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Review Article

The Neurotherapeutic Attributes of Indian Citrus Pickle: A Tangy Tradition with Neuroprotective Secrets

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1. Abstract

Citrus limon (*C. Limon*), commonly known as lemon, represents one of the most significant crops in fruit production. Its unique tangy flavor lends itself to diverse culinary and beverage applications, including use in desserts, ice creams, beverages, and as a quintessential cooking ingredient. This review aims to synthesize the existing literature on the neuroprotective effects of phytochemicals present in lemon pickle, a traditional condiment made from *Citrus limon*. We extracted data from published studies that examine a wide array of phytochemicals found in lemon, including nobiletin, hesperidin, hesperetin, naringin, naringenin, rutin, heptamethoxyflavone (HMF), tangeretin (TGN), quercetin, limonene, eriodictyol, isoimperatorin (IMP), apigenin, luteolin, and vitamin C. This review focuses on *in-vitro*, animal, and human clinical studies exploring the impact of these phytochemicals on neurodegenerative diseases. Our findings showed that Phytochemicals found in lemon pickle demonstrate multi-targeted mechanisms that have the potential to ameliorate various aspects of neurodegenerative diseases. These include decreasing oxidative stress, anti-neuroinflammatory effects, modulation of multiple signaling pathways, and protection against neurotoxicity. In human clinical trials, consumption of citrus phytochemicals was associated with improvements in cognitive performance and other biomarkers, although the underlying mechanisms were not consistently specified. In conclusion, lemon pickle emerges as a promising dietary inclusion that offers a plethora of neuroprotective phytochemicals. Their collective intake through lemon pickle consumption could offer a simple strategy for reducing the risk of neurodegenerative diseases and improving brain health.

2. Keywords: Neuroprotective; Lemon Pickle; *Citrus limon*; Citrus Phytochemicals; Neurodegenerative Diseases; Cognitive Function; Nimbu Achar; Neurotherapeutic Spices

3. Introduction

Lemon pickle, a traditional fermented Indian relish prepared from *Citrus limon*, presents a unique food supplement to harness the collective neuroprotective potential inherent in various phytochemicals found in lemons. These phytochemicals, namely nobiletin, hesperidin, hesperetin, naringin, naringenin, rutin, heptamethoxyflavone (HMF), tangeretin (TGN), quercetin, limonene, eriodictyol isoimperatorin (IMP), apigenin, luteolin, and vitamin C, exhibit substantial efficacy in safeguarding against neurodegenerative processes in experimental studies conducted *in-vitro* and in animal models. Furthermore, the evidence derived from human studies also increasingly points towards the

neuroprotective benefits of the phytochemicals found in citrus fruits, which are also abundant in lemon pickle. These studies, employing various research designs, focus on different citrus-derived compounds and their impact on cognitive health across diverse participant groups.

Moreover, traditional Indian lemon pickle also contains condiments like Carom seeds, rock salt (sendha namak), and red chili powder, all of which offer a blend of phytochemicals, such as quercetin, limonene, eriodictyol, isoimperatorin, apigenin, luteolin, vitamin C, capsaicin and carvacrol, several of which have demonstrated protective effects against neurodegeneration in experimental studies. These compounds effectively reduce the levels of reactive oxygen species (ROS), enhance cognitive function, and mitigate inflammation markers [1]. Lemon peel is perhaps more beneficial than the pulp. The composition of the lemon peel (LP) is stratified into two layers, the outer layer known as epicarp or flavedo, and inner layer called mesocarp or albedo [23]. Notably, the flavedo of lemon peel (LP), contains elevated levels of phenolic compounds and dietary fibers in comparison to the flesh.

The flavedo is notably abundant in phenolic compounds, with a significant presence of flavonoids such as hesperidin, diosmin, eriocitrin, and narirutin. Conversely, the albedo is primarily rich in dietary fibers, particularly pectin [2,3]. Lemon has a traditional and widespread use in pickling. The pickling process not only prolongs the lemon's shelf life, but also has the potential to enhance its nutritional value and health benefits through fermentation. Lemon pickle provides a remarkable combination of flavor and nutrition, making it a perfect condiment and side dish in numerous culinary traditions.

