Role of the Genus *Cinnamomum* in the Management of Neurodegenerative Diseases: Outcomes and Shortcomings

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Kaur *et al.*: Genus *Cinnamomum* in Neurodegenerative Diseases

The genus *Cinnamomum* (family Lauraceae) is revered for the pleasant essential oils isolated from various species. *Cinnamomum* species are extensively employed all around the world not only as a spice but also in traditional and modern systems of medicine. These possess wide range of activities that included neuroprotective properties. Neurodegenerative disorders cause immense mortality and morbidity. Hence search for newer therapeutic targets for the management of such disorders has made herbals an important area for research. The present paper integrates and critically examines the scientific evidence on the role of *Cinnamomum* species in neuroprotection in *in vitro* and *in vivo* models of different neurodegenerative disorders. Literature was reviewed extensively by searching databases such as Google Scholar, ScienceDirect, PubMed, and Scopus to compile scientific data from 2003 to 2015, on the role of different species of *Cinnamomum* in various neurodegenerative disorders. Plants/phytoconstituents have demonstrated effects crucial for the management of neurodegenerative disorders. Various extracts, volatile oil and phytoconstituents isolated from *Cinnamomum* species diminished selective pathological and histological hallmarks in different neurodegenerative disorders such as inhibition of oxidative stress, neuroinflammatory mediators, and ischemic injury. This review summarized different research studies with *Cinnamomum* species to throw light on the promise held by these species as well as prospects for new drug development to manage neuronal damage. This genus appears to be a valuable source for developing new neuroprotective agents.

Key words: *Cinnamomum* species, antioxidant, antineuroinflammatory, antiAlzheimer's, antiParkinson's, neuroprotection

Neurodegenerative disorders (NDD) comprise of disorders marked by pathological events resulting from slow progressive and irreversible deterioration of certain areas of nervous system, ultimately leading to neuronal and synaptic deficit[1]. These disorders include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, amyotrophic lateral sclerosis and frontotemporal dementia[2]. These are multifactorial in nature and they share neuropathological traits such as oxidative stress leading to free radical development, aberrant protein dynamics, which results in faulty protein degradation and accumulation, marred bioenergetics, mitochondrial dysfunctions and neuroinflammatory activities[3]. A brief pathology of all the diseases mentioned above is explained in this article.

AD is a NDD characterized by formation of amyloid plaques due to aberrant cleavage of amyloid precursor protein (APP) by β- and γ-secretases. It causes unevenness in the fabrication and clean-up of amyloid peptide leading to aggregation. Ultimately, the aggregates get deposited in the form of senile plaques. Formation of amyloid peptide stimulates oxidative damage, induces tau hyperphosphorylation, and results in noxious effects on synapses and mitochondria[4]. Loss of cholinergic activity is also one of the main factors contributing to AD[5]. There is reduction in the levels of acetylcholine, a neurotransmitter important in learning and memory[6]. Different studies have also linked insulin and insulin resistance with AD. Enhanced

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levels of insulin in the brain promote limited clearance of amyloid peptide as they both compete for a common degrading mechanism 'insulin degrading enzyme'[7].

PD pathology is characterized by loss of dopaminergic neurons in substantia nigra and deposition of intraneuronal protein aggregates known as Lewy bodies[8]. Relapsed neurons in PD are characterized by the presence of aggregated α-synuclein. It is one of the main constituent of Lewy body fibrils[9]. In some sporadic and autosomal recessive forms of PD there occur mutations in parkin and DJ-1 genes. Parkin is a protein crucial for functioning of mitochondria whereas DJ-1 provides resistance against oxidative stress[10].

Huntington's disease is a rare NDD, which is caused by a mutation that expands the polymorphic nucleotide (CAG) tract in HTT (Huntington) gene[11]. The disease is exemplified by motor, cognitive and psychiatric symptoms[12]. Motor symptoms include chorea, dystonia, bradykinesia, rigidity, loss of postural reflexes; cognitive symptoms consist of inadequacy due to lack of planning, complexity in coordinating thoughts and activities, problematic communication, absence of insight, obscurity in gathering new skills; anxiety, depression, irritability, apathy and obsessive-compulsive disorder are some of the psychiatric symptoms[13].

Amyotrophic lateral sclerosis is a NDD of human motor system. The disease is characterized by upper and lower motor neuron degeneration. Intracellular inclusion bodies are present in neuronal soma and proximal dendrites. In some cases of the disease, mutations occur in superoxide dismutase 1 gene thus inducing oxidative stress. Other pathogenic mechanisms include excitotoxicity, mitochondrial dysfunction, apoptosis, glial activation and growth factor abnormalities. The consequences of disease include muscle weakness, progressive motor disability, and ultimately loss of life due to respiratory failure or an allied illness[14].

