Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-5 || October 2024 || PP. 147-159

https://doi.org/10.55544/jrasb.3.5.16

Investigation of Phytochemical and Antidepressants Activity of Cinnamon Powder Extract

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www.jrasb.com || Vol. 3 No. 5 (2024): October Issue

Received: 13-10-2024	**Revised:** 16-10-2024	**Accepted:** 24-10-2024

ABSTRACT

Neurodegenerative disease is the most common type of mobility issue, but unfortunately, there is now no medication that can alter the course of the disease. We don't know what causes this ailment. In mouse models of Parkinson's disease induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, the oral administration of cinnamon powder and sodium benzoate may prevent the death of dopaminergic cells, dysregulation of striatal neurotransmitters, and motor impairments. The mechanisms driving its function include controlling autophagy, antioxidant effects, Parkin, DJ-1, and glial cell line-derived neurotrophic factor activation, TLR/NF-κB pathway modulation, and excessive proinflammatory response prevention. Moreover, research carried out in both laboratory and living organism settings has shown that cinnamon extracts may impact the oligomerisation and aggregation of α-synuclein. This article's goal is to discuss recent findings about this phytochemical's potential as a novel treatment for Parkinson's disease (PD). We highlight additional areas of mechanism that require investigation and possible constraints that must be overcome before this phytochemical may be used in PD trials. Neurodegenerative disease is the most common type of mobility impairment, and unfortunately, there is now no medication that can alter this disease.

We don't know what causes this ailment. There has been a recent uptick in interest in medicinal plant use because of the novelty, safety, and relative affordability of this field. The characteristic flavour and aroma of cinnamon, a spice that is often used, may have neuroprotective effects on people with Parkinson's disease (PD) and other neurodegenerative diseases. The essential oils of Cinnamomum species, such as cinnamaldehyde and sodium benzoate, have shown in vitro that they can protect cells from oxidative stress, ROS generation, and autophagy dysregulation. Consequently, these oils may exert a neuroprotective effect. The in vivo evidence suggests that cinnamon powder and sodium benzoate, when administered orally to Parkinson's disease models in mice, may prevent the death of dopaminergic cells, dysregulation of striatal neurotransmitters, and motor deficits. In this essay, we will go over the latest research on this phytochemical and its potential as a novel treatment for Parkinson's disease (PD). Incorporating this phytochemical into experimental PD treatments requires further investigation into additional molecular aspects and the potential overcoming of constraints and obstacles.

Keywords- Neurodegenerative, Cinnamon, Disease, Chemical Constituents.

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-5 || October 2024 || PP. 147-159

https://doi.org/10.55544/jrasb.3.5.16

I. INTRODUCTION

Neurodegenerative disease is the most common type of mobility impairment, and unfortunately, there is now no medication that can alter this disease. We don't know what causes this ailment. Therefore, in the present setting, there is an increasing emphasis on novel, risk-free, and cost-effective approaches that make use of medicinal plants [1]. A growing amount of studies suggests that cinnamon, a spice often used for its aromatic and flavourful qualities, may have neuroprotective effects in various neurodegenerative diseases, including [2,3] Parkinson's disease (PD). There is some evidence from in vitro experiments that the essential oils of Cinnamomum species, particularly cinnamaldehyde and sodium benzoate, may have neuroprotective effects by preventing cell death caused by oxidative stress [4]. ROS formation, and autophagy dysregulation. Oral administration of cinnamon powder and sodium benzoate may buffer the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced [5]. Parkinson's disease in mice, including cell death of dopaminergic neurones, dysregulation of striatal neurotransmitters, and motor impairments [6]. Its activity is supported by a series of activities that include controlling autophagy, antioxidant actions, inducing Parkin, DJ-1, and glial cell line-derived neurotrophic factor, manipulating the TLR/NF-źB pathway, and preventing excessive proinflammatory responses [7-9]. In addition, studies done in both labs and living organisms have shown that cinnamon extracts may affect α-synuclein oligomerization and aggregation. The novel therapeutic potential of this phytochemical in the treatment of Parkinson's disease (PD) is the focus of this paper [10]. We highlight potential limitations and obstacles that must be addressed before this phytochemical can be included in experimental PD therapies, as well as further molecular issues that require investigation [11]. Neurodegenerative disease is the most common type of mobility impairment, and unfortunately, there is now no medication that can alter this disease [12]. We don't know what causes this ailment. Because they are novel, safe, and inexpensive, therapeutic plant uses are currently garnering a lot of interest [13]. A number of neurodegenerative diseases, including Parkinson's disease (PD), have demonstrated that cinnamon, a spice widely used for its aromatic and flavourful qualities, may have neuroprotective effects [14]. Evidence from in vitro studies shows that cinnamaldehyde and sodium benzoate, two components of Cinnamomum essential oils, can protect cells from oxidative stress, ROS generation, and autophagy dysregulation [15]. Accordingly, these oils may exert a neuroprotective effect [16]. Oral administration of cinnamon powder and sodium benzoate has been shown in vivo to mitigate motor deficits, dysregulation of striatal neurotransmitters, and dopaminergic cell death in Parkinson's disease animal models [17]. Recent research on this phytochemical's potential as a novel treatment for Parkinson's disease (PD) is reviewed in this article [18][19]. Incorporating this phytochemical into experimental PD treatments requires further investigation into additional molecular aspects and the potential overcoming of constraints and obstacles [20][21].

Life satisfaction is worsened by major depressive illness compared to debt, divorce, and diabetes, according to research [22][23]. Comorbidities like cancer, anxiety, and heart disease are also increased. Worldwide, major depressive illness ranks high among the leading causes of disability. There is a large treatment resistance rate among people with serious depressive illness, even though many of these patients do well with medication and psychotherapy [24]. Also, many depressed persons have trouble getting the help they need. Countries with high incomes cover therapy at 51% of the cost, but poor and lower-middle income countries cover treatment at 20% [25]. Consequently, there needs to be an increase in treatments backed by evidence. The mental illness known as major depressive disorder (MDD) is both prevalent and severely disabling [26-28]. It is crucial that we learn more about the causes of major depressive disorder (MDD) and how it impacts various aspects of health and wellbeing. In spite of advances in treatment, the incidence of major depressive disorder (MDD) is not going down. Our World in Data reports that major depressive disorder affects one-third of women and one-half of men throughout their lifetimes [29]. In addition to accounting for 4.3% of all YLD, MDD has a substantial impact on quality of life. It is linked to excessive treatment use, poor socioeconomic results, and negative clinical outcomes. In addition, it is significantly associated with a broad range of medical issues, the most prominent of which are cardiovascular disease and death from any cause whatsoever. Also, having a history of suicide thoughts, feeling hopeless, and having major depressive illness are the top three factors that can lead to suicidal thoughts. There is strong evidence that suicidal thoughts precede actual suicide attempts. However, whether MDD is a factor in many outcomes is unclear [30][31]. An example of a situation where mental comorbidity has a role in the interaction between the two is suicide. Reverse causation is a potential conclusion for other events. One example is the well-documented relationship between cardiovascular disease and major depressive disorder (MDD). Many things can put someone at risk for developing major depressive disorder (MDD)[32][33]. Having a low income, a low level of education, being single, and suffering from emotions of loneliness are all examples of important social risk factors. Among the many risk factors for major depressive disorder (MDD), childhood trauma and stressful experiences stand out as particularly important. Numerous risk variables may be susceptible to bidirectional connections, and the link may have other, non-causative pathways. For example, it may not be the events themselves that generate the well-known effect of stressful life events. The notoriously difficult task of

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

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drawing conclusions about causation from observational data usually necessitates the use of longitudinal or within-family designs [34][35]. Cinnamomum cassia bark is known for its flavour and aroma, but it also has several medicinal uses. Several studies found that cinnamon reduced levels of malondialdehyde and increased the activity of antioxidant enzymes, making it an effective defence against free radical damage [36][37]. Cinnamonaldehyde is one of cinnamon's active compounds; it can change the cellular redox homeostasis function electrophilically. The polyphenols in cinnamon are thought to have a major therapeutic impact on TBI treatment. This function is linked to reducing inflammation and oxidative damage [38-40].