4. Phytochemicals in *Citrus limon*

Citrus limon, commonly known as lemon, is a rich repository of diverse phytochemical compounds **(Figure a)**. The phenolic components present in lemons are primarily composed of flavonoids, a category of secondary metabolites prevalent in plants. Flavonoids are further classified into three main groups: flavanones, flavones, and flavonols, encompassing a collection of more than sixty distinct flavonoids identified within citrus species [1,4,5] .

Figure a

Flavanones comprise the predominant fraction of flavonoids in lemons, constituting as much as 90% of the total. Notably, eriocitrin and hesperidin stand out within the category of flavanones. Different flavonoids exist as glycosides and offer distinct taste characteristics based on their specific structures. Neohesperidosides, commonly found in grapefruits, tend to be distinctly bitter, while rutinosides, present in lemons, are essentially devoid of taste [4,5]. Flavones form an additional category of prevalent phenolic compounds found in lemon fruit. Lemon peels or zest, exhibit notable abundance in flavones like diosmetin 6,8-di-C-glucoside, vicenin-2, and diosmin [4,5].

Within the realm of flavonols, lemon juice boasts substantial amounts of rutin and myricetin. Quercitin and kaempferol are discernible in both the peel (zest) and the juice. Alongside flavonoids, a range of other phenolic compounds are also detectable, albeit in smaller proportions. These encompass hydroxycinnamic acids such as caffeic, cholorogenic, ferulic, sinapic, and p-coumaric acids, as well as benzoic acids like protocatechuic, p-hydroxybenzoic, and vanillic acids [1,4,5].

Regarding its nutritional composition, lemon is characterized by a substantial presence of both nutrient and non-nutrient (fiber) components. It stands out for its remarkable Vitamin C content , supplemented by smaller quantities of vitamins A and B group vitamins. Furthermore, lemon serves as a commendable source of minerals encompassing potassium, calcium, magnesium, phosphorus, copper, iron, manganese, selenium, sodium, and zinc, all present in different levels of concentration [4,5]. Lemon

additionally serves as a notable source of dietary fiber, particularly evident in its peel or zest. Essential oils, with d-limonene being a prominent component , are also present, along with carotenoids. Among these beta-cryptoxanthin is the predominant carotenoid in mature lemons. A significant organic acid found in lemon is citric acid, constituting as much as 8% in dry weight [4,5].

An extensive study unveiled a discernible distribution of these phytochemicals across various segments of the lemon. The zest, encompassing the outer layer of the lemon, is notably rich in total phenolic compounds, boasting an average content of 204.4 ± 9.62 milligrams per gram of extract, expressed in terms of gallic acid equivalents. On the other hand, the inner, fleshy portion, referred to as the Flesh, showcases elevated total flavonoid content, approximately 56.16 ± 14.14 milligrams per gram of extract in quercetin equivalents [4,5].

However, the zest exhibits notably higher levels of flavonols , averaging 26.66 ± 7.07 milligrams per gram of extract in terms of rutin equivalents. Additionally, the zest demonstrates an elevated content of condensed tannins, measuring around 138.33 ± 35.36 milligrams of catechin equivalent per gram of extract. Through Liquid Chromatography-Mass Spectrometry (LC-MS) analysis, the zest extract was found to encompass six specific phenolic compounds: Caffeoyl N-Tryptophan, Hydroxycinnamoyl-Oglucoside acid, Vicenin 2, Eriocitrin, Kaempferol-3-O-rutinoside, and Quercetin-3-rutinoside (Rutin) [4,5].