Frontotemporal dementia is illustrated by degeneration of prefrontal and anterior temporal lobes[15]. There is loss of large cortical nerve cells along with microvacuolation of superficial neurophil. The prominent characteristics of the disease include modifications in social behaviour, emotional disturbances which consist of inability in expressing feelings, dietary alterations and disturbances in speech[16]. Various modifiable and non-modifiable factors lead to neurodegeneration as shown in fig. 1.

Conventional pharmacotherapy includes use of cholinesterase inhibitors for AD[17] and anticholinergics, dopamine precursors, MAO-B inhibitors, catechol-O-methyltransferase inhibitors, dopamine receptor
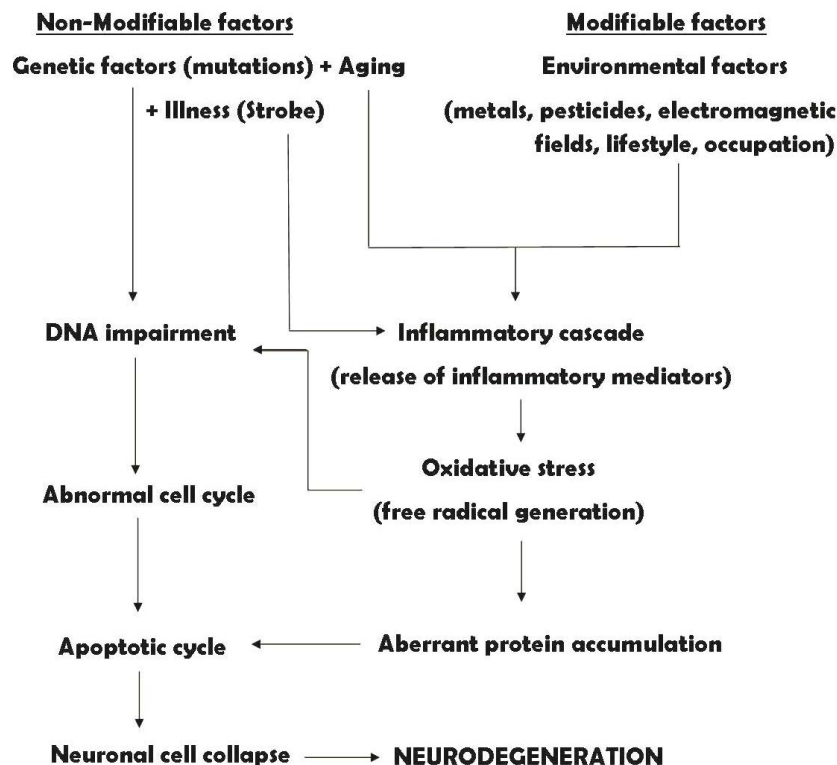
Fig. 1: Various modifiable and non-modifiable factors responsible for neurodegeneration

agonists for PD, the two most common NDD[18]. However, so far there is no well-established agent to prevent the onset or progression of NDD. Thus natural sources are being investigated to track down neuroprotective agents. Various plants (*Curcuma longa*, *Ginkgo biloba*, *Panax ginseng*, *Scutellaria baicalensis*) have shown beneficial results[19-26] in cellular and animal models of NDD.

Spices are reported to prevent or delay neurodegeneration[27,28]. Different species of *Cinnamomum* are widely used as spice and condiment. Moreover, these possess significant antioxidant and antiinflammatory activities, which may be beneficial in neuroprotection[29,30]. In this context, the present paper summarizes research reports on various species of *Cinnamomum* that have been explored for the management of NDD.

The objective of this study was to review *Cinnamomum* species as effective measure for various NDDs. Herbals and their diverse constituents are being established as potent neuroprotective agents against different neuropathologies. In this regard, the present review incorporates the scientific evidence on the role of *Cinnamomum* species in neuroprotection.

Literature search:

Extensive literature review was performed by searching databases that included Google Scholar, ScienceDirect, PubMed, and Scopus; and considering various books so as to gather scientific data from 2003 up to 2015, on the role of different species of *Cinnamomum* in various NDD.

Genus *Cinnamomum*, a brief look:

The genus *Cinnamomum* belongs to family Lauraceae and includes more than 250 aromatic evergreen trees and shrubs, chiefly located in Asia and Australia[31,32]. The plant is widely cultivated in tropical areas in various types of soils[33]. Different species of the genus that have been explored for various biological activities relevant to neuroprotection were mentioned in Table 1[34].

