



Herbal Extract as Potential Modulator and Drug for Synaptic Plasticity and Neurodegenerative Disorders

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ABSTRACT

Ayurveda, an ancient system of Indian medicine has defined a number of plants with therapeutic benefits for the treatment of neurodegenerative disorders, having antioxidant activities. Traditional medicines derived from medicinal plants are used on about 60% of the world's population. This review focus on herbal plants and their active components which are used in the modulation of synaptic plasticity and neurodegenerative disorders (like Alzheimer disease (AD), Parkinson), epilepsy, stroke etc. Neurodegenerative disorders are a major health problem and directly associated with synaptic plasticity. There are various approaches to modulate synaptic plasticity and treat neuronal disease and its secondary complications. Herbal treatment / formulation are beneficial due to lesser side effects and low cost. Extracts of *Bacopa monniera* had proved to improve human cognitive function. *Bacopa* extract is claimed to have antioxidative function. *Ginkgo biloba* is reported to reduce free radical levels, age-related effects and improve memory and learning behavior. Extracts of *Withania somnifera* improves brain functions, antioxidant status in oxidative stress induced neurodegeneration. Neurodegenerative disease like Alzheimer's will cost the nation \$203 billion in 2013 and this number is expected to rise to \$1.2 trillion by 2050. In this review we reviewed more than 15 plant species which is used for neuroprotection and synaptic plasticity in the world. There are still a large number of plants that need to be examined for their potential neuroprotective properties. Assays based on genomics and proteomics are expected to offer comprehensive information about molecular mechanism of neurological ailments and their protection by plant extracts. This will greatly help in identifying more potent compounds with potential applications in prevention of human ailments. These approaches hold promise for the treatment of a variety of neurological conditions, including neuropathic pain, Alzheimer, epilepsy, depression, stroke etc.

Keywords: Alzheimer, Antioxidant, Epilepsy, Neurodegenerative disorders, Stroke, Synaptic plasticity.

INTRODUCTION

The adult human brain contains more than one thousand million neurons. Neurons are the basic structural and functional unit of central nervous system (brain and spinal cord) and they receive input from other neuronal cells. A typical neuron has four physically distinct parts. First part is the cell body (soma) which is not only the "metabolic control centre" of the neuron but it is also the "manufacturing and recycling part of the cell". Second and third parts are axon and dendrites respective. Incoming information from other neurons is received through dendrites and outgoing information to other neurons flow towards axon. A neuron may have many thousands of dendrites, but it will have only one axon. Fourth part of the neuron lies at the end of the axon, the axon terminals. Axon terminals are structures that contain neurotransmitters. Neurotransmitters are the chemical through which "information" flows from one neuron to the next. The specific point of contact between axon of one neuron and a dendrite of another neuron is called as a synapse. Human brain is composed of billions of nerve cells which communicate through these specialized synapses. At each synapses a chemical neurotransmitter is released from one neuron and bind to receptors on the second neuron (shown in figure 1). Binding of neurotransmitter to the receptor of second neuron trigger a wave of action potential and thus a signal is propagated. Synapse is the

basic unit of the communication in the brain. Most neuroscientist believes that learning and memory formation occurs by changing the strength of synaptic connections, elimination of some synapses and building new connection. A ubiquitous property of all synapses is their ability to undergo activity- dependent changes in synaptic strength that is synaptic plasticity. Donald Hebb in 1949 developed a hypothesis about the mechanism of learning and memory at the neuronal level. He mention "Let us assume that the persistence or repetition of a reverberatory activity (or "trace") tends to induce lasting cellular changes that add to its stability. When an axon of neuron A is near enough to excite a neuron B and stimulate it repeatedly or persistently, some growth process or metabolic change takes place in one or both neuron such that A's efficiency role as one of the neuron firing B, is increased".¹ The theory is often summarized as "Cells that fire together, wire together".

Clinical observations enabled investigators to link human memory dysfunction to the hippocampus.^{2,3} These developments stimulated research in the field of synaptic plasticity in the mammalian brain.⁴ Plasticity can generally be divided into four main classes:

- Short-term synaptic plasticity, where activation of a synapse increases or decreases the efficacy of synaptic transmission at that particular synapse for seconds or minutes.



- Long-term synaptic plasticity, which is like short-term plasticity but where the synapse-specific changes last from minutes to a lifetime.⁵
- Metaplasticity, where synaptic or cellular activity regulates the capacity of individual synapses to undergo subsequent synaptic plasticity. This is sometimes termed the “*plasticity of synaptic plasticity*.”⁶
- Homeostatic plasticity or synaptic scaling, in which a neuron adjusts sensitivity of its excitatory synapses up or down in response to network activity in order to tune synaptic gain and stabilize firing.⁷