II. MATERIAL & METHODS

We are searching from different sources like PubMed, Publon, NCBI, Scopus, Google Scholar. "Keywords: Neuro Disease, Cinnamon, Depressive

Role of Cinnamon active Components in depression

The many volatile chemical components that make up essential oils allow them to travel quickly throughout the body. An innovative administrative approach has been developed using nanotechnology to enhance the absorption of essential oils [41]. Encapsulating essential oils (EOs) into nanoparticles enhances their absorption and impact. Inhaled essential oil molecules will get to the brain area via different pathways depending on their molecular sizes. One possible route of administration by inhalation involves the respiratory and olfactory systems (figure 1). Beginning with the nasal cavity and its connection to the olfactory bulb is where the olfactory system is initiated [42]. The nasal cavity is an important pathway for odorant messages to travel. The olfactory system is linked to various brain regions, including the hippocampus and hypothalamus, despite its close proximity to the brain [43]. It is conceivable for specific little chemical molecules to modify the emotional response by travelling straight to the central nervous system (CNS) via the olfactory mucosa or the axon of sensory neurone cells [44]. Conversely, gas exchange is mostly the responsibility of the respiratory system. Vapour molecules can reach different areas of the respiratory system via diffusion [45]. Chemicals that enter the bloodstream through the respiratory epithelium, diffuse to the alveoli and blood, and ultimately reach the brain through the bloodstream via the heart are an example of this [46].

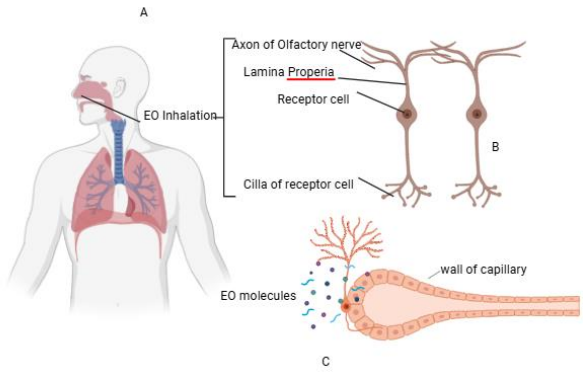

Fig. 1: Inhaled essential oils (EOs) reach the brain via the respiratory and olfactory systems (a) Olfactory or respiratory systems receive inhaled EO after it travels through the nasal passages. (b) A synopsis of the olfactory system's route for delivering EO molecules (c) A general outline of the steps necessary for EO molecules to pass through the blood-air barrier and enter the bloodstream.

For the better part of two decades, people have held the view that impaired neurogenesis is the root cause of depression [47]. This notion was derived from the finding that experimental mice treated with continuous antidepressant medication had an increase in neurogenesis in their hippocampus [48-50]. On the flip side, neurogenesis was found to be diminished by stress, a known risk factor for the development of mental illnesses [51]. Suppression of neurogenesis is often shown to be a common characteristic when investigating animal models of depression. The antidepressant therapeutic effects would be nullified if x-irradiation inhibits neurogenesis [52][53]. In light of the above, it seems that neuronal proliferation is involved in the pathophysiology of depression and influences the efficacy of antidepressants. Several studies published recently suggest that essential oils' (EOs) therapeutic advantages might be due to their pro-neurogenic activity [54]. In a study involving corticosterone-induced behaviour mimicking that of depressed patients, animals exposed to lavender essential oil for an extended period of time were able to avoid the negative consequences of depression, such as reduced neurogenesis, inhibited dendritic development of immature neurones, and decreased blood BDNF levels [55]. Exposure to musk was discovered to enhance neurogenesis and decrease neuronal death in the hippocampus, according to the results of an additional investigation that used a chronic unpredictable mild stress model to induce depression-like behaviour in mice. Researchers discovered a correlation between this and increased levels of BDNF in the hippocampus. To promote neurogenesis and increase neuroplasticity, a class of growth factors known as neurotrophins is essential [56]. The neurotrophic hypothesis of depression was created based on the fact that BDNF has received more attention than the other neurotrophins [57]. Stress

ISSN: 2583-4053

Volume-3 Issue-5 || October 2024 || PP. 147-159

https://doi.org/10.55544/jrasb.3.5.16

and its effects on synaptic plasticity between neurones are believed to have a role in the aetiology of depression by reducing the availability of neurotrophic substances. The evidence from clinical studies and the function of BDNF both point to its potential role in the development of depression [58]. When it comes to neurotrophic factors, the brain contains the highest concentration of BDNF. Its function is to promote neuronal plasticity and the growth of the nervous system [59][60]. Regarding depression, it was found that patients without antidepressant medication had a lower serum BDNF level, while patients with antidepressant treatment had this decline reversed [61]. Consistent with the previous point, most studies examining EOs and neurotrophic factors have focused on BDNF expression levels. For a clinical trial, researchers sought out mothers whose children had an ADD/ADHD diagnosis.[62] It was assumed by the researchers that this specific group was under a great deal of stress, which affected their psychological well-being [63][64]. Patients' anxiety and depression levels decreased after four weeks of using essential oils (EOs) as part of a treatment program, and their plasma BDNF level, an indicator of the BDNF level in brain tissue, rose significantly [65]. A number of animal models of depression have also shown similar results when testing the efficacy of essential oils.[66].Therapy with musk relieved depression-like behaviour in an animal model of depression generated by persistent mild stress [67]. This was associated with an increase in BDNF expression in the hippocampus [68]. The animal model confirmed this. In a separate study, mice were given a blend of lemon and rosemary essential oils for two months [69]. After that, the mice showed a slightly higher level of BDNF and better cognitive ability. One study looked at the signalling system and tried to determine if the antidepressant effects of d-limonene, a component of orange essential oils, would promote the development of sensory neurons [70]. D-limonene treatment of PC12m3 cells resulted in enhanced neurite outgrowth and p38MAPK pathway activation [71]. The pathway's activity was linked to this. Giving the subject a p38MAPK inhibitor reduced the severity of the d-limonene side effects. The activation of ERK and JNK on the d-limonene route was milder than on the MAPK pathway [72]. Evidence suggests that essential oils (EOs) can have a therapeutic impact on neurotrophic factor regulation [73]. Scientific and clinical investigations are also encompassed in these studies. However, essential oils' active components may modulate neurotrophic factors and directly activate trophic pathways, two processes that could impact brain growth [74][75]. If we want to know how essential oils work as medicines, we need to conduct more mechanistic studies on neurotrophic factor regulation and the signal transduction pathway [76].

Trans-Cinnamaldehyde Reverses Depressive-Like Behaviors in Chronic Unpredictable Mild Stress

Perhaps TCA's capacity to repair morphological damage in hippocampus pyramidal cells is responsible for its antidepressant-like action. On top of that, it blocks the NLRP3 inflammasome and NF-κB pathway, both of which are amplified in rats' prefrontal cortex and hippocampus when exposed to CUMS [77]. For thousands of years prior to its discovery, C. cassia was used in Chinese medicine to treat dyspepsia, anomalies in blood circulation, and inflammatory illnesses. TCA, the principal active ingredient of C. cassia, has potent pharmacological effects, such as reducing oxidative stress, neuroinflammation, and apoptosis. A potent therapy, TCA is useful in the treatment of neurodegenerative diseases including cerebral ischaemic damage [78]. Furthermore, in BV2 microglial cells activated with LPS, TCA can inhibit microglial activation and enhance neuronal survival against neuroinflammation [79]. Cognitive symptoms, a change in motivation, and behavioural coping mechanisms are all hallmarks of clinical depression, and the CUMS rats exhibited actions that were very similar to these symptoms when exposed to various pressures [80]. After extensive testing, researchers have confirmed that the CUMS model accurately describes depressive symptoms. Classical tests that validate behaviours related to depression, the SPT and the FST, are used to evaluate anhedonia and behavioural despair in rats. The CUMS group of rats showed increased behavioural similarities to patients with depression compared to the control group. Significant reductions in body weight gain, increases in immobility time during the FST experiment, and decreases in sucrose consumption were indicators of these behaviours [81]. Finally, we proved that TCA could fix the CUMS rats' faulty conduct. In contrast to the control group, these rats significantly increased their body weight, spent significantly less time immobile during the FST, and ingested significantly more sucrose, all of which proved that this was the case. It was proven that TCA has an antidepressant effect in the lab [82]. Our findings are in line with what we would expect from FLU. The medial prefrontal cortex (Hippocampus) is mainly responsible for emotion control, knowledge acquisition, and the establishment and activation of situational memory [83]. It is also the most susceptible region of the brain to stress injuries. Hippocampal atrophy and decreased numbers of pyramidal cells are observed in depressed patients [84]. The results of this study demonstrated that the hippocampus of CUMS rats was severely altered. Symptoms of this damage included morphological changes, cell arrangement disorder, and a reduction in pyramidal cells in the CA3 region of the hippocampus [85]. Several peer-reviewed scientific journals published the study's conclusions. The CA3 region showed signs of trauma-induced changes in the ultrastructure of pyramidal cells. Among these alterations was a shrinkage or complete absence of the mitochondrial crest, which accompanied the growth of the mitochondria. After inflicting pathological damage to pyramidal cells in the hippocampus CA3 area of CUMS mice, FLU and TCA restored normal cell function. Not only that, but they also