Cinnamomum species are valued greatly for the pleasant, aromatic essential oils present[35,36]. Main source of cinnamon oil is Sri Lanka and the oil has been largely used by both pharmaceutical and food industries[37]. Mucilage, tannin, sugar and resin are also present along with essential oil. Oil from different morphological parts of cinnamon possesses the same type of monoterpene hydrocarbons in varied proportions

but with a different characteristic constituent e.g. presence of cinnamaldehyde, eugenol and camphor in the bark oil, leaf oil and root-bark oil, respectively[38]. Cinnamon also contains phenolic compounds mainly flavonoids like quercetin and kaempferol[39,40].

ROLE OF *CINNAMOMUM* SPECIES IN NDD

Effect on pathways linked to neurodegeneration:

Neuroinflammation is an important pathological cascade in all the NDD. It is mainly mediated by activated microglia in the brain, which are further responsible for the release of numerous proinflammatory and cytotoxic factors, such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), IL-6, nitric oxide (NO) and reactive oxygen species (ROS). All these act bluntly and cause neuronal damage[41]. Various studies showing the role of *Cinnamomum* species in neuroinflammation are given as follows: antiinflammatory activity of sodium benzoate, a main metabolite of cinnamon (fig. 2), was explored in human astrocytes and mouse microglia using lipopolysaccharide (LPS)-induced inflammation[42]. Table 2 displays the beneficial effects of sodium benzoate; Hwang *et al*.[43] evaluated two phytoconstituents isolated from *C. cassia* bark, 2-hydroxycinnamaldehyde (HCA) and its derivative 2′-benzoyloxycinnamaldehyde (BCA), against neuroinflammation in LPS-stimulated microglial cultures and microglia/neuroblastoma co-cultures. Both the compounds, HCA (1.25-20 μM) and BCA (0.3125-

TABLE 1: VARIOUS SPECIES OF *CINNAMOMUM* EXPLORED FOR NEUROPROTECTION

Species	Common name	Reference
Cinnamomum burmanii	Indonesian cinnamon	[56]
Cinnamomum cassia	Chinese cinnamon	[34]
Cinnamomum philippinensis	Philippine cinnamon	[53]
Cinnamomum zeylanicum	Ceylon cinnamon	[77]
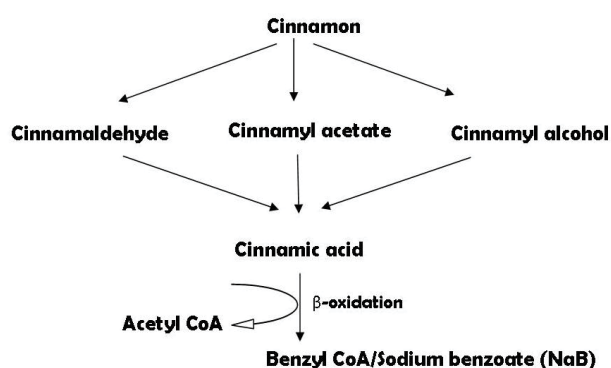
Fig. 2: Formation of sodium benzoate from cinnamon metabolites

20 µM), exhibited following beneficial effects: reduction in the levels of NO; decrease in the release of TNF-α; reduced expression of NO synthase (iNOS), IL-1β, TNF-α; inhibition of LPS-induced extracellular signal regulated kinase, c-Jun N-terminal kinase, p38 mitogen activated protein kinase and nuclear factor kappa-light chain enhancer of activated B cells pathways; blockade of microglia mediated neuroblastoma B35 death; Ho et al.[29] studied antineuroinflammatory effect of ethanol extract (50 µg/ml) of C. cassia bark and its major constituents i.e. cinnamaldehyde, coumarin, cinnamyl acetate, cinnamic acid, 2-methoxy cinnamaldehyde, α-methoxy cinnamaldehyde, cinnamyl alcohol, eugenol (100 µM for all the compounds) using LPS-activated BV2 microglia culture model. The extract significantly inhibited 65 % of NO production whereas all the constituents exhibited inhibition ability in the sequence cinnamaldehyde>2-methoxy cinnamaldehyde>a-methyl cinnamaldehyde>eugenol.

Other significant results obtained by the administration of extract and cinnamaldehyde are as follows: decreased levels of iNOS and mRNA; reduction in TNF-α, IL-1β, IL-6; inhibition of NF-κB binding activity; trans-cinnamaldehyde (TCA), one of the main components of young twigs of C. cassia was evaluated for antiinflammatory activity using in vitro and in vivo models. The results are given in the Table 3[44].