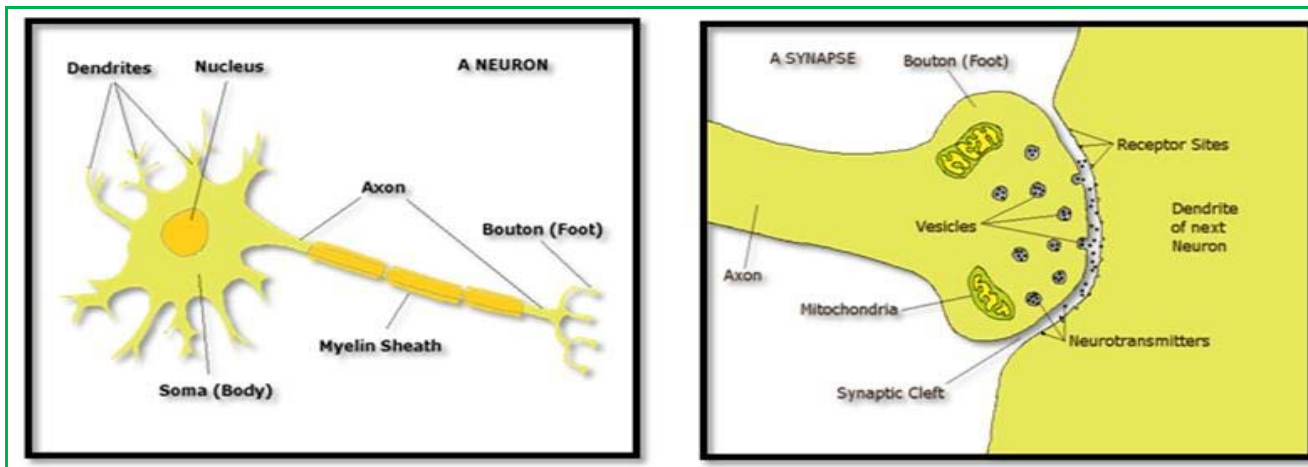
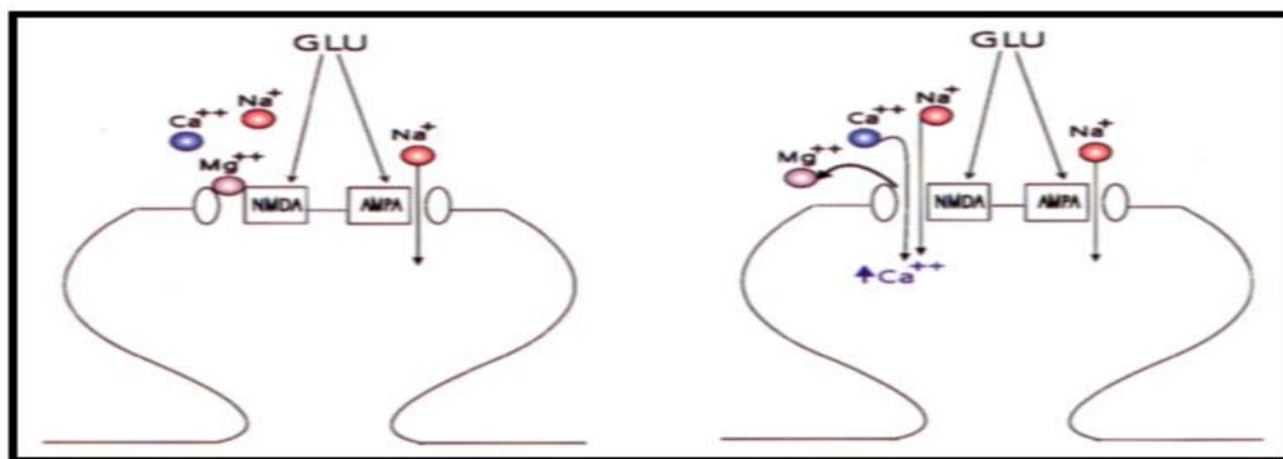


Figure 1: (a) A typical neuron and its parts and (b) Chemical transmission between axon and dendrites (Adapted from Dr. C.G.Boeree)⁸



1. Normal synaptic transmission; 2. During depolarization (Adapted from Robert C. Malenka 1994)¹³

Figure 2: Model for the Induction of LTP in the CA1 Region of the Hippocampus during normal synaptic transmission, glutamate (GLU) acts on both NMDA and AMPA receptors. Na⁺ flows through the AMPA receptor channel but not through the NMDA receptor channel because of the “Mg²⁺” block of this channel. Depolarization of the postsynaptic cell relieves the Mg²⁺ block of the NMDA receptor channel, allowing Na⁺ and Ca²⁺ to flow through this channel. The resultant rise in Ca²⁺ in the dendritic spine is a necessary trigger for subsequent events leading to LTP.

There are two forms of synaptic plasticity found at excitatory synapses in the mammalian brain.

- (a) Long term potentiation (LTP)
- (b) Long term depression (LTD)

Long Term Potentiation (LTP)

In neuroscience, long-term potentiation (LTP) is a long-lasting enhancement and input specific (changes can be induced at one set of synapses on a cell without affecting other synapses) in signal transmission between two neurons that results from stimulating them synchronously. It is one of several phenomena underlying

synaptic plasticity, the ability of chemical synapses to change their strength. Memories are thought to be encoded by modification of synaptic strength. LTP is widely considered as one of the major cellular mechanisms that underlies learning and memory.^{9, 10} LTP was discovered in the rabbit hippocampus by Terje Lømo¹¹ in 1966 and has remained a popular subject of research since. Many modern LTP studies seek to better understand its basic biology, while others aim to draw a causal link between LTP and behavioral learning. LTP is also a subject of clinical research, for example, in the areas of Alzheimer’s disease and addiction medicine.¹²