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-5 || October 2024 || PP. 147-159

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restored the ultrastructure of pyramidal cells and increased their number [86].

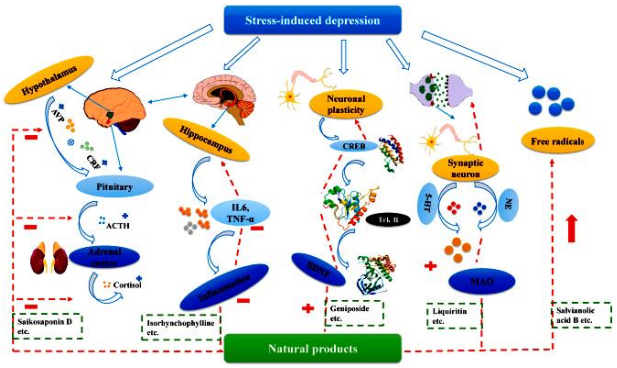

Fig: 2 Treatment of Chronic Unpredictable Mild Stress with Trans-Cinnamaldehyde Reverses Symptoms of Depression

Cinnamon treatment upregulates Neuroprotective Protein Parkin & Dj-1

It has also been used medicinally for a long time. The mediaeval medical community used cinnamon in a variety of remedies for aches and pains, coughs, hoarseness, sore throats, and more. Cinnamaldehyde is a key component of cinnamon, which also contains manganese, dietary fibre, iron, and calcium [88]. By exposing it to oxygen, this chemical can be transformed into cinnamic acid. The liver performs β-oxidation on cinnamic acid, which leads to the creation of benzoate, which can be found as sodium salt (NaB) or benzoyl-CoA. Furthermore, it has been demonstrated that genuine Ceylon cinnamon (Cinnamonum verum) when given orally to mice significantly increases the concentration of NaB in their serum and brain [89]. One reason NaB is significant in medicine is its role as an ingredient in Ucephan, a drug that treats hepatic metabolic disorders linked to hyperammonemia, including urea cycle disorder in children. Ucephan has FDA approval. Along with this, it is widely used as a preservative in numerous food and beauty products. In addition, our previous work demonstrated that NaB modifies T cells at numerous phases and prevents experimental allergic encephalomyelitis, an animal model of multiple sclerosis.

Additionally, we have found that normal astrocytes have an upregulation of DJ-1 due to NaB [90]. Here, we show that activated astrocytes have reduced DJ-1 and Parkin expression, and that activation cells are protected from these harmful proteins when NaB is administered to them. Similarly, mice exposed to MPTP can have DJ-1 and Parkin protected in vivo in the SNpc by cinnamon and NaB. Furthermore, we looked into the potential of cinnamon to protect the nigrostriatum in MPTP-exposed mice. Cinnamon therapy protected TH from the negative effects of MPTP, even if nigral TH disappeared in mice that had been drunk with the drug. Also, the cinnamon therapy restored neurotransmitter levels and blocked the harmful effects of MPTP from reaching the striatal TH fibres. Cinnamon ameliorated functional deficits in MPTP-intoxicated mice, which was the most striking result [91]. No drug-related adverse effects, such as alopecia, a lack of appetite, an infection, etc., were observed in any of the mice utilised during the trial. Based on this, we may conclude that cinnamon probably has no negative side effects. Since cinnamon is a widespread, inexpensive, non-toxic, and all-natural substance, these results may have therapeutic value in Parkinson's disease (PD). The signal transduction mechanisms that govern the expression of DJ-1 and Parkin remain mostly unknown to us [92].

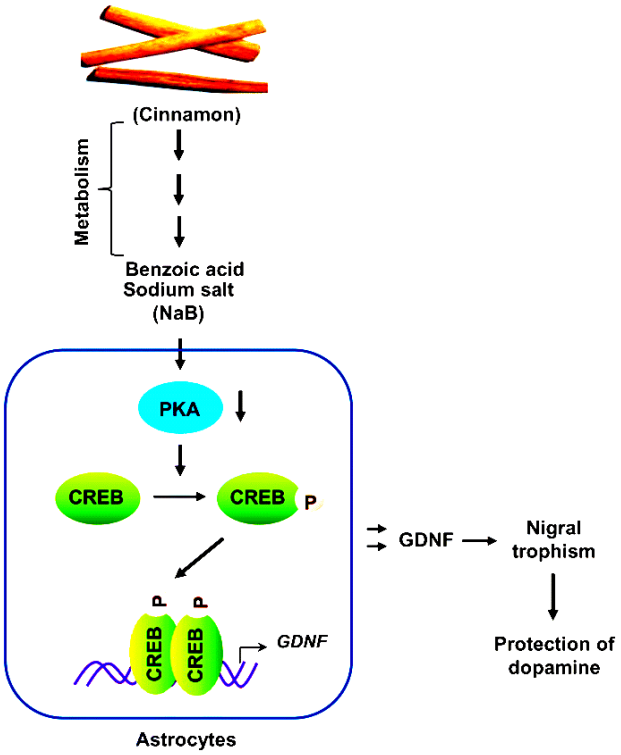

Fig: 3 Cinnamon and its Metabolite Protect the Nigrostriatum in a Mouse Model of Parkinson's Disease Via Astrocytic GDNF

Oxidative stress in neurodegenerative diseases

Neurodegenerative disorders are pathologically defined by a progressive breakdown and eventual death of cells within particular neurological systems. From a clinical perspective, neurodegenerative diseases are defined by their slow onset and long duration [93]. The morphological loss of neurones is associated with gliosis and, more frequently, with protein misfolding and aggregation, which leads to the persistent buildup of aberrant intracellular and extracellular filamentous deposits in some cell types. Many different types of neurodegenerative diseases share these deposits as their defining feature. A higher level of oxidative stress can damage specific types of brain cells [94]. This is called selective neuronal vulnerability, and it happens in neurological diseases. While the majority of brain

ISSN: 2583-4053

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neurones can handle elevated levels of oxidative stress, some subsets of neurones are more vulnerable. One definition of "selective neuronal vulnerability" is the different degrees to which different populations of neurones in the brain are vulnerable to pressures that cause cell death or damage and neurodegeneration. An example of this is how neurones in the entorhinal cortex, hippocampal CA1 area, frontal cortex, and amygdala are particularly vulnerable to the neurodegeneration associated with Alzheimer's disease. In Parkinson's disease, cell death mostly affects dopaminergic neurones in the substantia nigra [95]. Degeneration of neurones in the brain stem, cortex, and spinal cord is a hallmark of amyotrophic lateral sclerosis. Degeneration of spinal motor neurones does, however, happen. The fact that different neurodegenerative diseases affect different parts of the brain in different ways suggests that the causes of these diseases are unique; furthermore, it's plausible that some of the cells involved in the pathophysiology of these diseases may have a common susceptibility to the harmful effects of oxidative stress. Because (1) their energy production is largely dependent on oxidative phosphorylation and (2) they are exposed to high oxygen concentrations—using about 20% of the oxygen we breathe in, even though the brain only makes up 5% of our body weight—neuronal cells are very susceptible to oxidative stress. (3) they have an abundance of metal ions, which build up in the brain with age and can be a powerful catalyst for the creation of oxidative species;[96] (4) they contain a lot of polyunsaturated fatty acids, which are easy to oxidise; and (5) they have low amounts of antioxidants and enzymes that are related to them. The conversion of 1-2% of oxygen consumed to reactive oxygen species (ROS) causes oxidative stress under physiological settings. This percentage grows substantially in the brains of people who are getting on in years. Compared to other tissues, the brain's antioxidant activity is lower. For example, the liver's antioxidant activity is around 10% higher than the brain's. Normally, cells can protect themselves from oxidant attacks by maintaining a homeostatic equilibrium in their surroundings. But when age-related neurodegenerative diseases progress, cells' redox balance-maintaining capabilities deteriorate, resulting in free radical accumulation, mitochondrial dysfunction, and brain damage. Parkin and DJ-1 expressiveness [97].