Effect on oxidative stress:

Brain is more vulnerable to negative effects of ROS than any other organ due to high metabolic rate and diminished ability for cellular regeneration. In case of NDD, specific brain regions express various indices of ROS damage that ultimately enhance the process of neurodegeneration e.g. markers of lipid peroxidation including, 4-hydroxyneonal and malondialdehyde

have been identified in the cortex and hippocampus of patients with AD and the substantia nigra of patients with PD[45]. Since antioxidants are reported to be linked to neuroprotection, plants with antioxidant activity can be an excellent source for prevention of neurodegeneration.

Different Cinnamomum species have exhibited efficacious inhibition of oxidative stress though they have not been correlated with neuroprotective effect[46-50]. One of the muscarinic cholinergic antagonists namely scopolamine causes memory deficits which have been linked to Alzheimer[51]. C. zeylanicum bark has displayed significant effect in scopolamine-induced cognitive impairment and oxidative stress model. The bark extract of plant (200 and 400 mg/kg) significantly inhibited the oxidative stress in brain tissue of rats as evidenced by decrease in MDA levels and increase in glutathione levels in rats[30].

Effect on ischemic injury:

The neuronal death in NDD involves apoptotic biochemical surges involving mitochondrial modifications and caspase activation. Initiation of such neuronal apoptosis is affected by aging, environmental and genetic factors. At the cellular level, neuronal apoptosis in NDD is prompted by oxidative stress, metabolic compromise and disturbance of calcium homeostasis[52]. Cinnamomum species have shown protective effect in ischemic injuries in brain as given underneath.

Preventive effect of cinnamophilin (CINN), isolated from C. philippinense roots, in oxidative damage and transient cerebral focal ischemia was explored by Lee et al.[53]. Pretreatment with CINN (20-80 mg/kg) caused significant reduction in brain infarction by

TABLE 2: BENEFICIAL EFFECTS OF SODIUM BENZOATE IN HUMAN ASTROCYTES AND MOUSE MICROGLIA USING LIPOPOLYSACCHARIDE (LPS)-INDUCED INFLAMMATION

Affected cell	Pathological event	Beneficial effect of sodium benzoate
Microglia	Induction of NO production	Inhibition of NO production
Microglia	Expression of pro-inflammatory cytokines	Reticence of expression
Microglia	Expression of iNOS due to stimulation of cells by reagents of neurological disorders such as fibrillar Aβ peptides (AD), fibrillar PrP peptides (prion diseases), dsRNA in the form of polyinosinic-polycytidylic acid (viral encephalopathy), IL-12 p402 (multiple sclerosis), and 1-(methyl-4-phenylpyridinium) (Parkinsonian toxin)	Impedetion of iNOS expression
Microglia	Activation of p21 ras	Suppression of activation
Human astrocytes	IL-1β-induced expression of iNOS	Obstruction of expression
Human astrocytes	Activation of iNOS promoter	Hampered the activation

TABLE 3: *IN VITRO* AND *IN VIVO* STUDIES ON TRANS-CINNAMALDEHYDE

Type of study	Model	Concentration	Result
In vitro	LPS-induced inflammatory BV2 microglial cells	1 and 3 µM	Inhibition of NO production
In vivo	6-Oxidopamine	30 mg/kg	Suppression of iNOS and COX-2

33-46 %. Post ischemic treatment also exhibited decrease in brain infarction by 43 %. Animals treated with the compound displayed reduced levels of oxidative damage.

CINN was also evaluated for therapeutic efficacy in oxygen glucose deprivation (OGD) and transient focal cerebral ischemia using *in vitro* and *in vivo* studies by Lee *et al*.[54]. Following results were obtained: *in vitro* assays revealed that CINN effectively inhibited Fe^{3+}-induced lipid peroxidation with IC_{50} value of 8.5 µM and DPPH radical scavenging with IC_{50} value 242.5 µM. Reduction in the generation of pro-inflammatory cytokines in LPS-stimulated RAW 264.7 and BV2 cells was also shown by CINN at concentration range of 30-100 µM and 10-100 µM, respectively; *in vivo* results showed reduced levels of malondialdehyde by CINN (80 mg/kg) in rat brain after ischemic onset.

Polyphenolic aqueous extract of *C. burmanii* was evaluated for astrocyte cell swelling and depolarization of inner mitochondrial membrane followed by OGD. Extract (0.01, 0.05, 0.1 mg/ml) significantly attenuated cell swelling and depolarization of inner mitochondrial membrane potential[55].