The induction of LTP by NMDA receptors and Ca^{2+}

It is well accepted that the induction of LTP requires activation of post synaptic NMDA (N-methyl-D-aspartic acid receptors, a sub type of glutamate receptor) during post synaptic depolarization, which is normally generated by high frequency afferent activity. This results in a rise in Ca^{2+} concentration, a necessary trigger for LTP. At normal low frequency synaptic transmission, the excitatory neurotransmitter glutamate is released from a presynaptic terminal and binds to postsynaptic NMDA and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors that are colocalized on a dendritic spine. The AMPA receptor channel, which is permeable primarily to Na^+ , provides the majority of current responsible for generating synaptic responses at the resting membrane potential (-60 to -80 mV). In contrast, the NMDA receptor does not contribute to the postsynaptic response because extracellular Mg^{2+} sits and blocks its ion channel of NMDA receptor. When the postsynaptic membrane is depolarized during the generation of LTP, Mg^{2+} is removed from the NMDA receptor channel (depolarization of the postsynaptic cell relieves the Mg^{2+}), allowing Ca^{2+} as well as Na^+ to enter the cell. With repeated activation, sufficient Ca^{2+} enters the dendritic spine to activate the signaling mechanisms that result in LTP.¹³ (Shown in figure 2).

AMPA Receptors and LTP

The α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype glutamate receptors are the principal mediators of the fast excitatory synaptic transmission in the mammalian CNS and are important for the expression of various forms of long lasting synaptic plasticity, including long-term potentiation^{14,15} (LTP). AMPARs are highly mobile proteins that undergo constitutive and activity-dependent translocation to, recycling at, and removal from, synapses.^{16, 17} LTP effected threw phosphorylation of the AMPA receptor, an ionotropic glutamate receptor that mediate baseline chemical transmission. Phosphorylation by CaMKII enhances the conductance of these channels. LTD by contrast, results, in part, from the dephosphorylation of the AMPA receptor by phosphatases. Trafficking of AMPA receptor plays a major role in the expression of LTP and LTD by increasing or decreasing the number of receptors in the postsynaptic membrane.¹⁸

Long Term Depression (LTD)

LTD is an activity dependent reduction in the efficacy of neuronal synapses. It can generally last for hours or longer. It brings about a long lasting decrease in synaptic strength. LTD can be defined as a long lasting decrease in the synaptic response of neurons to stimulation of their afferents following a long patterned stimulus. LTD occurs in many areas of the CNS with varying mechanisms depending upon brain region and developmental progress. LTD in the hippocampus and cerebellum have been the best characterized. LTD has also been found to occur in different types of neurons that release various

neurotransmitters. The most common neurotransmitter involved in LTD is L-glutamate. L-glutamate acts on the N-methyl-D-aspartate receptors¹⁹ (NMDARs), α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs), kainate receptors (KARs) and metabotropic glutamate receptors (mGluRs). It can result from strong synaptic stimulation (as occurs in the cerebellar Purkinje cells) or from persistent weak synaptic stimulation (as in the hippocampus). LTD is also considered to be the initial step in synaptic elimination^{20,21} as it is known that those synapses which lose their efficacy are eliminated.

LTD is induced via two pathways involving

- (1) NMDA receptors
- (2) mGlu Receptors

The induction of LTD by NMDAR – dependent LTD

NMDAR- dependent LTD is induced by weak activation of NMDARs and is thought to result from a smaller rise in postsynaptic Ca^{2+} than is required for LTP²². This triggers a different subset of Ca^{2+} dependent intracellular signalling molecules than those required for LTP, including serine/threonine phosphatases, which dephosphorylate critical synaptic substrates, including the AMPARs themselves. The depression of synaptic strength during NMDAR-dependent LTD is due to the removal of synaptic AMPARs via dynamin- and clathrin-dependent endocytosis.²² An intriguing feature of NMDAR-dependent LTD is that NMDAR-mediated synaptic responses are also depressed by mechanisms that are distinct from those responsible for the LTD of AMPAR-mediated responses. This observation suggests that after this form of LTD is induced, further NMDAR-dependent synaptic plasticity will be limited, at least temporarily.

Metabotropic glutamate receptor-dependent LTD

Activation of metabotropic glutamate receptors (mGluRs) can also lead to a postsynaptically induced and expressed LTD, this was first described at parallel fibre synapses on cerebellar Purkinje cells.²³ Other forms of mGluR-dependent LTD using somewhat overlapping cellular mechanisms have subsequently been described in the hippocampus and the neocortex. At the parallel fibre synapse, LTD is associative, requiring both postsynaptic Ca^{2+} influx through voltage-gated ion channels and postsynaptic group I mGluR activation, whereas at other synapses, activation of postsynaptic mGluRs alone appears to be sufficient. In most cases, however, this form of LTD is mediated by clathrin-dependent endocytosis of synaptic AMPARs. Interestingly, at certain developmental stages, rapid protein synthesis is required for both mGluR-triggered AMPAR endocytosis and LTD.²⁴

MOLECULAR MECHANISM OF LTP AND LTD

Long-term potentiation and long-term depression are enduring changes in synaptic strength, induced by specific patterns of synaptic activity, that have received much attention as cellular models of information storage in the central nervous system. Work in a number of brain



regions, from the spinal cord to the cerebral cortex, and in many animal species, ranging from invertebrates to humans, has demonstrated a reliable capacity for chemical synapses to undergo lasting changes in efficacy in response to a variety of induction protocols. In addition to their physiological relevance, long-term potentiation and depression may have important clinical applications.