III. EFFECT ON ACETYLCHOLINESTERASE (ACHE) INHIBITION IN NEURO DISEASE

Tacrine

When it came to treating Alzheimer's disease, tacrine was the pioneering AChE inhibitor. In 1993, it was approved for use in the US with the indication of alleviating symptoms of mild to moderate Alzheimer's disease [99]. The drug was marketed in 10, 20, 30, and 40 milligramme capsules under the brand name Cognex®. The typical dosage of the chemical was 20–40 milligrammes, taken four times day. Clinical trials with tacrine were conducted on a total of 9861 Alzheimer's disease patients and 2706 individuals with Alzheimer's disease as part of a treatment investigational new drug (TIND) program. about the first two years following tacrine's approval for marketing or distribution, the drug's clinical effects were studied in about 190,00 Alzheimer's disease patients in the US. When comparing tacrine's impact on cognitive function to that of the placebo on the Mini Mental State Examination (MMSE), no statistical difference was found. An almost statistically significant benefit of treatment was found within the framework of the Alzheimer's Disease Assessment Scale-cognitive (ADAS-Cog) scale. According to the ADAS noncognitive scale, there was no significant difference between tacrine and in terms of behavioural aberrations [100]. The frequency of cholinergic side effects was substantially higher in those using tacrine. The following symptoms were reported in 29% of the treated patients: three times the normal elevation, nausea and vomiting in 28%, diarrhoea in 14%, dyspepsia or anorexia in 9%, myalgia in 7.5%. Serum aminotransferase levels rose asymptomatically in nearly half of tacrine-treated patients within six to eight weeks of starting treatment. The care of those with Alzheimer's disease was related to this. Due to the fact that it has undesirable side effects, requires four daily doses, is inconvenient, and there are alternative options for treating ChE—!As a result, tacrine was pulled off sale in 2013 [101].

Rivastigmine

The acetylcholinesterase (AChE) inhibitor rivastigmine, whose trade name is carbamoylatine, has a long half-life and selectively affects certain brain areas. The level of inhibition of acetylcholinesterase (AChE) in the CNS compartment is substantially higher than in the periphery, according to both preclinical and human volunteer investigations of rivastigmine [102]. To be more precise, rivastigmine inhibits central AChE by 40%, in contrast to the 10% suppression of plasma butylcholinesterase in healthy volunteers. In addition, the G1 enzymatic form of AChE is the most common in AD brains, and rivastigmine lowers this form positively. Based on data obtained from animal studies, rivastigmine is a more potent AChE inhibitor in the cortex and hippocampus, the brain regions most affected by Alzheimer's and dementia. Rivastigmine can be rapidly and nearly entirely absorbed (amounting to over 96% of the supplied dose) [103]. Contrarily, substantial and saturable first-pass metabolism causes nonlinear pharmacokinetics and a bioavailability of about 35% of the consumed dose. The main metabolite of rivastigmine has at least a tenfold reduced activity against AChE compared to the parent drug. The principal route of elimination for the metabolites of rivastigmine, which undergo complete metabolism, is renal elimination [104].

ISSN: 2583-4053

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Rivastigmine has a short pharmacokinetic half-life, which is in line with the lack of evidence of drug buildup. This is so even though rivastigmine and its principal metabolite concentrations in the plasma of Alzheimer's disease patients are 30–50% higher than in older, healthy individuals [105]. In both healthy volunteers and Alzheimer's disease (AD) patients, the inhibition of acetylcholinesterase (AChE) can be detected in cerebrospinal fluid (CSF) approximately 1.2 hours after oral intake of rivastigmine, which has a widespread distribution throughout the CNS. The inhibitory effects remain for a longer duration in Alzheimer's disease patients compared to healthy people, and the beginning of peak activity is slightly slower in these patients (6.0 against 2.4 hours and 12.0 versus 8.5 hours, among other variations)[106]. When rivastigmine interacts with and inhibits acetylcholinesterase (AChE), it becomes inactive. Also, unlike other AChE inhibitors, rivastigmine is not metabolised by the hepatic cytochrome P-450 (CYP-450) system. Because of this, it is less likely to interact with drugs that are metabolised by specific CYP-450 isoenzymes. Rivastigmine has demonstrated efficacy and safety as a therapy for Alzheimer's disease (AD) in Phase II and Phase III clinical trials [107]. The drug's known pharmacokinetic and pharmacodynamic characteristics are consistent with these results.

Galantamine

The leading cause of dementia and the sixth leading cause of death worldwide is Alzheimer's disease (AD), a progressive neurological disease defined by memory loss and diminished cognitive functioning [107]. Presently, there is no proof that there are therapeutic benefits from the symptomatic treatments used to treat Alzheimer's disease. New, effective medicinal medications are the focus of current research and development efforts. The pharmacological treatment for the illness is still based on cholinesterase inhibitors like galantamine. The reason behind this is the drastic decrease in acetylcholine levels and the resulting loss of cholinergic neurones in the body [108]. This study used a scopolamine model to examine the efficacy of four recently synthesised galantamine derivatives—Gal 34, Gal 43, Gal 44, and Gal 46—in reducing dementia symptoms in mice. Behavioural and biochemical methods were employed to analyse the findings of this research [109]. They were created to have all the advantages of galantamine plus the ability to inhibit β-secretase and positively impact plasma lipids due to their unique makeup. The behavioural tests included the hole-board, T-maze, and step-through inhibitory avoidance tests. However, the biochemical tests included measuring total glutathione and evaluating acetylcholinesterase, monoamine levels in the brain, lipid peroxidation, catalase, glutathione peroxidase, and superoxide dismutase activities, among other things. Evidence suggests that Gal 43, Gal 44, and Gal 46 work particularly well to improve recollection of recent events as well as information stored in longer-term memory [110]. There is also evidence that Gal 46 has a major effect on exploratory behaviour. Although Gal 34's behavioural effects were not as compelling as those of the other three galantamine derivatives, its antioxidant and restorative capabilities were compelling. The fact that all four galantamine derivatives outperformed galantamine in numerous of our trials makes them attractive candidates for the treatment of Alzheimer's disease and encourages additional investigation into this area [111].