The distribution of flavonoids in the lemon exhibits intriguing diversity. The zest prominently holds notable quantities of neoeriocitrin, neohesperidin, and naringin, while traces of narirutin are found. In contrast, the seeds are predominantly rich in eriocitrin, albeit with a lesser presence of naringin. Lemon juice is enriched with diosmetin 6,8-di-C-glucoside, vicenin-2, and diosmin. Both the Zest and the juice contain quercetin, kaempferol, rutin, and myricetin. It is worth noting that while the presence of hydroxycinnamic acids is evident, their quantities are comparatively lower [4,5].

This abundant and varied bioactive profile contributes significantly to the pronounced antioxidant attributes and health-enhancing properties of *Citrus limon*. This wealth of nutritional constituents provides valuable insights into its health advantages, rendering it an indispensable resource within the domains of nutrition and health **(Table 1)**.

Class	Phytochemicals
Flavanones	Eriocitrin, Hesperidin, Neoeriocitrin, Naringin
Flavones	Diosmetin 6,8-di-C-glucoside, Diosmetin 6-C-d-glucoside, Vicenin-2, Diosmin
Flavonols	Rutin, Myricetin, Quercetin, Kaempferol
Hydroxycinnamic Acids	Caffeic Acid, Chlorogenic Acid, Ferulic Acid, Sinapic Acid, p-Coumaric Acid
Benzoic Acids	Protocatechuic Acid, p-Hydroxybenzoic Acid, Vanillic Acid
Vitamins	Vitamin C, Vitamin A, B Group Vitamins
Minerals	Potassium, Calcium, Magnesium, Phosphorus, Copper, Iron, Manganese, Selenium, Sodium, Zinc
Other Phenolic Compounds	Caffeoyl N-Tryptophan, Hydroxycinnamoyl-Oglucoside Acid, Vicenin 2, Eriocitrin, Kaempferol-3-O-rutinoside, Rutin
Carotenoids	Beta-Cryptoxanthin
Essential Oils	d-Limonene
Other Organic Acids	Citric Acid
Other Compounds	Scopoletin, Citropten, Dihydroferulic Acid, p-Hydroxybenzoic Acid, Propanoic Acid, Quinic Acid, Dietary Fiber

Table 1: List of Phytochemicals Found in *Citrus limon.*

5. Neurodegenerative diseases (NDDs)

Neurodegenerative disorders encompass a wide range of conditions that result from progressive damage to neuronal cells and nervous system circuitry that is essential for mobility, coordination, strength, sensation, and cognition. These neurodegenerative conditions pose a significant threat to the quality of life for both young and older individuals. In particular, older adults are more susceptible to common neurodegenerative disorders like Alzheimer's disease (AD) [6]. Neurodegenerative disorders include AD and other memory disorders, Ataxia, Huntington's disease, Parkinson's disease, Motor neuron disease, Progressive supranuclear palsy and Amyotrophic Lateral Sclerosis. A few important ones are briefly described below.

Alzheimer's disease (AD)

Alzheimer's disease is a leading neurodegenerative disorder primarily affecting older adults and is characterized by dementia and cognitive decline. Discovered by German scientist Alois Alzheimer, the disease features amyloid plaques and significant neuronal loss [7]. According to the World Health Organization, approximately 50 million people are affected by AD worldwide, and this number is expected to soar to 152 million by 2050. The global economic burden of AD is also staggering, with an annual cost of around $1 trillion [8]. The progression of AD can be divided into four main stages, each characterized by varying degrees of cognitive decline and neuropathological changes [9]. In the pre-symptomatic stage, individuals display no overt clinical signs, although they may experience minor memory loss and subtle neuropathological alterations. As the disease advances to the mild or early stage, symptoms become more noticeable and can include disorientation, depression, and difficulties with daily activities such as managing finances or preparing meals. By the moderate stage, the disease has a more pronounced impact on cognitive function, manifesting as significant memory loss, challenges in performing intellectual tasks, and even failure to recognize close friends and family. Finally, in the severe stage, the pathological changes, caused by aggregation of amyloid-β (Aβ) and tau, spread throughout the entire cortex, leading to profound cognitive and functional impairments **(Figure b)**. This stage is often the precursor to death, as individuals lose the ability to perform basic tasks and require full-time care [9].