Molecular mechanism

As per Bliss and Cooke, molecular mechanism / steps (Fig. 3) involved in LTP and LTD are:

- A. Activation of the NMDA class of glutamate receptor triggers the induction of both LTP and LTD. The coincidence of presynaptic and strong postsynaptic activity is detected by this glutamate receptor which is an ionotropic receptor by a mechanism that involves both the binding of transmitter and depolarization-induced repulsion of the Mg^{2+} ions that block its ionophore at near-resting membrane potentials. In its unblocked state Ca^{2+} ions are able to enter the channel, gaining access to Ca^{2+} dependent processes in the spine and triggering synaptic plasticity.
- B. Ca^{2+} binds to Ca^{2+} /calmodulin which, in turn activates numerous kinases and phosphatases, including CaMKII, PKC and Calcineurin (PP2B) directly and PKA and PP1 indirectly. The balance of kinase and phosphatase activity depends on the concentration and temporal profile of the postsynaptic Ca^{2+} transient (including Ca^{2+} released from intracellular stores). The Ca^{2+} transient determines the polarity of the induced plasticity, with low and prolonged Ca^{2+} transients inducing LTD and brief, steeper transients inducing LTP.
- C. Phosphorylation of the AMPA receptor, which is an ionotropic glutamate receptor is a mean by which LTP is expressed. AMPA receptor mediates baseline chemical transmission at excitatory synapses in the CNS. Phosphorylation by CaMKII enhances the conductance of these channels. LTD, by contrast, results, in part, from the dephosphorylation of the AMPA receptor by phosphatases.
- D. Increasing or decreasing the number of receptors in the post synaptic membrane by trafficking of AMPA receptors plays a major role in the expression of LTP and LTD.
- E. Presynaptic mechanisms leading to a sustained increase in the probability of transmitter release also contribute to the expression of LTP. The relative contributions of pre and post-synaptic mechanisms may vary at different times after induction and also across different classes of synapse. Since induction of LTP and LTD is controlled by the post-synaptic NMDA receptor, any presynaptic component of expression requires a retrograde messenger that can signal to the pre-synaptic terminal that coincidence has occurred. Two candidates are nitric oxide (NO) and endocannabinoids (EC).
- F. Glutamate binds to group 1 metabotropic glutamate receptors (mGluR) which is essential for a second form of LTD. The binding of glutamate to this receptor initiates a signal cascade, involving the breakdown of the membrane lipid PIP2 by phospholipase C (PLC) to the important signaling molecules IP3, which releases Ca^{2+} from Ca^{2+} stores (not shown) and diacylglycerol (DAG), which leads to the activation of the calcium sensitive kinase PKC. This enzyme then phosphorylates the AMPA receptor but in such a manner that the conductance is reduced. An offshoot is the production of NO.
- G. Brain-derived neurotrophic factor (BDNF) plays a complicated role in both LTP and LTD and contributes in different ways to short-term and long-term plasticity.
- H. LTP and LTD, persisting for more than a few hours which are also called "late" forms, require the synthesis of new proteins, either through novel gene transcription or through initiation of local translation of existing transcripts. Novel gene expression requires signaling to the nucleus from newly potentiated or depressed synapses. cAMP-dependent signaling cascade initiated by calcium influx and involving adenylyl cyclase (AC) and cAMP-dependent kinase (PKA), which also acts directly on the AMPA receptor in LTP expression play a major role in the signaling to the molecules from newly potentiated or depressed synapses. Catecholaminergic modulatory input plays a major role in determining the longevity of LTP and LTD, through interaction with AC which increases levels of cAMP and thereby activates PKA. PKA then sets in action a chain of signals that leads to the expression of new transcripts which, in turn are translated into proteins contributing to the long-term expression of synaptic plasticity. This signaling pathway has been a major recent target of attempts to find nootropic substances.
- I. There are parallel signaling pathways, involving mitogen activated protein kinases (MAPK), that also result in the synthesis of new proteins. However, in this case existing transcripts are locally translated into proteins, without further requirement for nuclear signaling. The MAPK pathway is strongly implicated in mGluR-dependent LTD.
- J. PKMf is one newly synthesized protein that acts as a maintenance mechanism for late LTP. PKMf comprises the active subunit of PKM. PKM is now known to maintain the presence of AMPA receptors inserted during LTP induction, and thereby maintain LTP and it is an isoform of PKC. Inhibition of PKMf can erase LTP and memory many days after induction.
- K. Lastly as a newly synthesized product that alters the structure of the synapse to enforce long-term

changes in synaptic strength has also been studied and it has been determined that BDNF can also play a

second role in synaptic plasticity. (All process shown in figure 3) (Adapted from Bliss and Cooke 2011)¹⁸