Polyphenols isolated from water soluble extract of *C. burmanii* were evaluated for key features of ischemic injury followed by OGD. Procyanidin type A trimer 1 isolated from the extract completely prevented OGD-induced glial cell swelling at concentration range of (10^{-2} to 10^{-7} mg/ml). It also attenuated OGD-induced increase in ROS, RNS (reactive nitrogen species), mitochondrial membrane depolarization, increased intracellular calcium, reduction in glutamate uptake and decline in ATP[56].

Two herbal formulations have also shown protective effect of *C. cassia* in focal cerebral ischemia as given below: *C. cassia* is a component of Chinese medical formulation, *Guizhi-Fuling* capsules, which has shown protective effects in rat *in vivo* model of focal cerebral ischemia. Administration of formulation (0.3 and 0.9 g/kg, po) after cerebral ischemia exhibited reduced brain infarction and water content in rats following ischemia. The formulation also down regulates pro-inflammatory cytokines in ischemic brain[57]; the plant is also a component of *Joongpoongtang* 05, traditional Korean medicine for preventing transient focal cerebral ischemia[58].

Effect on neurotrophic factors:

Animal models of various NDD have shown the protective role of neurotrophic factors[59-61]. The following study explained the protective role of *C. verum* and its metabolite sodium benzoate in the upregulation of neuroptrophic factors in the brain of mice. Sodium benzoate (250 µM) led to increase in the mRNA expression of both brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) in a time-dependent and dose-dependent manner in primary human neurons. Oral administration of cinnamon powder (200 mg/kg) to mice caused production of sodium benzoate in the brain of mice and both led to increase in the manifestation of BDNF and NT-3 in mice brain[62].

Role in AD:

AD is the most widespread NDD. The disease is characterized by build-up of amyloid plaques, neurofibrillary tangles, cholinergic deficit, neuroinflammation and neuronal diminution along with a progressive waning of cognition and functional aptitudes which eventually leads to dementia[63]. No synthetic medication has been able to cure AD so far. Researchers are exploring herbal remedies to find an effective cure for the disease. Several imbalances in AD have been amended by various *Cinnamomum* species.

Effect on acetylcholinesterase (AChE) inhibition:

Acetylcholine is the neurotransmitter involved in memory and learning. Cholinergic hypothesis of AD suggested that deterioration of cholinergic neurons in basal forebrain and the accompanying loss of cholinergic neurotransmission in the cerebral cortex and other areas interposed appreciably to the depreciation in cognitive function in AD patients[64]. Cinnamon has shown significant beneficial effect by efficient inhibition of AChE.

Ethanol extract of *C. cassia* bark at 200 µg/ml displayed 63 % inhibition of enzyme in the Ellman's method and came out to be a good anticholinesterase agent[65]. Anticholinesterase potential of aqueous and

ethanol extracts of *C. zeylanicum* bark, at 100 µg/ml was evaluated using Ellman's method. Percent inhibition displayed by the extracts was 46.84±0.003 and 40.83±0.005, respectively[66]. Methanol extract and cinnamon oil from *C. zeylanicum* leaves were evaluated for anticholinesterase potential using Ellman assay. Results revealed that oil showed better activity with IC_{50} value 45.88±1.94 µg/ml as compared to 77.78±0.3 µg/ml for the extract[67].

Methanol extract, cinnamon oil and the chief biomarker of the oil i.e. linalool from *C. tamala* leaves were explored for anticholinesterase potential employing Ellman's method. Cinnamon oil showed better inhibition than the methanol extract. Linalool also possessed good inhibition against the enzyme with IC_{50} value of 55.10±0.191 µg/ml. Inhibition was in the order linalool>cinnamon oil>methanol extract[68].

Effect on experimentally-induced dementia:

Malik *et al*.[69] evaluated the effect of standardized lyophilized aqueous extract (LCZE) of *C. zeylanicum* bark (50, 100, 200 mg/kg, po) on learning and memory against streptozotocin-induced memory impairment. Morris water maze test (MWM) and object recognition test (ORT) were used as behavioural models for effect on learning and memory. The effect of LCZE on the AChE activity and oxidative stress parameters in the cerebral cortex and hippocampus of rat brain were also evaluated. Results displayed by LCZE are given as follows: LCZE considerably decreased the transfer latency and increased the time spent by the animals in target quadrant in MWM along with improvement in the discrimination between a familiar object and a novel object in ORT, thus indicating the reversal of STZ-induced memory impairment; STZ-induced alterations in AChE activity and oxidative stress parameters in brain parts were also restored by LCZE.