Figure b

Parkinson's disease (PD)

Parkinson's disease is another progressive neurodegenerative condition, impacting the motor functions of the central nervous system [10]. Patients experience tremors in limbs, muscular rigidity, postural instability, and cognitive deficits. The causes are generally unknown but are thought to involve genetic mutations in specific genes such as PTEN, PARK7, PINK1, LRRK2, SNCA, and ATP13A2.

Amyotrophic lateral sclerosis (ALS)

Also known as Lou Gehrig's disease, ALS is a severe neurodegenerative disease that affects both lower and upper motor neurons [11]. The disease manifests itself in muscle twitching, weakness, and stiffness, progressing to muscle wasting over time. This leads to difficulties in swallowing, breathing, and speaking. One of the significant etiological factors is mutations in the superoxide dismutase type 1 (SOD1) gene, leading to a cascade of events that damage cellular integrity. Currently, there is no cure for ALS, but treatments exist that can mitigate symptoms and improve quality of life.

Neurodegenerative diseases and conditions severely impact the life quality and physiological functions of those afflicted. Research is ongoing to find effective therapies and cures. While therapies for some of these conditions can alleviate symptoms and improve life quality, there remains an urgent need for curative treatments.

6. Neuropharmacological Targets for pathological dysfunctions in NDDs

Since NDDs represent a complex array of conditions, they are characterized by a multitude of pathological changes, including misfolded proteins, cellular disruptions, and inflammatory processes. These changes culminate in neuronal dysfunction and loss, thereby manifesting the clinical presentations. The complex neuropathological landscape of NDDs presents a fertile ground for therapeutic interventions. Understanding the interconnected pathways and various cellular targets is imperative for the development of effective treatments. The key neuropathological targets reported in various research studies include;

- **Protein Misfolding and Aggregation:** Misfolded proteins play a pivotal role in NDDs, leading to the term "conformational diseases". [12]. Examples include α-synuclein in Parkinson's

Disease (PD), amyloid-β (Aβ) and tau in Alzheimer's Disease (AD), and huntingtin in Huntington's Disease (HD). The misfolding and subsequent aggregation of these proteins sets off a series of detrimental cellular events. Therapeutic strategies could aim at stabilizing the native conformations of these proteins, preventing their misfolding, or enhancing mechanisms that can clear these aggregates from the nervous system.

- **Protein Elimination Pathways:** Cellular pathways responsible for protein turnover, such as the ubiquitin-proteasome system and the autophagy-lysosome pathway, have significant roles in preventing the accumulation of protein aggregates [13]. Dysregulation in these pathways can amplify the pathological accumulation of misfolded proteins. Therapeutic interventions that can restore the functional efficiency of these systems offer a promising approach to managing NDDs.
- **Cellular Stress and Unfolded Protein Response:** The unfolded protein response serves as a cellular mechanism for quality control, aimed at either correcting misfolding or triggering apoptosis if repair is not possible [14]. In NDDs, this system often fails, leading to the accumulation of misfolded proteins. Strategies aimed at bolstering this response could decelerate disease progression by enhancing cellular quality control mechanisms.
- **Energetic Dysregulation and Mitochondrial Dysfunction:** Mitochondrial dysfunctions and energy metabolism imbalances are implicated in various NDDs, like PD and AD [15]. Targets such as the voltage-dependent anion channel and lipid rafts also feature prominently. Interventions aimed at correcting these imbalances could restore neuronal health and slow disease progression.
- **Ion Homeostasis:** Ion imbalances, such as l-glutamate-mediated acute excitotoxicity, are implicated in both acute conditions like cerebral ischemia and status epilepticus, and chronic diseases like AD, ALS, and HD [16]. Interventions that can regulate ion channels or neurotransmitter systems can potentially ameliorate these symptoms.
- **Neuroinflammation and Oxidative Stress:** The activation of microglial cells and the role of nitric oxide in inflammation are increasingly recognized as significant contributors to NDDs [17]. In addition, oxidative stress pathways involving free radicals and reactive oxygen species present therapeutic targets. Anti-inflammatory and antioxidant agents are thus significant in managing NDDs.