IV. AMYLOID B-TARGETED INHIBITORY PEPTIDES FOR ALZHEIMER'S DISEASE

In cellular and animal settings, numerous peptide-based inhibitors have been studied to prevent Aβ aggregation. These inhibitors show promise as new medicines. Although promising outcomes have been observed in experimental research, clinical trials for just a small number of these inhibitory peptides have been initiated [112]. Davunetide peptide with NAPVSIPQ sequence (NAP) was first described by Gozes et al. in 2003. An activity-dependent neuroprotective protein (ADNP) was the source of this peptide. The neuronal cells were protected from toxicity caused by Aβ because NAP could prevent its aggregation, break down pre-formed fibrils, and restore their normal function [113]. While NAP demonstrated promise in phase II trials, a phase III study on moderate cognitive impairment revealed no improvement. The N-methylated peptide PPI-1019, or APAN, has the following sequence: D-(H-[(Me-L)-VFFL]NH2. In laboratory studies, it has the ability to prevent Aβ aggregation and induce toxicity; it is made from the D-enantiomeric Cholyl-LVFFA-NH2 [114]. There is no recognised cure or treatment for Alzheimer's disease at this time; the disease is incurable. Hope is the only thing that remains. And this is why finding potential peptides to test in clinical trials is so important. The existing inhibitory peptides suffer from a great deal of cytotoxicity and poor blood-brain barrier penetration, among other issues [115]. The peptide-nanostructure conjugates (PNCs) method has been the focus of several investigations in an effort to overcome these problems and improve the inhibitory effect even more. Both of these types of materials have the potential to have their capabilities improved by implementing this technique [116][117]. Nanostructures, due to their size and surface modification capabilities, may be considered a vehicle for overcoming poor blood-brain barrier permeability and offering promise for the treatment of neurodegenerative diseases. It is feasible to create multivalent inhibitors that effectively prevent the aggregation of Aβ by coating gold nanoparticles with VVIA and LPFFD. In addition to paving the way for the creation of high-performance peptides, the PNCs method offers an intriguing new viewpoint on the diagnostic and therapeutic domains [118][119].

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https://doi.org/10.55544/jrasb.3.5.16

V. EFFECT ON EXPERIMENTALLY ALLERGIC ENCEPHALOMYELITIS (EAE)

When studying MS (inflammatory demyelinating disease) in humans, this is the model that researchers turn to most often. Multiple sclerosis (MS) is characterised by inflammation, demyelination, axonal loss, and gliosis; the EAE model attempts to approximate these clinical features by simulating the interplay between various immunopathological and neuropathological processes [120]. All of them are brought about by the illness. Brahmachari and Pahan found that sodium benzoate helped with clinical symptoms and slowed the progression of the disease in both the acute and chronic stages of EAE [121]. In both the laboratory and the real world, these tests were carried out. Some of the positive outcomes that NaB produced are detailed below: Myelin basic protein-primed T cells showed less encephalitogenicity when exposed to 1 millimolar NaB in vitro. At dosages ranging from 2.5 to 10 millimolar, it also showed resistance against actively and passively produced EAE in mice [122]. Donor mice had been producing encephalitogenic T cells in vivo, but treatment put a halt to that. Furthermore, it was discovered that 5 mg/ml of NaB caused inflammation, demyelination, and infiltration of mononuclear cells in the central nervous systems of mice that had been passively induced to develop EAE. When tested on mice, Mondal and Pahan found that C. verum powder effectively prevented EAE [123]. The following information describes how the powder, when administered orally to mice at doses of 50 and 100 mg/kg, suppressed the clinical symptoms of acute and chronic EAE: In models of transgenic mice and adoptive transfer of EAE, cinnamon reduced illness severity and blocked the transfer of the virus, respectively. Cinnamon also prevented demyelination in the central nervous system of EAE mice [124]. Blocked inflammation, stabilised gene expression, prevented perivascular cuffing, and maintained the dependability of the blood-brain and blood-spinal cord barriers. The administration of cinnamon also reduced NO generation, which led to an improvement in the control of T regulatory cells [125].

VI. CONCLUSION

Cinnamon may improve cognitive performance, among its many other possible health advantages. Memory, focus, and general brain function are all enhanced by cinnamon. Primarily, cinnamon contains cinnamonaldehyde, epicatechin, eugenol, cinnamic acid, proanthocyanidins, methyl eugenol, and polyphenols, all of which may improve mental well-being. Researchers have shown that cinnamon extract, when taken orally, may alleviate anxiety and depression symptoms while simultaneously enhancing cognitive function and memory. Cinnamon may have natural therapeutic uses in the treatment of neurological disorders and cognitive decline, such as Parkinson's disease and Alzheimer's disease, according to certain studies. For the sake of your liver and other organs, it's crucial that you take cinnamon in moderation and only buy cinnamon from reputable vendors. Following these instructions is essential if you want to enjoy cinnamon's many potential health advantages.

REFERENCES

[1] Jellinger KA. Basic mechanisms of neurodegeneration: a critical update. J Cell Mol Med 2010;14:457-87.

[2] Nieoullon A. Neurodegenerative diseases and neuroprotection: current views and prospects. J Appl Biomed 2011;9:173-83.

[3] Cacciatore I, Baldassarre L, Fornasari E, Mollica A, Pinnen F. Recent Advances in the Treatment of Neurodegenerative Diseases Based on GSH Delivery Systems. Oxid Med Cell Longev 2012;2012:1-12.

[4] Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: An update. Pharmacol Rep 2015;67:195-203.

[5] Craig LA, Hong NS, McDonald RJ. Revisiting the cholinergic hypothesis in the development of Alzheimer's disease. Neurosci Biobehav Rev 2011;35:1397-409.

[6] Francis PT. The interplay of neurotransmitters in Alzheimer's disease. CNS Spectr 2005;10:6-9.

[7] Barbagallo M, Dominguez LJ. Type 2 diabetes mellitus and Alzheimer's disease. World J Diabetes 2014;5:889-93.

[8] Wood-Kaczmar A, Gandhi S, Wood NW. Understanding the molecular causes of Parkinson's disease. Trends Mol Med 2006;12:521-8.

[9] Wakabayashi K, Tanji K, Mori F, Takahashi H. The Lewy body in Parkinson's disease: Molecules implicated in the formation and degradation of a-synuclein aggregates. Neuropathology 2007;27:494-506.

[10] Dodson MW, Guo M. Pink1, Parkin, DJ-1 and mitochondrial dysfunction in Parkinson's disease. Curr Opin Neurobiol 2007;17:331-7.

[11] Warby SC, Montpetit A, Hayden AR, Carroll JB, Butland SL, Visscher H,*et al*. CAG Expansion in the Huntington disease gene is associated with a specific and targetable predisposing haplogroup. Am J Hum Genet 2009;84:351-66.

[12] Craufurd D, Snowden J. Neuropsychological and neuropsychiatric aspects of Huntington's disease. In: Bates GP, Harper PS, Jones L, editors. Huntington's disease. UK: Oxford University Press; 2002. p. 63-94.

ISSN: 2583-4053
Volume-3 Issue-5 || October 2024 || PP. 147-159
https://doi.org/10.55544/jrasb.3.5.16