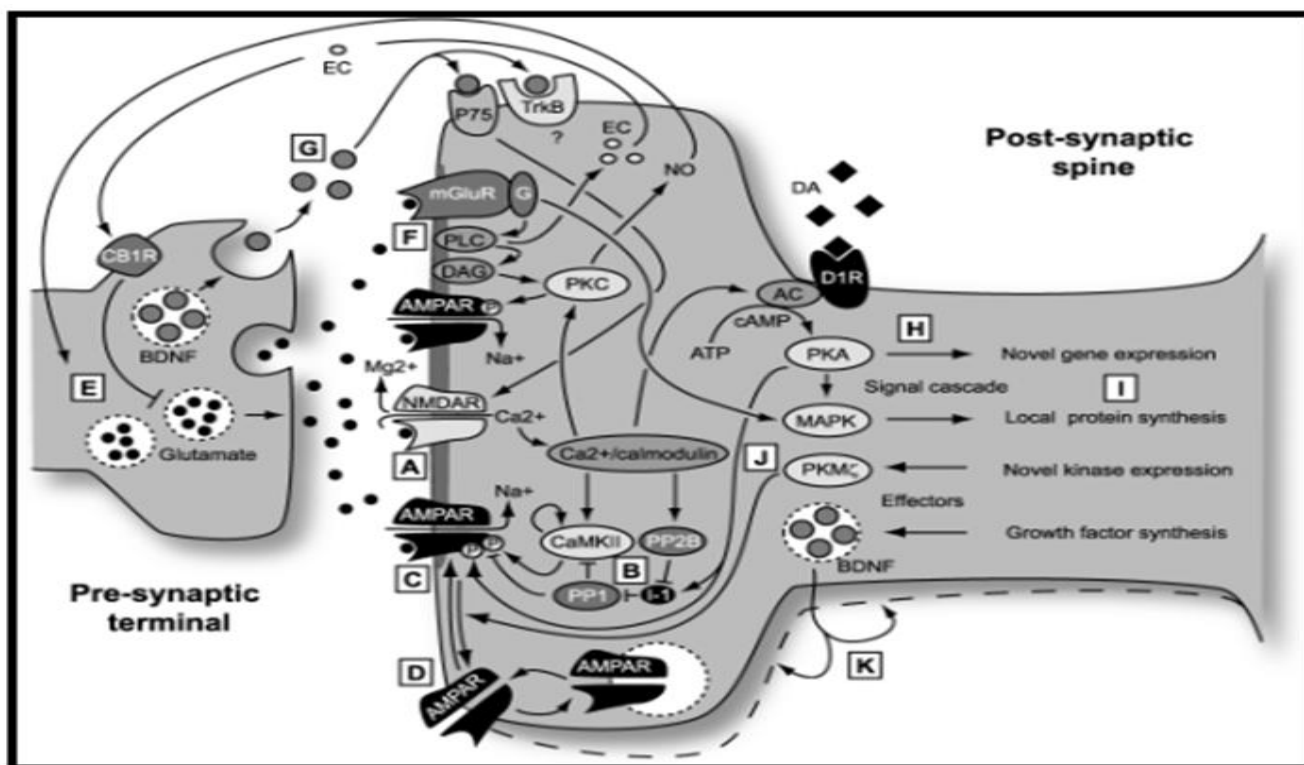


Figure 3: Adapted from Bliss and Cooke 2011¹⁸

Synaptic Plasticity Related With Neurodegenerative Disorders

Neurodegenerative disorders are a major cause of mortality and disability and as a result of increasing life spans represent one of the key medical research challenges. Among hundreds of different neurodegenerative disorders, so far lion's share of attention has been given Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD) and amyotrophic lateral sclerosis (ALS). The number of neurodegenerative diseases is currently estimated to a few hundred and among these many appear to overlap with one another clinically and pathologically rendering their practical classification quite challenging. Different neurodegenerative diseases are recognized by neuronal phenotypes that are primarily lost and neurological defects that accompany this loss. Neurodegenerative disorders of the Central Nervous System may be grouped into diseases of cortex, the basal ganglia, the brain stem, and the cerebellum or the spinal cord.²⁵

The role of LTP in disease is less clear than its role in basic mechanisms of synaptic plasticity. However, alterations in LTP contribute to a number of neurological diseases, including depression, Parkinson's disease, epilepsy, and neuropathic pain.²⁶ Impaired LTP also has a role in Alzheimer's disease and drug addiction. Misprocessing of amyloid precursor protein (APP) in Alzheimer's disease disrupts LTP and is thought to lead to early cognitive decline in individuals with the disease.²⁷ Research on the

role of LTD in Alzheimer's disease (AD) is ongoing. It has been suggested that a reduction in NMDAR-dependent LTD may be due to changes not only in postsynaptic AMPARs but also in NMDARs, and these changes are perhaps present in early and mild forms of Alzheimer-type dementia.²⁸ Additionally, researchers have recently discovered a new mechanism (which involves LTD) linking soluble amyloid beta protein (A β) oligomers, causes early memory problems by disrupting LTP and LTD mechanisms.²⁹⁻³² Direct application or overproduction of A β oligomers both inhibits LTP and triggers LTD-like changes. The net result is weaker synapses that have difficulty generating LTP. Furthermore, the toxic A β also decreases synaptic NMDARs, a change that contributes to the impaired LTP.³³ Based on these findings, there is great interest in finding compounds that prevent the synaptic effects of A β oligomers with the hope that such compounds will be therapeutically beneficial if given to patients early enough during disease progression. Sheng *et al.* in 2012 reported comprehensive discussion of synaptic changes associated with AD.³⁴

Role of Herbal Components In Synaptic Plasticity And Neurodegenerative Disorders

The Indian traditional system of medicine (Ayurveda), is gaining greater attention and acceptability these days because of its disease preventive approach. The revitalization and rejuvenation treatment therapy in Ayurveda is known as the 'Rasyana chikitsa'. Rasyana drugs act inside the human body by modulating the

neuro-endocrino-immune systems and have been found to be a rich source of antioxidants.^{35,36} Researches had proved that certain non-nutritive chemicals in plants viz terpenoids and flavonoids possess antioxidant properties which can modulate the synaptic plasticity (show in table 1). The lack of effective and widely applicable pharmacological treatments in the modern therapy for neurodegenerative disorders may explain a growing

interest in the traditional medicines³⁷ (show in table 2). According to estimation of WHO, 70-80% of the world population relies on traditional medicine, mostly plant based drug for their primary healthcare need.³⁸ Moreover particular component responsible for activity have also been isolated and some of which have been synthesized. There are some medicinal plants and their active components describe in table 3.