Recent research has indicated that *Citrus limon* juice could potentially enhance memory performance. In a study involving a fear-based passive avoidance test in mice, those administered with moderate doses of *Citrus limon* juice exhibited a significant memory improvement after 3 hours, and a slight but significant enhancement after 24 hours. These findings suggest that the flavonoid content in *Citrus limon* juice may have memory-boosting properties, making it beneficial for neurodegenerative conditions [18]. Moreover, Citrus lemon, traditionally used in Indian folk medicine, has been investigated for its potential in treating neurodegenerative conditions. In a study involving stressed and unstressed mice, the administration of lemon oil resulted in memory enhancement, similar to donepezil, a drug used to treat Alzheimer's. This was evident from reductions in brain acetylcholinesterase (AChE) activity, improvements in antioxidant defense (increased catalase, superoxide dismutase, and reduced glutathione levels), and a decrease in plasma corticosterone levels. Lemon oil also reduced TBARS (thiobarbituric acid reactive substances), which are markers of oxidative stress. Thus, lemon oil could potentially ameliorate cognitive impairment and neurodegeneration [19].

7. Methodology

To comprehensively explore the beneficial effects of citrus pickles, specifically lemon pickle, in mitigating the symptoms and pathological processes associated with neurodegenerative disorders, we conducted a rigorous literature review. The search included human clinical trials, lab-based studies, and animal experiments that have been published in peer-reviewed journals. Our inclusion criteria were studies focused on neurological conditions and outcomes positively impacted by the consumption or use of lemon, lemon phytochemicals, or phytochemicals found in citrus fruits. We primarily sourced studies written in the English language, utilizing databases such as PubMed, Google Scholar, and Science Direct for our search. Non-English studies were excluded from this review to maintain the uniformity and comprehensibility of the information gathered.

Search terms used included "citrus pickles," "lemon pickle," "neurodegenerative disorders," "Alzheimer's Disease," "Parkinson's

Disease," "Citrus phytochemicals," "nobiletin," "hesperidin for neurodegenerative disorders," "naringin for neurodegenerative disorders," "rutin for neurodegenerative disorders," "heptamethoxyflavone for neurodegenerative disorders," "tangeretin for neurodegenerative disorders," "quercetin for neurodegenerative disorders," "limonene for neurodegenerative disorders," "eriodictyol for neurodegenerative disorders," "isoimperatorin for neurodegenerative disorders," "apigenin for neurodegenerative disorders," "luteolin for neurodegenerative disorders," "vitamin C for neurodegenerative disorders," " *Citrus limon* and oxidative stress," " *Citrus limon* and neuroinflammation," and " *Citrus limon* for cognitive dysfunction," among others. Subsequently, the selected articles were thoroughly reviewed and synthesized to form the basis of this paper's findings. The research has been classified into three categories: *in-vitro* studies involving cellular and tissue models (Table 2), animal studies (Table 3), and human clinical trials (Table 4).

8. Role of Lemon phytochemicals in ameliorating neurodegeneration

The neuroprotective attributes of lemon are not limited solely to its fresh fruit; they also extend to its preserved forms such as lemon pickle, a traditional culinary preparation rich in these advantageous phytochemicals. The pickling process effectively retains the phytochemical content found in lemons, providing a convenient method for integrating them into one's dietary intake. The incorporation of lemon pickle as a source of these phytochemicals in one's diet, introduces an easy and promising pathway for safeguarding against neurodegenerative diseases.