[13] Novak MJ, Tabrizi SJ. Huntington's disease. BMJ 2010;341:34-40.
[14] Shook SJ, Pioro EP. Racing against the clock: recognizing, differentiating, diagnosing, and referring the amyotrophic lateral sclerosis patient. Ann Neurol 2009;65:10-6.
[15] Neary D, Snowden J, Mann D. Frontotemopral dementia. Lancet Neurol 2005;4:771-80.
[16] Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. Br J Psychiatry 2002;180:140-3.
[17] Lleo A, Greenberg SM, Growdon JH. Current Pharmacotherapy for Alzheimer's disease. Annu Rev Med 2006;57:513-33.
[18] Chen JJ, Swope DM. Pharmacotherapy for Parkinson's Disease. Pharmacotherapy 2007;27:161S-73S.
[19] Bastianetto S, Ramassamy C, Dore S, Christen Y, Poirier J, Quirion R. The *Ginkgo biloba* extract (EGb 761) protects hippocampal neurons against cell death induced by β-amyloid. Eur J Neurosci 2000;12:1882-90.
[20] Lebeau A, Esclaire F, Rostene W, Pelaprat D. Baicalein protects cortical neurons from β-amyloid (25-35) induced toxicity. Neuroreport 2001;12:2199-202.
[21] Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J Neurosci 2001;21:8370-7.
[22] Ono K, Hasegawa K, Naiki H, Yamada M. Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils *in vitro*. J Neurosci Res 2004;75:742-50.
[23] Zhu M, Rajamani S, Kaylor J, Han S, Zhou F, Fink AL. The flavonoid baicalein inhibits fibrillation of α-synuclein and disaggregates existing fibrils. J Biol Chem 2004;279:26846-57.
[24] Joo SS, Lee DI. Potential effects of microglial activation induced by ginsenoside Rg3 in rat primary culture: enhancement of type a macrophage scavenger receptor expression. Arch Pharm Res 2005;28:1164-9.
[25] Chen F, Eckman EA, Eckman CB. Reductions in levels of the Alzheimer's amyloid β peptide after oral administration of ginsenosides. FASEB J 2006;20:1269-71.
[26] Mazza M, Capuano A, Bria P, Mazza S. *Ginkgo biloba* and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. Eur J Neurol 2006;13:981-5.
[27] Aggarwal BB, Harikumar KB, Dey S. Prevention and Treatment of neurodegeneration by spice-derived phytoconstituents. In: Packer L, Sies H, Eggersdorfer M, Cadenas E, editors. Micronutrients and Brain Health. Florida: CRC Press; 2004. p. 281-308.
[28] Srinivasan K. Traditional Indian Functional Foods. In: Shi J, Ho C, Shahidi F, editors. Functional foods of the East. Florida: CRC Press; 2010. p. 51-84.
[29] Ho SC, Chang KS, Chang PW. Inhibition of neuroinflammation by cinnamon and its main components. Food Chem 2013;138:2275-82.
[30] Jain S, Sangma T, Shukla SK, Mediratta PK. Effect of *Cinnamomum zeylanicum* extract on scopolamine-induced cognitive impairment and oxidative stress in rats. Nutr Neurosci 2015;18:210-6.
[31] Barceloux DG. Cinnamon (*Cinnamomum* Species). Dis Mon 2009;55:327-35.
[32] Ranasinghe P, Jayawardana R, Galappaththy P, Constantine GR, de Vas Gunawardana N, Katulanda P. Efficacy and safety of 'true' cinnamon *(Cinnamomum zeylanicum*) as a pharmaceutical agent in diabetes: a systematic review and meta-analysis. Diabet Med 2012;29:1480-92.
[33] Thankamani C, Sivaraman K, Kandiannan K, Peter K. Agronomy of tree spices (clove, nutmeg, cinnamon and allspice)-A review. JOSAC 1994;3:105-23.
[34] Rao PV, Gan SH. Cinnamon: A Multifaceted Medicinal Plant. Evid Based Complement Alternat Med 2014;2014:1-12.
[35] Wong YC, Ahmad-Mudzaqqirand MY, Wan-Nurdiyana WA. Extraction of Essential Oil from Cinnamon (*Cinnamomum zeylanicum*). Orient J Chem 2014;30:37-47.
[36] Hamidpour R, Hamidpour M, Hamidpour S, Shahlari M. Cinnamon from the selection of traditional applications to its novel effects on the inhibition of angiogenesis in cancer cells and prevention of Alzheimer's disease, and a series of functions such as antioxidant, anticholesterol, antidiabetes, antibacterial, antifungal, nematicidal, acaracidal, and repellent activities. J Tradit Complement Med S2015;16:66-70.
[37] Senanayake UM, Wijesekera ROB. Chemistry of Cinnamon and Cassia. In: Ravindran P, Nirmal Babu K, Shylaja M. Cinnamon and Cassia-The Genus *Cinnamomum*. Boca Raton, USA: CRC Press; 2004. p. 80.
[38] Gruenwald J, Freder J, Armbruester N. Cinnamon and Health. Crit Rev Food Sci Nutr 2010;50:822-34.
[39] Prasad KN, Yang B, Dong X, Jiang G, Zhang H, Xie H, *et al*. Flavonoid contents and antioxidant activities from *Cinnamomum* species. IFSET 2009;10:627-32.
[40] Nabavi SF, Di Lorenzo A, Izadi M, Sobarzo-Sanchez E, Daglia M, Nabavi SM. Antibacterial

ISSN: 2583-4053
Volume-3 Issue-5 || October 2024 || PP. 147-159
https://doi.org/10.55544/jrasb.3.5.16

Effects of Cinnamon: From Farm to Food, Cosmetic and Pharmaceutical Industries. Nutrients 2015;7:7729-48.

[41] Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell 2010;140:918-34.

[42] Brahmachari S, Jana A, Pahan K. Sodium Benzoate, a Metabolite of Cinnamon and a Food Additive, Reduces Microglial and Astroglial Inflammatory Responses. J Immunol 2009;183:5917-27.

[43] Hwang H, Jeon H, Ock J, Hong SH, Han YM, Kwon BM, *et al*. Hydroxycinnamaldehyde targets low-density lipoprotein receptor-related protein-1 to inhibit lipopolysaccharide-induced microglial activation. J Neuroimmunol 2011;230:52-64.

[44] Pyo JH, Jeong YK, Yeo S, Lee JH, Jeong MY, Kim SH, *et al*. Neuroprotective Effect of trans-Cinnamaldehyde on the 6-Hydroxydopamine-Induced Dopaminergic Injury. Biol Pharm Bull 2013;36:1928-35.

[45] Anderson JK. Oxidative stress in neurodegeneration: cause or consequence? Nat Med 2004;5:S18-S25.

[46] Hsu FL, Li WH, Yu CW, Hseih YC, Yang YF, Liu JT, *et al. In Vivo* Antioxidant Activities of Essential Oils and Their Constituents from Leaves of the Taiwanese *Cinnamomum osmophloeum*. J Agric Food Chem 2012;60:3092-7.

[47] Kumar S, Vasudeva N, Sharma S. GC-MS analysis and screening of antidiabetic, antioxidant and hypolipidemic potential of *Cinnamomum tamala* oil in streptozotocin induced diabetes mellitus in rats. Cardiovasc Diabetol 2012;11:1-11.

[48] Pandey AK, Mishra AK, Mishra A. Antifungal and antioxidative potential of oil and extracts derived from leaves of Indian spice plant *Cinnamomum tamala*. Cell Mol Biol 2012;58:142-7.

[49] Yang CH, Li RX, Chuang LY. Antioxidant activity of various parts of *Cinnamomum cassia* extracted with different extraction methods. Molecules 2012;17:7294-304.

[50] Abdelwahab SI, Mariod AA, Taha MME, Zaman FQ, Abdelmageed AHA, Khamis S, *et al*. Chemical composition and antioxidant properties of the essential oil of *Cinnamomum altissimum* Kosterm. (Lauraceae). Arab J Chem 2017;10:131-5.

[51] Broks P, Preston GC, Traub M, Poppleton P, Ward C, Stahl SM. Modelling dementia: effects of scopolamine on memory and attention. Neuropsychologia 1988;26:685-700.

[52] Mattson MP, Duan W, Pedersen WA, Culmsee C. Neurodegenerative disorders and ischemic brain diseases. Apoptosis 2001;6:69-81.

[53] Lee EJ, Chen HY, Lee MY, Chen TY, Hsu YS, Hu YL, *et al*. Cinnamophilin reduces oxidative damage and protects against transient focal cerebral ischemia in mice. Free Radic Biol Med 2005;39:495-510.

[54] Lee EJ, Chen HY, Hung YC, Chen TY, Lee MY, Yu SC, *et al*. Therapeutic window for cinnamophilin following oxygen–glucose deprivation and transient focal cerebral ischemia. Exp Neurol 2009;217:74-83.

[55] Panickar KS, Polansky MM, Anderson RA. Cinnamon polyphenols attenuate cell swelling and mitochondrial dysfunction following oxygen-glucose deprivation in glial cells. Exp Neurol 2009;216:420-7.

[56] Panickar KS, Polansky MM, Graves DJ, Urban JF Jr, Anderson RA. A procyanidin type A trimer from cinnamon extract attenuates glial cell swelling and the reduction in glutamate uptake follwing ischemia-like injury *in vitro*. Neuroscience 2012;202:87-98.

[57] Li TJ, Qiu Y, Mao JQ, Yang PY, Rui YC, Chen WS. Protective Effects of Guizhi-Fuling-Capsules on Rat Brain Ischemia/Reperfusion Injury. J Pharmacol Sci 2007;105:34-40.

[58] Jung HW, Mahesh R, Bae SH, Kim YH, Kang JS, Park YK. The antioxidant effects of *Joongpoongtang* 05 on brain injury after transient focalcerebral ischemia in rats. J Nat Med 2011;65:322-9.

[59] Phillips HS, Hains JM, Armanini M, Laramee GR, Johnson SA, Winslow JW. BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. Neuron 1991;7:695-702.