Table 1: Previous work done in synaptic plasticity by using herbal extract

| Herbal extract / plant name | Title / work | Effect on behavior | Authors name | Journal/year |
|--|---|--|--|--|
| Galantamine, isolated from several plants including <i>Lycoris radiata</i> Herb (used in traditional Chinese medicine (TCM)). | Plants used in Chinese and Indian traditional medicine for improvement of memory and cognitive function. | Cognitive-enhancing or antiageing effects. | Melanie Jayne R. Howes, Peter J. Houghton | <i>Pharmacology Biochemistry and Behavior</i> (2003) ⁵⁰ |
| Extract from <i>Fructus cannabis</i> (EFC). | Extract from <i>Fructus cannabis</i> activating calcineurin improved learning and memory in mice with chemical drug-induced dysmnesia. | Improve the impaired learning and memory induced by chemical drugs in mice. | LUO Jing, YIN Jiang-Hua, WU He-Zhen, WEI Qun | <i>Acta Pharmacol Sin.</i> (2003) ⁵¹ |
| EGb 761 is a standardized extract from the <i>Ginkgo biloba</i> leaf. | Age-related effects of <i>Ginkgo biloba</i> extract on synaptic plasticity and excitability. | Improve age related memory. | Bryn Williams, Coran M.H. Watanabe, <i>et al.</i> | <i>Neurobiology of Aging</i> (2004) ⁵² |
| EGb 761 is a standardized extract from the <i>Ginkgo biloba</i> leaves. | The <i>in vivo</i> synaptic plasticity mechanism of EGb 761-induced enhancement of spatial learning and memory in aged rats. | Enhancement of synaptic plasticity of the hippocampus. | Yongfu Wang, Lei Wang, Jing Wu, <i>et al.</i> | <i>British Journal of Pharmacology</i> (2006) ⁵³ |
| Bu-Wang-San (Chinese herb). | The neuroprotective effects of Bu-Wang-San (BWS) and its effects on spine synapse plasticity were investigated in ovariectomised rats. | Improve cognitive ability learning and memory. | Hui Li, Shu-Ling Li, <i>et al.</i> | <i>Journal of Pharmacy and Pharmacology</i> (2009) ⁵⁴ |
| <i>Garcinia buchananii</i> bark extract (African traditional plant). | The traditional antidiarrheal remedy, <i>Garcinia buchananii</i> stem bark extract, inhibits propulsive motility and fast synaptic potentials in the guinea pig distal colon. | <i>Garcinia buchananii</i> extract has the potential to provide an effective, nonopiate antidiarrheal drug. | Balemba, Bhattarai, <i>et al.</i> | <i>Neuro- gastroenterol Motility</i> (2010) ⁵⁵ |
| <i>Mitragyna speciosa</i> Korth or <i>ketum</i> or <i>kratom</i> leaf extract (Thailand and Malaysia). | <i>Mitragyna speciosa</i> Korth standardized methanol extract induced short-term potentiation of CA1 subfield in rat hippocampal slices. | Induction of long-term potentiation (LTP) and induced only short-term potentiation (STP) in CA1 neurons. | M.H.Senik, S.M.Mansor, G.Rammes, <i>et al.</i> | <i>Journal of Medicinal Plants Research</i> (2012) ⁵⁶ |
| <i>Polygala tenuifolia</i> root extract (TEN). | Tenuigenin treatment improves behavioral Y-maze learning by enhancing synaptic plasticity in mice. | TEN enhancing learning and memory may result from inhibiting AChE activity, improving antioxidation and enhancing synaptic plasticity in mice. | Jun-ni Huang, Chun-yang Wang, Xiu-li Wang, <i>et al.</i> | <i>Behavioural Brain Research</i> (2013) ⁵⁷ |
| Radix <i>Astragali</i> , Radix <i>Codonopsis</i> , Rhizoma <i>Atractylodis Macrocephalae</i> , and <i>Cistanches</i> Herb (TCM). | The effect of PN-1, a Traditional Chinese Prescription, on the Learning and Memory in a Transgenic Mouse Model of Alzheimer's Disease. | PN-1 could improve learning and memory ability through multiple mechanisms without detectable side effects on mice. | Zhi-Gang Yao, Ling Zhang, Liang Liang, <i>et al.</i> | <i>Hindawi Publishing Corporation</i> (2013) ⁵⁸ |