8A. *IN-VITRO* studies

This section provides an in depth exploration of the empirical laboratory evidence that forms the basis of our understanding regarding the influence of lemon's phytochemicals, including those found in lemon pickle, on neurodegenerative diseases. The findings are summarized in **(Table 2)**.

Phytochemical	Experimental Type	Mechanism Involved	Ref No.
Nobiletin/3',4'-didemethylnobiletin (DTF)	*In vitro* studies	Stimulation of cAMP/PKA/ERK/CREB signalling pathway, Anti-inflammatory, Suppression of BACE1 and promotion of neprilysin expression for Aβ reduction, Amelioration of oxidative stress	[21]
		Regulation of the mitochondrial membrane potential (ΔΨm), Augmentation of cell viability, Reduction of calcium overload	[22]
		Cytoprotection against oxidative stress, Enhancement of glutathione levels, Suppression of ROS accumulation	[23]
Naringin	*In vitro* studies	Enhancement of antioxidant enzyme activity, Elevation of GDNF expression and mTORC1 activity, Activation of Nrf2/ARE pathway	[24-26]
Naringenin	*In vitro* studies	Anti-inflammatory activity, Diminishment of TNF-alpha production and iNOS expression	[27]
		Anti-inflammatory and antioxidant properties, Alzheimer's disease symptom alleviation, Modulation of immune responses in MS	[28,29]
		Impacts on hippocampal function, Suppression of microglial cell activation	[30]
Hesperetin	*In vitro* studies	Mitigation of mitochondrial dysfunction, Anti-neuroinflammatory effects, Suppression of oxidative stress-induced neuronal apoptosis	[31-35]
Apigenin	Cellular studies	Neuroprotective effects against Parkinson's disease, Restoration of cell viability, Activation of MAPK and Nrf2 signaling pathways	[36,37]
Tangeretin (TGN)	*In vitro*	Antioxidant and anti-inflammatory properties, Alleviation of neuroinflammation, Inhibition of microglial activation	[38,39]
Quercetin	Cellular studies	Reduction of proinflammatory genes, Minimization of inflammation-induced neuronal cell death	[40]

3,5,6,7,8,3′,4′-Heptamethoxyflavone (HMF)	Cellular studies	Modulation of ERK/CREB cascade, Anti-neuroinflammatory effects, Induction of BDNF expression	[41]
Rutin	Cellular models	Inhibition of amylin aggregation, Reduction of oxidative stress, Suppression of reactive oxygen species and nitric oxide induced by PrP	[42,43]
Eriodictyol	Cellular studies	Attenuation of inflammation and oxidative stress, Modulation of the MAPKs and NF-κB pathways, Diminishment of oxidative stress through the Nrf2/Keap1 pathway	[44]
Didymin	Cellular studies	Antioxidant activity, Improvement of cell viability, Reduction of intracellular ROS levels, Inhibition of caspase-3 activation	[45]

Table 2: *In-Vitro* studies in cell models of Neurodegenerative conditions demonstrating Neuro-protective actions of phytochemicals contained in Lemons.

Lemon Peel

Citrus limon (lemon) peel research has uncovered six compounds exhibiting potent acetylcholinesterase inhibitory effects, thereby suggesting their potential utility in therapeutic strategies for Alzheimer's disease. Neoeriocitrin, isonaringin, naringin, hesperidin, neohesperidin, and limonin have displayed significant bioactivity in a PC12 cell model, indicating promising implications for Alzheimer's disease management [20].

