is oxidative stress and to prevent the effects of any neurodegeneration, considering neuroprotective agents may be beneficial for long-term brain health. Administration of a neuroprotective agent may help minimize the effects of chronic conditions that could: kill brain cells, decrease brain volume, and lead to long-term functional impairment. The neuroprotective natures based on its antioxidant activity of *Psidium guajava, Citrulus lanatus and Cucumis sativus* of the traditional plants are given below.

***Psidium Guajava* Leaves:**

Psidium guajava Linn. (Guava) family Myrtaceae is an important medicinal plant in tropical and subtropical countries. It is widely used in folk medicine around the world. Leaves contain volatile oil with the most important components being α-pinene, β-pinene, limonene, menthol, terpenyl acetate, isopropyl alcohol, longicyclene, caryophyllene, β-bisabolene, cineol, caryophyllene oxide, β -copanene, farnesene, humulene, selinene, cardinene and curcumene [16, 17]. Flavonoids, and saponins combined with oleanolic acid have been isolated from the leaves. Nerolidiol, β-sitosterol, ursolic, crategolic, and guayavolic acids have also been identified [18]. In addition, the leaves contain triterpenic acids as well as flavonoids; avicularin and its 3-l-4-pyranoside with strong antibacterial action [19], fixed oil 6%, 3.15% resin, and 8.5% tannin, and a number of other fixed substances, fat, cellulose, tannin, chlorophyll and mineral salts. Also have been isolated from the leaves of *Psidium guajava* guavanoic acid, guavacoumaric acid, 2 α –hydroxy ursolic acid, jacoumaric acid, isoneriucoumaric acid, asiatic acid, ilelatifol D and β-sitosterol-3-*O*-β-Dglucopyranoside [20, 21]. In mature leaves, the best concentrations of flavonoids were found in July: Myricetin (208.44 mg kg−1), quercetin (2883.08 mg kg−1), luteolin (51.22 mg kg−1) and kaempferol (97.25 mg kg−1) [22]. 2 triterpenoids, 20β-acetoxy- 2α, 3β-dihydroxyurs-12-en-28-oic acid (guavanoic acid), and 2α,3β-dihydroxy-24-*p*-*z*-coumaroyloxyurs-12-en-28-oic acid (guavacoumaric acid), along with six well known compounds 2 α -hydroxyursolic acid, jacoumaric acid, isoneriucoumaric acid, asiatic acid, ilelatifol D and β-sitosterol-3-*O*-β-Dglucopyranoside, have been isolated from the leaves of *Psidium guajava*. guajavolide (2a-,3β-6β-,23-tetrahydroxyurs- 12-en-28,20β-olide, and guavenoic acid, were isolated from fresh leaves of *Psidium guajava.*

Fig. 1*: Psidium guajava* leaves

Oxidative stress occurs once free radical production exceeds the antioxidant capability of a cell which can harm crucial cellular compounds, such as lipids, carbohydrates, proteins, and DNA. Cellular damage or oxidative injury arising from free radicals or reactive oxygen species (ROS) now appears to be the fundamental mechanism underlying a number of human neurodegenerative disorders, diabetes, inflammation, viral infections, autoimmune pathologies and digestive system disorders. Free radicals are generated through normal metabolism of drugs, environmental chemicals and alternative xenobiotics as well as endogenous chemicals, particularly stress hormones (epinephrine and norepinephrine) [23].

The antioxidant activity of lyophilized leaf extracts was determined using free radical DPPH (2, 2-diphenyl-1-picrylhydryzyl) scavenging. The results obtained showed that vitamin C was a substantially more powerful antioxidant than the extracts from guava leaf [24, 25]. These antioxidant properties are associated with its phenolic compounds such as protocatechunic acid, ferulic acid, quercetin, guavin, vitamin C, gallic acid and caffeic acid. Guava leaf extracts and fruits are a important source of natural antioxidents.

Citrulus Lanatus Seeds:

The *Citrullus lanatus* (watermelon) family cucurbitaceae is one of the most popular species with high water content as high as 92% of the total weight**.** Watermelon seeds are excellent sources of protein (both essential and non-essential amino acids) and oil. Watermelon seed is about 35% protein, 50% oil, and 5% dietary fiber. Watermelon seed is also rich in micro- and macro-nutrients such as magnesium, calcium, potassium, iron, phosphorous, zinc etc [26]. Watermelon seeds are a source of healthy fat (unsaturated), almost 90%, vitamins, antioxidants, minerals, proteins and phytochemical, which is very good.

The flat brown seeds have a much higher food value than the flesh and have a nice nutty taste. significant amounts of vitamin C, minerals, fat, starch and riboflavin have been obtained from them. They are dried, roasted and eaten as such or ground into flour to make bread. The flour is said to consist of saponins and is also used as a detergent. The seed consists of a high percentage of oil and it is similar to pumpkin seed oil and can be used in cooking [27]. *Watermelon* seeds are mostly used for their oil in semi-arid regions and also the utilization of the oil in the cosmetic and pharmaceutical industry is increasing. There are also prospects for use of the seeds in the improvement of infant nutrition in view of their high protein and fat content [28].

The In-vitro anti-oxidant activity of the n-Hexane, Chloroform and Ethanol extract of *Citrullus lanatus* seeds were studied using 1, 1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging activity, Ferric reducing power activity, Hydrogen peroxide(H2O2) scavenging activity and Nitric Oxide(NO) scavenging activity. The total Phenolic contents and Flavanoids contents were evaluated taking Gallic Acid and Quercetin calibration curve respectively. In this study, it was found that all the extracts possess In-vitro antioxidant activities. But the order of possessing anti- oxidant activities were n-hexane>ethanol>chloroform extracts of *Citrullus lanatus* seeds [29].