Table 2: Previous work done in neurodegenerative disorders by using herbal extract

| Herbal extract / plant name | Title / work | Authors name | Journal/year |
|---|--|--|---|
| Standardized <i>Ginkgo biloba</i> extract (EGb 761). | Neuroprotective effects of <i>Ginkgo biloba</i> extract (a review). | B.Ahlemeyer and J. Krieglstein | (CMLS) <i>Cellular and Molecular Life Sciences</i> (2003) ⁵⁹ |
| Extract of <i>Fructus cannabis</i> (EFC). | The effect of calcineurin activator, extracted from Chinese herbal medicine, on memory and immunity in mice. | Jing Luo, Jiang-Hua Yin, and Qun Wei | <i>Pharmacology Biochemistry and Behavior</i> (2003) ⁶⁰ |
| Seed extract of <i>Cassia obtusifolia</i> . | The Seed Extract of <i>Cassia obtusifolia</i> Ameliorates Learning and Memory Impairments Induced by Scopolamine or Transient Cerebral Hypoperfusion in Mice. | Dong Hyun Kim, Byung Hoon Yoon, et al. | <i>Journal of Pharmacological Sciences</i> (2007) ⁶¹ |
| Seed extract of <i>Cassia obtusifolia</i> . | The seed extract of <i>Cassia obtusifolia</i> offers Neuroprotection to mouse Hippocampal cultures. | Benjamin, William, Gernot, et al. | <i>Journal of Pharmacological Sciences</i> (2008) ⁶² |
| Eleutherococcus senticosus Rhizome extract (TCM). | Inhibitory Effects of Eleutherococcus senticosus Extracts on Amyloid β (25-35)-Induced Neuritic Atrophy and Synaptic Loss. | Chihiro Tohda, Mahoko Ichimura, Yanjing Bai, Ken Tanaka, Shu Zhu, and Katsuko Komatsu. | <i>Journal of Pharmacological Sciences</i> (2008) ⁶³ |
| Bacopa leaf extract. | <i>Bacopa monniera</i> leaf extract ameliorates hypobaric hypoxia induced spatial memory impairment. | Sunil Kumar Hota, Kalpana Barhwal, Iswar Baitharu, Dipti Prasad, et al. | <i>Neurobiology of Disease</i> (2009) ⁶⁴ |
| Alkaloids(caffeine, nicotine), terpenes (ginkgo, ginseng, valerian, Melissa officinalis, sage), and phenolic compounds etc. | Herbal Extracts and Phytochemicals: Plant Secondary Metabolites and the Enhancement of Human Brain Function (Review). | David O. Kennedy and Emma L. Wightman | <i>American Society for Nutrition</i> (2011) ⁶⁵ |
| Ashwagandha Leaf Extract. | Protective Role of Ashwagandha Leaf Extract and Its Component Withanone on Scopolamine-Induced Changes in the Brain and Brain-Derived Cells. | Arpita Konar, Navjot Shah, Ruman Singh, et al. | <i>PLOS/one</i> (2011) ⁶⁶ |
| Turmeric extract. | Optimized Turmeric Extract Reduces β -Amyloid and Phosphorylated Tau Protein Burden in Alzheimer's Transgenic Mice. | R. Douglas Shytle, Jun Tan, Paula C. Bickford, et al. | <i>Current Alzheimer Research</i> (2012) ⁶⁷ |
| The ethanolic extract of the <i>Morinda citrifolia</i> fruit, <i>Caulis piperis futokadsurae</i> , The extracts from several traditional Chinese herbs. | Amyloidosis in Alzheimer's Disease: The Toxicity of Amyloid Beta ($A\beta$), Mechanisms of Its Accumulation and Implications of Medicinal Plants for Therapy (Review Article). | Anchalee Prasansuklab and Tewin Tencomnao. | <i>Hindawi Publishing Corporation</i> (2013) ⁶⁸ |

Plant Active Constituents Cross Bbb (Blood Brain Barries) or Not

Yes, a few plant active ingredients do cross the BBB via different transporters. There are many transporters which are responsible for the transport across the blood brain barrier (Table 2). Carrier Mediated Transporters (CMT), Active Efflux Transporters (AET), and Receptor Mediated Transporters (RMT). CMT and AET Systems are responsible for the transport of small molecules between blood and brain, the RMT systems are responsible for the transport across the BBB certain endogenous large molecules.

Blood brain barrier

The blood–brain barrier (BBB) is a separation of circulating blood from the brain extracellular fluid (BECF) in the central nervous system (CNS). It occurs along all capillaries and consists of tight junctions around the capillaries that do not exist in normal circulation.⁴⁰ Endothelial cells restrict the diffusion of microscopic objects (e.g., bacteria) and large or hydrophilic molecules into the cerebrospinal fluid (CSF), while allowing the diffusion of small hydrophobic molecules (O_2 , CO_2 , hormones).⁴¹ Cells of the barrier actively transport metabolic products such as glucose across the barrier with specific proteins. This barrier also includes a thick

basement membrane and astrocytic endfeet.⁴² (Show in table 4)

The CMT systems usually mediate brain to blood influx of substrate, although the CMT systems can also mediate brain to blood efflux. The AET systems usually mediate brain to blood efflux of substrate.^{44, 45}

| Herbal plants | Useful parts | Active constituents ³⁹ |
|---------------------------------|--------------|---|
| <i>Allium sativum</i> | Bulb | Sallylcysteine |
| <i>Bocopa monniera</i> | Whole plant | Bacosides A & B |
| <i>Nicotiana tobaccum</i> | Leaves | Nicotine |
| <i>Withania somnifera</i> | Roots | Withanolides |
| <i>Ricinus communis</i> | Beans | Ricinine |
| <i>Salvia officinalis</i> | Leaves | Monoterpenoid |
| <i>Ginkgo biloba</i> | Leaves/bark | Ginkgolides |
| <i>Huperzia serrata</i> | Moss | Huperzine |
| <i>Uncaria tomentosa</i> | Bulbs | Total alkaloids |
| <i>Physostigma venenosam</i> | Beans | Physostigmine |
| <i>Acorus calmus</i> | Rhizomes | α -Asarone & Methyl isoeugenol |
| <i>Terminalia chebula</i> | Rhizome | Chebulic acid |
| <i>Centella asiatica</i> | Leaves/Roots | Madicasoside, Asiaticoside & Brahmoside |
| <i>Cassia obtusifolia</i> | Seeds | Alkaloids, Tannins, Flavonoids & Anthroquinones |
| <i>Termeric (Curcuma longa)</i> | Roots | Curcuminoids |