Nobiletin

Nobiletin, a naturally occurring flavonoid, has shown extensive neuroprotective capabilities across cellular cultures and tissue samples, facilitated through multiple mechanisms. It has demonstrated potential to stimulate the cAMP/PKA/ERK/CREB signalling pathway, which is integral to memory formation. This compound can mitigate the decrease in CREB phosphorylation triggered by amyloid-beta (Aβ) in AD. Moreover, nobiletin exhibits capability in ameliorating oxidative stress, including endoplasmic reticulum (ER) stress in various cell models, thereby offering resistance against apoptosis. Its anti-inflammatory properties have been demonstrated by its inhibition of proinflammatory mediator production and secretion in microglial cell models, suggesting a potential role in neuroinflammation mitigation. Furthermore, nobiletin may aid in reducing Aβ levels by suppressing BACE1, an enzyme crucial to Aβ production, and promoting the expression and activity of neprilysin, a vital protease in Aβ degradation. These encouraging *in vitro* results highlight nobiletin's potential as a therapeutic agent in neurodegenerative conditions [21].

Nobiletin has also demonstrated potential in averting neurotoxic calcium overload and cell death by regulating the mitochondrial membrane potential (ΔΨm). Studies have shown that nobiletin treatment considerably augments cell viability and reduces calcium overload and reactive oxygen species generation in neurons exposed to toxic levels of glutamate. A study by Lee., *et al*. 2018, revealed that the neuroprotective effects of nobiletin were due to the latter's actions on the influx of potassium ions (K+) into mitochondria, highlighting the significance of mitochondrial K+ channels [22].

Investigation on nobiletin's metabolite, 3',4'-didemethylnobiletin (DTF), has revealed its robust cytoprotective effects against oxidative stress-induced cell death. Nobiletin and DTF both enhance intracellular levels of the antioxidant glutathione, by increasing the expression of glutamate-cysteine ligase. Particularly, DTF suppressed reactive oxygen species accumulation, stimulated heme oxygenase-1 expression, and hindered the inflammatory transcription factor NF-κB. Both compounds also triggered the ERK, JNK, and Akt pathways involved in cell survival and proliferation, with the PI3K/Akt pathway proving essential for their protective effects [23]. These observations indicate potential applications in combating neurodegenerative conditions.

Naringin

Naringin, a flavanone unique to citrus, has demonstrated noteworthy neuroprotective qualities in PC12 cells (a cell line derived from a pheochromocytoma of the rat adrenal medulla,

having an embryonic origin from the neural crest), when exposed to cytotoxic milieu induced by hydrogen peroxide. It effectively preserves cell viability and reduces oxidative stress. Furthermore, it enhances the activity of antioxidant enzymes and reduces lipid peroxidation positioning itself as a potential dietary antioxidant for interventions related to neurodegenerative disease [24]. In a neurotoxin-induced model of Parkinson's disease, naringin has shown the ability to elevate the expression of glial cell line-derived neurotrophic factor and activate the mammalian target of rapamycin complex 1 activity within dopaminergic neurons in the brains of rats. Its anti-inflammatory effects and promotion of neurotrophic factor production collectively contribute to the protection of the nigrostriatal dopaminergic projection, suggesting its potential for preventing dopaminergic degeneration [25]. Moreover, naringin has displayed promise in slowing the progression of Parkinson's disease progression through its antioxidant properties, reduction of lipid peroxidation , and activation of the Nrf2/ARE pathway [26]. Additionally, naringin and its metabolite, naringenin, have exhibited neuroprotective effects in the context of cerebral ischemia. They achieve this by enhancing blood circulation, modulating the HIF-1α/AKT/mTOR signaling pathway, and alleviating oxidative stress [26]. Crucially , in primary mixed glial cells, naringenin has demonstrated robust anti-inflammatory activity by reducing TNF-alpha production, inhibiting iNOS expression and decreasing nitric oxide production. These potent anti-inflammatory effects are mediated through the inhibition of p38 MAPK phosphorylation and downstream STAT-1 signaling [27].