Effect on amyloid-β:

Formation of amyloid-β peptide is the most crucial step in AD. It is formed by proteolytic cleavage of a large transmembrane protein i.e. APP by the action of two proteases, β-secretase and γ-secretase. With time, stacks of amyloid peptide lead to neuronal loss and dementia by instigating a pathogenic gush[70]. Cinnamon has shown efficacious results against amyloid peptide formation.

Methanol and chloroform extracts of *C. cassia* exhibited marginal protection from beta amyloid insult in PC12 cells and primary neuronal cells. EC_{50} i.e.

sample concentration that is required to achieve 50 % cell viability was found out to be 104 µg/ml in primary neurons and 110 µg/ml in PC12 cells for chloroform extract whereas it was found to be >150 µg/ml in both the cells for methanol extract[71].

Frydman-Marom *et al*.[72] evaluated aqueous cinnamon extract precipitation (CEP) in AD using both *in vitro* and *in vivo* models. The study exhibited following results: extract inhibited the formation of amyloid beta oligomer in a dose-dependent manner in *in vitro* study. It also eliminated the process of fibrillization of amyloid beta; two models were used for *in vivo* study i.e. AD fly model and aggressive AD mouse model.

In AD fly model, CEP (0.75 mg/ml) repaired the diminished longevity, one of the characteristic symptoms of the AD flies. It also ameliorated the locomotive defects of the AD flies. AD affected flies fed with CEP exhibited climbing capability nearly similar to the control flies. In aggressive AD mouse model, CEP (100 µg/ml) improved cognition in the animals.

Effect of aqueous extract of *C. verum* on amyloid formation was explored using hen egg-white lysozyme (HEWL) as model protein by Ramshini *et al*.[73]. Reduced pH and high temperature led to the conversion of HEWL to amyloid. Following results were exhibited by the extract: dose-dependent inhibition of HEWL aggregation by the extract (0.1-1 mg/ml); significantly prevented the cytotoxicity of lysozyme oligomers and improved cell viability at 1 mg/ml dose.

In another study, Ramshini and Ayoubi[74] have compared the inhibitory effect of *C. zeylanicum* and *Camellia sinensis* in the dose range of 0.1-1 mg/ml on HEWL fibrillization. Formation of fibrillar assemblies was dose-dependently inhibited by cinnamon but less efficiently than *C. sinensis*.

Effect on tau aggregation:

Another hallmark of AD is accumulation of tau to form abnormal fibers i.e. paired helical filaments that form higher-order aggregates namely neurofibrillary tangles or neuropil threads in neurons and other brain cells[75]. Taupathies are also present in other brain disorders e.g. fronto-temporal dementia, Parkinsonism, pick's disease, progressive supranuclear palsy[76].

Aqueous extract of *C. zeylanicum* was evaluated for tau aggregation and filament formation using *in vitro* tau aggregation assay. The extract at 0.22 mg/ml

concentration inhibited the aggregation of tau along with formation of filaments. It also caused disassembly of pre formed tau filaments. Proanthocyanidin trimer (100 µM) from the extract also exhibited tau aggregation inhibition but efficacy was one-fourth that of the extract[77].

Polyamines also play a vital role in number of diseased conditions. Studies have linked tau pathology with arginase 1. Overexpression of this enzyme has reduced phospho-tau species and tangle pathology in transgenic mice. It also reduces capability of various kinases causing tau phosphorylation and eliminates hippocampal atrophy in tau transgenic mice. On the other hand, inhibition of the enzyme results in enhanced tau accumulation[78]. One study has reported inhibitory action of methanol extract of *C. cassia* bark on arginase enzyme using *in vitro* inhibition assay[79]. This study shows that this species may enhance tau pathology as it blocks the expression of arginase enzyme. Although the species has shown significant AChE inhibition potential along with protection against amyloid insult, but the possible involvement of this species in tau pathology has made it a doubtful candidate for management of Alzheimer. Further exploration of this species is required in order to identify the possible phytoconstituent responsible for arginase inhibition.

Effect on brain insulin resistance:

Insulin resistance has been incriminated in the pathogenesis of AD and the term "type 3 diabetes" has been used to portray AD. Massive instabilities in brain insulin and insulin-like growth factor signalling mechanisms denote early and progressive anomalies and could be a reason for the molecular, biochemical, and histopathological lesions in AD. Brain diabetes fabricated experimentally by intracerebral administration of streptozotocin shares several features with AD, including cognitive damage and disruptions in acetylcholine homeostasis[80].

Effect of cinnamon on brain insulin signalling and Alzheimer associated changes was evaluated by feeding *C. burmanni* powder (20 g/kg) in the diet comprising of high proportions of fat and fructose, to male Wistar rats. The diet fed rats exhibited impaired cognition in Y-maze and increased anxiety in elevated plus maze. The diet had negative effects on mRNA coding for proteins associated with AD and memory loss thus causing increase in tau and APP. *Cinnamon* led to the reversal of all the negative effects of diet. It also led to increase in the coding of proteins involved in insulin signaling[81].