[60] Arenas E, Persson H. Neurotrophin-3 prevents the death of adult central noradrenergic neurons *in vivo*. Nature 1994;367:368-71.

[61] Mamounas LA, Blue ME, Siuciak JA, Altar CA. Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. J Neurosci 1995;15:7929-39.

[62] Jana A, Modi KK, Roy A, Anderson JA, van Breemen RB, Pahan K. Up-regulation of neurotrophic factors by cinnamon and its metabolite sodium benzoate: Therapeutic implications for neurodegenerative disorders. J Neuroimmune Pharmacol 2013;8:739-55.

[63] Lista S, Dubois B, Hampel H. Paths to Alzheimer's disease prevention: from modifiable risk factors to biomarker enrichment strategies. J Nutr Health Aging 2015;19:154-63.

[64] Francis P, Palmer A, Snape M, Wilcock G. The cholinergic hypothesis of Alzheimer's disease: a

ISSN: 2583-4053
Volume-3 Issue-5 || October 2024 || PP. 147-159
https://doi.org/10.55544/jrasb.3.5.16

review of progress. J Neurol Neurosurg Psychiatry 1999;66:137-47.
[65] Boga M, Hacibekiroglu I, Kolak U. Antioxidant and anticholinesterase activities of eleven edible plants. Pharm Biol 2011;49:290-5.
[66] Kumar S, Brijeshlata, Dixit S. Screening of traditional Indian spices for inhibitory activity of acetylcholinesterase and butyrylcholinesterase enzymes. Int J Pharm Biol Sci 2012;3:59-65.
[67] Dalai MK, Bhadra S, Chaudhary SK, Chanda J, Bandyopadhyay A, Mukherjee P. Anticholinesterase activity of *Cinnamomum zeylanicum* L. leaf extract. TANG (Humanitas Medicine, HTM) 2014;4:21-6.
[68] Dalai MK, Bhadra S, Chaudhary SK, Mukherjee P. Anti-cholinesterase potential of *Cinnamomum tamala* (Buch.-Ham.) T. Nees & Eberm. Leaves. Indian J Tradit Know 2014;13:691-7.
[69] Malik J, Munjal K, Deshmukh R. Attenuating effect of standardized lyophilized *Cinnamomum zeylanicum* bark extract against streptozotocin-induced experimental dementia of Alzheimer's type. J Basic Clin Physiol Pharmacol 2014;26:275-85.
[70] Hardy J, Selkoe DJ. The Amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to Therapeutics. Science 2002;297:353-6.
[71] Kim DSHL, Kim JY, Han YS. Alzheimer's Disease Drug Discovery from Herbs: Neuroprotectivity from -Amyloid (1-42) Insult. J Altern Complement Med 2007;13:333-40.
[72] Frydman-Marom A, Levin A, Farfara D, Benromano T, Scherzer-Attali R, Peled S, *et al*. Orally Administrated Cinnamon Extract Reduces β-Amyloid Oligomerization and Corrects Cognitive Impairment in Alzheimer's disease Animal Models. PLoS One 2011;6:1-11.
[73] Ramshini H, Ebrahim-Habibi A, Aryanejad S, Rad A. Effect of *Cinnamomum verum* Extract on the Amyloid Formation of Hen Egg-white Lysozyme and Study of its Possible Role in Alzheimer's Disease. Basic Clin Neurosci 2015;6:29-37.
[74] Ramshini H, Ayoubi F. Inhibitory Effect of *Cinnamomum zeylanicum* and *Camellia sinensis* Extracts on the Hen Egg-White Lysozyme Fibrillation. J Kerman Univ Med Sci 2014;21:290-310.
[75] Bulic B, Pickhardt M, Schmidt B, Mandelkow EM, Waldmann H, Mandelkow E. Development of Tau Aggregation Inhibitors for Alzheimer's Disease. Angew Chem Int Ed Engl 2009;48:1740-52.
[76] Tolnay M, Probost A. The Neuropathological Spectrum of Neurodegenerative Tauopathies. IUBMB Life 2003;55:299-305.
[77] Peterson DW, George RC, Scaramozzino F, LaPointe NE, Anderson RA, Graves DJ, *et al*. Cinnamon Extract Inhibits Tau Aggregation Associated with Alzheimer's disease *in vitro*. J Alzheimers Dis 2009;17:585-97.
[78] Hunt JB, Nash KR, Placides D, Moran P, Selenica MB, Abuqalbeen F, *et al*. Sustained arginase 1 expression modulates pathological Tau deposits in a mouse model of Tauopathy. J Neurosci 2015;35:14842-60.
[79] Goswami SK, Inamdar MN, Jamwal R, Dethe S. Effect of *Cinnamomum cassia* methanol extract and Sildenafil on arginase and sexual function of young male Wistar rats. J Sex Med 2014;11:1475-83.
[80] de la Monte SM, Wands JR. Alzheimer's disease Is Type 3 Diabetes-Evidence Reviewed. J Diabetes Sci Technol 2008;6:1101-13.
[81] Anderson RA, Qin B, Canini F, Poulet L, Roussel AM. Cinnamon Counteracts the Negative Effects of a High Fat/High Fructose Diet on Behaviour, Brain Insulin Signalling and Alzheimer-Associated Changes. PLoS One 2013;8(12):e83243.
[82] Bergman H, Deuschl G. Pathophysiology of Parkinson's disease: from Clinical Neurology to Basic Neuroscience and Back. Mov Disord 2002;17:S28-S40.
[83] Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha synuclein in Lewy bodies. Nature 1997;388:839-40.
[84] Breydo L, Wu JW, Uversky VN. α-Synuclein misfolding and Parkinson's disease. Biochim Biophys Acta 2012;1822:261-85.
[85] Shaltiel-Karyo R, Davidi D, Frenkel-Pinter M, Ovadia M, Segal D, Gazit E. Differential inhibition of α-synuclein oligomeric and fibrillar assembly in Parkinson's disease model by cinnamon extract. Biochim Biophys Acta 2012;1820:1628-35.
[86] Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, *et al*. Mutations in the DJ-1 Gene Associated with Autosomal Recessive Early-Onset Parkinsonism. Science 2003;299:256-9.
[87] Choi J, Sullards MC, Olzmann JA, Rees HD, Weintraub ST, Bostwick DE, *et al*. Oxidative damage of DJ-1 is linked to sporadic Parkinson and Alzheimer diseases. J Biol Chem 2006;281:10816-24.
[88] Ariga H, Takahashi-Niki K, Kato I, Maita H, Niki T, Iguchi-Ariga SMM. Neuroprotective Function of DJ-1 in Parkinson's disease. Oxid Med Cell Longev 2013;2013:1-8.
[89] Dawson TM, Dawson VL. The Role of Parkin in Familial and Sporadic Parkinson's disease. Mov Disord 2010;25:S32-S39.

ISSN: 2583-4053
Volume-3 Issue-5 || October 2024 || PP. 147-159
https://doi.org/10.55544/jrasb.3.5.16