Drugs targeting the brain

Mechanisms for drug targeting in the brain involve going either "through" or "behind" the BBB. Modalities for drug delivery/Dosage form through the BBB entail its disruption by osmotic means; biochemically by the use of vasoactive substances such as bradykinin; or even by localized exposure to high-intensity focused ultrasound (HIFU).⁴⁶ Other methods used to get through the BBB may entail the use of endogenous transport systems, including

carrier-mediated transporters such as glucose and amino acid carriers; receptor-mediated transcytosis for insulin or transferrin; and the blocking of active efflux transporters such as p-glycoprotein. Methods for drug delivery behind the BBB include intracerebral implantation (such as with needles) and convection-enhanced distribution. Mannitol can be used in bypassing the BBB.

Nanoparticles

Nanotechnology may also help in the transfer of drugs across the BBB⁴⁷. Delivering drugs across the blood–brain barrier is one of the most promising applications of nanotechnology in clinical neuroscience. Nanoparticles could potentially carry out multiple tasks in a predefined sequence, which is very important in the delivery of drugs across the blood–brain barrier. A significant amount of research in this area has been spent exploring methods of nanoparticle-mediated delivery of antineoplastic drugs to tumors in the central nervous system. For example, radiolabeled polyethylene glycol coated hexadecylcyanoacrylate nanospheres targeted and accumulated in a rat gliosarcoma.⁴⁸ However, this method is not yet ready for clinical trials, due to the accumulation of the nanospheres in surrounding healthy tissue.

Peptides

Peptides are able to cross the blood-brain barrier (BBB) through various mechanisms, opening new diagnostic and therapeutic avenues.⁴⁹ However, their BBB transport data are scattered in the literature over different disciplines, using different methodologies reporting different influx or efflux aspects. Therefore, a comprehensive BBB peptide database (Brainpeps) was constructed to collect the BBB data available in the literature. Brainpeps currently contains BBB transport information with positive as well as negative results. The database is a useful tool to prioritize peptide choices for evaluating different BBB responses or studying quantitative structure-property (BBB behaviour) relationships of peptides. Because a multitude of methods have been used to assess the BBB behaviour of compounds, we classified these methods and their responses. Moreover, the relationships between the different BBB transport methods have been clarified and visualized. Casomorphin is a heptapeptide and could be able to pass the BBB.

Table 4: Blood brain barrier endogenous transporters⁴³

| Carrier-mediated transporters (CMT) | Active efflux transporters (AET) | Receptor-mediated transporters (RMT) |
|---|--|---|
| Glucose transporter (GLUT1) | Adenosine triphosphate binding cassette(ABC or P-gp) | Insulin receptor (INSR) |
| Large neutral amino acid transporter (LAT1) | ABC transporter, subfamily C (ABCC) | Transferrin receptor (TFR) |
| Cationic amino acid transporter (CAT1) | ABC transporter, subfamily G (ABCG2) | Insulin-like growth factor receptor (IGF1R) |
| Mono carboxylic acid transporter (MCT1) | Organic anion transporter (OAT or SLC22) | Insulin-like growth factor receptor (IGF2R) |
| Concentrative nucleoside transporter (CNT2) | Organic anion-transporting polypeptide (OATP or SLC21) | Leptin receptor (LEPR) |
| Choline transporter (CHT) | Glutamic acid amino acid transporter (EAAT or SLC1) | Fc fragment of IgG receptor transporter (FCGRT) |
| Nucleobase transporter (NBT) | Taurine transporter (TAUT or SLC6) | Scavenger receptor, class B (SCARB1) |

CONCLUSION

Ayurveda emphasizes use of herbs, nutraceuticals or lifestyle changes for controlling age related neurodegenerative disorders. In traditional practice of medicines, various plants have been used for neuroprotection and modulation in synaptic plasticity. An ethnopharmacological approach has provided which leads to identify potential of new drugs from plant sources, including those for neurodegenerative disorders. It is apparent from the manuscript that a variety of plant shows or has potential to show activities relevant to use in the neurodegenerative disorder. Certain plant like *Clitoria ternatea*, *Acorus calamus* etc. has shown beneficial effects on cognitive function. There are various traditional medicinal plants that need to be examined for their potential. However, further studies regarding the compounds responsible for exact mechanism involved are necessary. The typical scientific approach for selecting plants to investigate for the treatment of a neurodegenerative disease is relatively rational method to develop more acceptable and better substitute to the present pharmacotherapy. Research is required to explore active components involved in antioxidant activity. The revealed antioxidant property of extracts may provide potential therapeutic intervention against synaptic plasticity and neurodegenerative disorders.

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