Role in PD:

PD is the second most widespread neurodegenerative disorder. The characteristic hallmarks of PD are fibrillar aggregates known as Lewy bodies[9] and deterioration of dopaminergic cells inside the substantia nigra and the consequent dopamine reduction in the striatum[82]. Lewy bodies are said to be composed of α-synuclein as one of their major component[83]. Cinnamon has shown satisfactory results against PD as given below.

Effect on alpha synuclein:

Alpha synuclein comprises considerable portion of total proteins in Lewy bodies. The fabrication of wild type α-synuclein in transgenic mice leads to motor deficits and neuronal inclusions indicative of PD[84].

CEP (0-0.05 mg/ml) inhibited the formation of soluble and insoluble aggregates of α-synuclein *in vitro*. *Drosophila* fly model expressing mutant A53T α-syn exhibited a common behavioural phenotype for the flies i.e. age-dependent defective locomotion while normal flies tend to climb up the side of the rearing tube. Flies expressing A53T α-syn remain at the bottom. CEP (0.75 mg/ml) exhibited a significant therapeutic effect on the behavioural indications of the flies and on α-syn aggregation in their brain[85].

Effect on DJ-1 and parkin:

The DJ-1 is a gene contributing to familial PD[86]. Enhanced oxidation of DJ-1 has been observed in patients with sporadic PD[87]. It plays a defensive role against oxidative stress-induced cell death. Loss of function and diminished function of DJ-1 elicit the beginning of oxidative stress-related diseases, including PD. Activity of DJ-1 is controlled by oxidative status of cysteine 106 of DJ-1. Compounds that bind to C106 region of DJ-1 displayed neuroprotective activity in PD[88]. Parkin is an ubiquitin E3 ligase that regulates number of cellular procedures via monoubiquitination and polyubiquitination of proteins. Damage to E3 ligase activity of parkin is thought to have a pathogenic role in both inherited and sporadic PD. Mutations in the gene encoding for parkin causes autosomal recessive PD. It is the second most frequent cause of PD[89]. Cinnamon has exhibited protective role in PD by upregulating both DJ-1 and parkin. NaB, a metabolite of cinnamon, at concentration of 5 mM was proficient in increasing the level of DJ-1 in primary mouse and

human astrocytes along with human neurons, thus emphasizing its neuroprotective effect[90].

In vitro and *in vivo* studies were done to evaluate the effect of NaB and *C. verum* powder on dopaminergic neurons by Khasnavis and Pahan[91]. Following results were obtained: sodium benzoate (1 mM) upregulates parkin and DJ-1 in *in vitro* study by suppression of IL-1β-induced expression of iNOS in astrocytes thus exhibiting protection of both; *C. verum* powder and sodium benzoate protect dopaminergic neurons in a mouse model of PD. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) intoxication in mice led to increase in the level of iNOS and decreased level of parkin/DJ-1 *in vivo* in the nigra. Cinnamon powder (100 mg/kg) and sodium benzoate (50 mg/kg), administered orally via gavage, exhibited decrease in the expression of iNOS and upregulated parkin and DJ-1 in nigra. Functional impairment was also improved by cinnamon and sodium benzoate as evidenced from rotarod and open field experiments[91].

Effect on dopaminergic neurons:

The preferential and progressive loss of dopamine-containing neurons in the substantia nigra pars compacta and the consequent loss of their projecting fibres in the striatum are the major pathological changes in PD[92,93]. TCA, one of the main components of *C. cassia* was evaluated in 6-hydroxydopamine (6-OHDA)-induced dopaminergic degeneration in mice. TCA (30 mg/kg, ip) maintained the number of tyrosine hydroxylase-positive dopaminergic neurons, (which had undergone severe loss in 6-OHDA-treated mice) in the striatum and substatntia nigra regions of the 6-OHDA-treated mice[43].

Role in multiple sclerosis (MS):

MS is an immune-mediated demyelinating ailment of the human central nervous system. Permanent neurological disability in MS patients is caused by neurodegeneration[94]. Cinnamon has shown beneficial effect in the management of MS.

Effect on experimentally allergic encephalomyelitis (EAE):

It is the most frequently used investigational model for the human inflammatory demyelinating disease-MS. In EAE model there approximates the basic pathological aspects of MS i.e. inflammation, demyelination, axonal loss and gliosis, due to the collaboration between a range of immunopathological and neuropathological mechanisms[95].