[90] Khasnavis S, Pahan K. Sodium benzoate, a metabolite of cinnamon and a food additive, upregulates neuroprotective Parkinson disease protein DJ-1 in astrocytes and neurons. J Neuroimmune Pharmacol 2012;7:424-35.
[91] Khasnavis S, Pahan K. Cinnamon Treatment Upregulates Neuroprotective Proteins Parkin and DJ-1 and Protects Dopaminergic Neurons in a Mouse Model of Parkinson's disease. J Neuroimmune Pharmacol 2014;9:569-81.
[92] Hornykiewicz O, Kish SJ. Biochemical pathophysiology of Parkinson's disease. Adv Neurol 1987;45:19-34.
[93] Olanow CW, Tatton WG. Etiology and pathogenesis of Parkinson's disease. Annu Rev Neurosci 1999;22:123-44.
[94] Trapp BD, Nave KA. Multiple Sclerosis: An Immune or Neurodegenerative Disorder? Annu Rev Neurosci 2008;31:247-69.
[95] Constantinescu CS, Farooqi N, O'Brien K, Gran B. Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). Br J Pharmacol 2011;164:1079-106.
[96] Brahmachari S, Pahan K. Sodium benzoate, a food additive and a metabolite of cinnamon, modifies T cells at multiple steps and inhibits adoptive transfer of experimental allergic encephalomyelitis. J Immunol 2007;179:275-83.
[97] Mondal S, Pahan K. Cinnamon ameliorates experimental allergic encephalomyelitis in mice via regulatory T Cells: implications for multiple sclerosis therapy. PLoS One 2015;10:1-26.
[98] Moncke-Buchner E, Reich S, Mucke M, Reuter M, Messer W, Wanker EE, *et al*. Counting CAG repeats in Huntington's disease gene by restriction endonuclease EcoP15I cleavage. Nucleic Acids Res 2002;30:1-7.
[99] Patassini S, Begley P, Reid SJ, Xu J, Church SJ, Curtis M, *et al*. Identification of elevated urea as a severe, ubiquitous metabolic defect in the brain of patients with Huntington's disease. Biochem Biophys Res Commun 2015;468:161-6.
[100] Morris SM Jr. Enzymes of arginine metabolism. J Nutr 2004;134:2743S-7S
[101] Abd El-Mawla AM, Schmidt W, Beerhues L. Cinnamic acid is a precursor of benzoic acids in cell cultures of Hypericum androsaemum L. but not in cell cultures of Centaurium erythraea RAFN. Planta. 2001;212:288–293. doi: 10.1007/s004250000394.
[102] Akama KT, Albanese C, Pestell RG, Van Eldik LJ. Amyloid beta-peptide stimulates nitric oxide production in astrocytes through an NFkappaB-dependent mechanism. Proc Natl Acad Sci U S A. 1998;95:5795–5800. doi: 10.1073/pnas.95.10.5795.
[103] Benner EJ, Mosley RL, Destache CJ, Lewis TB, Jackson-Lewis V, Gorantla S, Nemachek C, Green SR, Przedborski S, Gendelman HE. Therapeutic immunization protects dopaminergic neurons in a mouse model of Parkinson's disease. Proc Natl Acad Sci U S A. 2004;101:9435–9440. doi: 10.1073/pnas.0400569101.
[104] Bian M, Liu J, Hong X, Yu M, Huang Y, Sheng Z, Fei J, Huang F. Overexpression of parkin ameliorates dopaminergic neurodegeneration induced by 1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. PLoS ONE. 2013;7:e39953. doi: 10.1371/journal.pone.0039953.
[105] Brahmachari S, Pahan K. Sodium benzoate, a food additive and a metabolite of cinnamon, modifies T cells at multiple steps and inhibits adoptive transfer of experimental allergic encephalomyelitis. J Immunol. 2007;179:275–283. doi: 10.4049/jimmunol.179.1.275.
[106] Brahmachari S, Fung YK, Pahan K. Induction of glial fibrillary acidic protein expression in astrocytes by nitric oxide. J Neurosci. 2006;26:4930–4939. doi: 10.1523/JNEUROSCI.5480-05.2006.
[107] Brahmachari S, Jana A, Pahan K. Sodium benzoate, a metabolite of cinnamon and a food additive, reduces microglial and astroglial inflammatory responses. J Immunol. 2009;183:5917–5927. doi: 10.4049/jimmunol.0803336.
[108] Bridges JW, French MR, Smith RL, Williams RT. The fate of benzoic acid in various species. Biochem J. 1970;118:47–51. doi: 10.1042/bj1180047. [
[109] Brosnan CF, Battistini L, Raine CS, Dickson DW, Casadevall A, Lee SC. Reactive nitrogen intermediates in human neuropathology: an overview. Dev Neurosci. 1994;16:152–161. doi: 10.1159/000112102.
[110] Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron. 2003;39:889–909. doi: 10.1016/s0896-6273(03)00568-3.
[111] Drapier JC, Hibbs JB., Jr Differentiation of murine macrophages to express nonspecific cytotoxicity for tumor cells results in L-arginine-dependent inhibition of mitochondrial iron-sulfur enzymes in the macrophage effector cells. J Immunol. 1988;140:2829–2838.
[112] Fahn S. Parkinson's disease: 10 years of progress, 1997–2007. Mov Disord. 2010;25(Suppl 1):S2–S14. doi: 10.1002/mds.22796.
[113] Ghosh A, Roy A, Liu X, Kordower JH, Mufson EJ, Hartley DM, Ghosh S, Mosley RL, Gendelman HE, Pahan K. Selective inhibition of NF-kappaB activation prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease. Proc Natl Acad Sci U S A.

ISSN: 2583-4053

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https://doi.org/10.55544/jrasb.3.5.16

2007;104:18754–18759. doi: 10.1073/pnas.0704908104.

[114] Ghosh A, Roy A, Matras J, Brahmachari S, Gendelman HE, Pahan K. Simvastatin inhibits the activation of p21ras and prevents the loss of dopaminergic neurons in a mouse model of Parkinson's disease. J Neurosci. 2009;29:13543–13556. doi: 10.1523/JNEUROSCI.4144-09.2009.

[115] Jana M, Anderson JA, Saha RN, Liu X, Pahan K. Regulation of inducible nitric oxide synthase in proinflammatory cytokine-stimulated human primary astrocytes. Free Radic Biol Med. 2005;38:655–664. doi: 10.1016/j.freeradbiomed.2004.11.021.

[116] Jana M, Jana A, Liu X, Ghosh S, Pahan K. Involvement of phosphatidylinositol 3-kinase-mediated up-regulation of I kappa B alpha in anti-inflammatory effect of gemfibrozil in microglia. J Immunol. 2007;179:4142–4152. doi: 10.4049/jimmunol.179.6.4142.

[117] Jana A, Modi KK, Roy A, Anderson JA, van Breemen RB, Pahan K. Up-regulation of neurotrophic factors by cinnamon and its metabolite sodium benzoate: therapeutic implications for neurodegenerative disorders. J Neuroimmune Pharmacol. 2013;8:739–755. doi: 10.1007/s11481-013-9447-7.

[118] Khasnavis S, Pahan K. Sodium benzoate, a metabolite of cinnamon and a food additive, upregulates neuroprotective Parkinson disease protein DJ-1 in astrocytes and neurons. J Neuroimmune Pharmacol. 2012;7:424–435. doi: 10.1007/s11481-011-9286-3.

[119] Khasnavis S, Jana A, Roy A, Mazumder M, Bhushan B, Wood T, Ghosh S, Watson R, Pahan K. Suppression of nuclear factor-kappaB activation and inflammation in microglia by physically modified saline. J Biol Chem. 2012;287:29529–29542. doi: 10.1074/jbc.M111.338012.

[120] Khasnavis S, Roy A, Ghosh S, Watson R, Pahan K. Protection of dopaminergic neurons in a mouse model of parkinson's disease by a physically-modified saline containing charge-stabilized nanobubbles. J Neuroimmune Pharmacol. 2014 doi: 10.1007/s11481-013-9503-3.

[121] Kubota K, Ishizaki T. Dose-dependent pharmacokinetics of benzoic acid following oral administration of sodium benzoate to humans. Eur J Clin Pharmacol. 1991;41:363–368. doi: 10.1007/BF00314969.

[122] Leonard JV, Morris AA. Urea cycle disorders. Semin Neonatol. 2002;7:27–35. doi: 10.1053/siny.2001.0085.

[123] Merrill JE, Ignarro LJ, Sherman MP, Melinek J, Lane TE. Microglial cell cytotoxicity of oligodendrocytes is mediated through nitric oxide. J Immunol. 1993;151:2132–2141.

[124] Mondal S, Martinson JA, Ghosh S, Watson R, Pahan K. Protection of Tregs, suppression of Th1 and Th17 cells, and amelioration of experimental allergic encephalomyelitis by a physically-modified saline. PLoS ONE. 2012a;7:e51869. doi: 10.1371/journal.pone.0051869.

[125] Mondal S, Roy A, Jana A, Ghosh S, Kordower JH, Pahan K. Testing NF-kappaB-based therapy in hemiparkinsonian monkeys. J Neuroimmune Pharmacol. 2012b;7:544–556. doi: 10.1007/s11481-012-9377-9.