In another study the antioxidant activity of *Citrullus lanatus* of chloroform, ethyl acetate and methanol extracts were studied [30]. Antioxidant activity of all the extracts (chloroform, ethyl acetate and methanol) was measured by DPPH method. Methanolic and ethanolic extract of *Citrullus lanatus* (MECL) seeds had shown maximum antioxidant and neuroprotective potential respectively [31, 32].

Fig. 2: *Citrulus lanatus*

***Cucumis Sativus* Peel:**

Cucumber (*cucumis sativus* L.) belongs to the cucurbitaceae family. It is widely consumed fresh in salads or fermented (pickles) or as a cooked vegetable [33]. It is believed that they promote refreshing, cooling, healing, soothing, emollient and anti itching effect to irritated skin [34]. The nutrient profile of cucumber includes water (96.4%), protein (0.4%), fat (0.1%), carbohydrate (2.8%), minerals (0.3%), calcium (0.01%), phosphorous (0.03%), iron (1.5mg/100g) and vitamin B (30 IU/100g). Ascorbic acid and enzymes such as crepsin, proteolytic enzyme, oxidase, succinic malic dehydrogenase have also been reported in the fruits [35]. The bioactive compounds isolated from cucumber include cucurbitacins, cucumegastigmanes I and II, cucumerin A and B, vitexin, orientin etc [36].

The qualitative phytochemical analysis revealed the presence of bioactive compounds in cucumber peel [37]. the cucumber peel has considerable amount of flavonoids and can be considered as chief source of flavonoids. Flavonoids have been reported to exert multiple biological property including antimicrobial, antioxidant, cytotoxicity, anti inflammatory as well as antitumor activities [38]. Although cucumber peel extracts exhibited poor free radical scavenging potential, the peel had good reducing power. The reductive capacity of a compound depends on the presence of reductones, which exhibit

antioxidative potential by breaking the free radical chain and donating a hydrogen atom [39, 40].

Cucumber exhibits wide range of *in vitro* and *in vivo* pharmacological effects. Its extracts showed antioxidant activities against various assays including DPPH reduction assay, total oxyradical scavenging capacity (TEAC), trolax equivqlent antioxidant capacity (TEAC)total radical trapping antioxidant parameter (TRAP) or ferric reducing antioxidant power (FRAP) assays [41-44]. Cucumber fruit and peel are shown to have antidiabetic and hypocholesterolemic activity [45, 46].

Fig. 3: *Cucumis sativus*

CONCLUSIONS AND PERSPECTIVES

Nature has packaged a wide array of phytochemicals that likely act in synergy to promote health and prevent aging. Currently, the nutritional neuroscience is quickly growing, and the therapeutic effects of whole foods and herbs as neuroprotective agents have become the focus of research by neuroscientists [47, 48], especially the health-beneficial aspects of phytobioactive components involving the reduction of oxidative stress and of immune-mediated inflammation and the exposure of various environmental factors and behavioral determinants, such as diet and exercise [49]. In fact, in the habitual diet of the elderly, the phytochemicals discussed in this review have been used to produce potential therapeutic values related to their antioxidative properties, based on this these herbs can be applied in the prevention of numerous neurodegenerative diseases, but the rate of regular administration in the aged population is limited and needs to be potentiated through the education and popularization of relevant nutritional procedures.

Collectively, the nutritional intervention can produce three major positive outcomes in the prevention and treatment of the geriatric diseases: the neuroprotective and anti-oxidative effect, the immunity-enhancing and anti-inflammatory effect, and the gastrointestinal improvement and nutritional effect [50]. Therefore, as a well-established conception, the regular administration of these phytochemicals is an important approach to enhance the basic nutrition of the elderly, a prerequisite for the maintenance of physical health, the reversal of brain function decline and disease resistance capability. Moreover, the synthetic bioactive compounds have various toxicity limitations and are still extensively used due to their anti-oxidative or anti-inflammatory attribution. Among the phytochemicals, the phenolic natural compounds (phenolic acids and flavonoids) are the most beneficial and oral administration is the most convenient for the repeated and routine delivery of these compounds [51].

In summary, phytochemicals exhibit a remarkable multipotent ability to control and modulate oxidative stress, chronic inflammation, and mitochondrial dysfunctions, three hallmarks of neurodegeneration [52]. To reduce the prevalence of neurodegenerative diseases and their pervasive health threat to the growing aged population, it is necessary to establish novel preventive and intervention procedures available in clinical nursing services for patients or healthy adults by direct usage and dietary supplementation of phytochemicals. The lack of toxic effects and the easy acquisition from natural sources are advantageous for adoption and generalization of dietary therapeutic programs in the aged population. Future research needs to aim towards a clinical acceptance of health claims from preclinical studies in vitro and in vivo, and human clinical trials of several potent compounds and their combinations should be carried out, including risk assessments and safety evaluations to observe any undesirable effects. The success in clinical research of polyphenols will decide their pharmacological relevance for humans, and nutritional intervention programs may decrease oxidative damage, slow the rate of aging, lessen the risk of neurodegenerative disorders, and increase the lifespan of older adults to achieve the goal of healthy aging [53], so that older adults can remain both physically and cognitively healthy into older age, with reduced social and economic burdens. Our review has acknowledged various herbal medicines such as *Psidium guajava, Citrulus lanatus and Cucumis sativus* with potential therapeutic effects for neurodegenerative diseases based on their antioxidative and neuroprotective properties. It is anticipated that the information provided through this review should help the researcher to provide some evidence and conceptual detail of the benefit of a wide range of herbs as neuroprotective agents.

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