Sodium benzoate ameliorated clinical symptoms and disease progression in acute and chronic phases of EAE, in both *in vitro* and *in vivo* studies as shown by Brahmachari and Pahan[96]. Following were the beneficial effects of NaB: NaB exhibited inhibition of encephalitogenicity of myelin basic protein-primed T cells *in vitro* at 1 mM; it also displayed reticence of both passively and actively induced EAE in mice at dose range of 2.5-10 mg/ml. It haltered the generation of encephalitogenic T cells *in vivo* in donor mice. NaB at 5 mg/ml dose also exhibited infiltration of mononuclear cells, inflammation, and demyelination in the CNS of passively induced EAE in mice.

C. verum powder was evaluated against EAE in mice by Mondal and Pahan[97]. Oral administration of the powder (50 and 100 mg/kg) led to the reticence of clinical indications of acute and chronic EAE in mice as given below: Cinnamon prevented severity of disease and adoptive transfer of EAE in transgenic mice and adoptive transfer mouse model, respectively; it also inhibited perivascular cuffing, maintained the reliability of blood-brain barrier and blood-spinal cord barrier, blocked inflammation, stabilized the expression of myelin genes, and impeded demyelination in the central nervous system of EAE mice; there was up regulation of T regulatory cells via reduction of NO production with cinnamon treatment.

Huntington disease:

The disease is a NDD with autosomal-dominant inheritance. It is caused by a CAG trinucleotide repeat expansion positioned in the first exon of the Huntington disease gene[98]. Patassini *et al*.[99] have reported that defective urea regulation causes an increase in levels of urea in the brain of Huntington disease patients. It has been identified as a major metabolic defect in the disease. l-arginine (a semi essential amino acid in mammals) is metabolized by arginase enzymes to form ornithine and urea[100]. Thus it can be inferred that the entities inhibiting arginase enzymes can offer novel therapeutic targets for Huntington disease as they will hamper the metabolism of arginine. Cinnamon can be a beneficial agent in this context as discussed below.

Methanol extract of *C. cassia* bark was explored using *in vitro* arginase inhibition assay. N-hydroxy-L-arginine (NOHA) was used as a positive control in the study. Extract was found to be more potent inhibitor than NOHA. IC_{50} value of former was found out to be 61.72±2.20 µg/ml whereas for latter it was 156.78± 7.76 µg/ml[79].

The frequency of occurrence of different NDD has increased over time. Changes in the lifestyle of people and increase in the stress-borne conditions have made the people more prone to such disorders. A well-established fact is that all such diseases are marked by multifactorial reactions that play a variety of roles in progression of these diseases and thus makes their management difficult. Although there are synthetic drugs available in the market that provide some relief from these disorders, full cure is yet to be achieved. Plants are promising agents with fewer side effects and having synergistic actions due to a number of phytoconstituents present in them, also different phytoconstituents may act on different targets in the neurodegenerative progression. *Cinnamomum* is a genus with wide utility in traditional and modern systems of medicine. Different plant parts namely stem bark, root bark and leaves are found to be effective in various pharmacological activities.

This review has given us a clear idea about the effectiveness of *Cinnamomum* species in the management of neurodegenerative diseases. Various species of the genus have multiple pharmacological activities relevant to neuroprotection as evident in *in vitro* and *in vivo* models. These species have been able to diminish selective pathological and histological hallmarks in different NDD e.g. amyloid and tau in AD, alpha synuclein in PD, neuroinflammation in MS. Various extracts, volatile oil and phytoconstituents isolated from *Cinnamomum* species have been able to inhibit the major neuropathological characters such as inhibition of oxidative stress, inhibiting the production of inflammatory mediators, ischemic injury inhibition, inhibition of different hallmarks of AD, PD and MS.

Although researchers have explored this genus to a large extent, we have not been able to implement this culinary plant in the treatment of any of the NDDs so far. There are many reasons responsible for this. Research should not be limited to extracts only but should be carried out with major constituents of different species of the genus. This will help to narrow down the zone of research to a particular class of compounds and hence will make possible further modifications, in those compounds, required for the activity. Emphasis should be given on mechanism-based *in vitro* bioassays combined with *in vivo* models which truly mimic the conditions for the disorder. The entities responsible for the formation of pathological hallmarks of a neurodegenerative disorder should be targeted so that their production can be restricted.

Cinnamon must be subjected to detailed experimental studies and clinical trials in order to develop a drug that can efficiently and safely cease the detrimental consequences of NDD on the human population.

Conflicts of interest:

There are no conflicts of interest among the authors.

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