Hesperidin

Citrus flavanones, including hesperidin, hesperetin, and neohesperidin have demonstrated protective effects against hydrogen peroxide-induced neurotoxicity in PC12 cells. They enhance cell viability, reduce oxidative stress, and maintain cellular integrity, suggesting their potential roles in mitigating neurodegenerative disease [28]. Hesperidin, which is abundant in citrus fruits, exhibits antioxidant and anti-inflammatory properties by scavenging free radicals and reducing pro-inflammatory mediators. It has shown promise in alleviating symptoms associated with Alzheimer's disease by regulating neuroinflammation and reducing beta-amyloid deposition. Additionally, hesperidin may ameliorate autoimmune demyelinating diseases, like multiple sclerosis, by modulating immune responses and promoting myelin repair [29]. Furthermore, hesperidin has a positive impact on hippocampal function, which is often compromised in neurodegenerative disorders. It exerts this by its neuroprotective effects, suppressing microglial cell activation, promoting neuronal survival, and enhancing memory consolidation. Interestingly, hesperidin also shows promise in alleviating depressive-like behaviors in various models, highlighting its therapeutic value in neurological conditions [30].

Hesperetin

Hesperetin nanocrystals (HstN) have displayed potential in alleviating mitochondrial dysfunction in a cellular model of Alzheimer's disease. This is evident through increased ATP levels, enhanced mitochondrial respiratory chain complex activity, and a reduction in reactive oxygen species [31]. In another research study hesperetin exhibited anti-neuroinflammatory effects in BV-2 microglial cells. These effects included a decrease in nitric oxide production, reduced secretion of inflammatory cytokines , and down-regulation of ERK1/2 and p38 MAPK (mitogen-activated protein kinase) phosphorylation [32]. Furthermore, hesperetin and its metabolite, 5-nitro-hesperetin, have demonstrated potential in preventing oxidative stress-induced neuronal apoptosis in cortical neurons exposed to hydrogen peroxide. This is primarily achieved through the activation of Akt/protein kinase B and ERK1/2 signaling pathways [33]. Other studies underscore hesperetin's neuroprotective potential, observed in its modulation of microglial cell activation, attenuation of neuroinflammatory responses, reduction in oxidative stress, and potential augmentation of autophagy. A regulatory role in inflammatory responses is further established by its inhibition of the activation of MAPK ERK1/2, p38, and the transcription factor NF-κB in LPS-stimulated BV-2 microglial cells [35]. All these findings buttress the suitability of hesperitin use for the prevention and treatment of neurodegenerative diseases [34].

Apigenin

The flavonoid apigenin has shown promise in terms of potential neuroprotective effects against Parkinson's disease. In a pre-treatment scenario apigenin protected rat adrenal pheochromocytoma cells (PC12) which serve as a Parkinson's disease model, from neurotoxicity induced by the neurotoxin 1-methyl-4-phenylpyridinium ion (MPP+). Apigenin increased cell viability, reduced oxidative damage, and suppressed apoptosis,

endorsing its neuroprotective potential [36]. Furthermore , a study examining the protective properties of both apigenin and luteolin against cytotoxicity induced by 4-hydroxy-2-nonenal (4-HNE) ,a compound associated with neurodegenerative disorders, demonstrated the restoration of cell viability and the upregulation of the unfolded protein response (UPR) following interventions with these flavones. Both flavones activated the MAPK and Nrf2 signaling pathways, facilitating adaptive stress responses, and restoring endoplasmic reticulum homeostasis [37].

Tangeretin

Tangeretin (TGN), a natural flavonoid found in citrus fruit peel, is renowned for its potent antioxidant and anti-inflammatory properties, has demonstrated therapeutic potential across various models of neurodegenerative disorders . TGN has been shown to bolster the viability of human brain microvascular endothelial cells and stimulate the activity of the antioxidant enzyme superoxide dismutase (SOD) . It also reduces the levels of reactive oxygen species (ROS) and malondialdehyde (MDA), a well established marker of oxidative stress . These protective effects are attributed to TGN's capacity to inhibit the c-Jun N-terminal kinases (JNK) signaling pathway, a pivotal mechanism in cellular stress responses [38]. Moreover, TGN has shown promise in mitigating neuroinflammation by inhibiting microglial activation, a process closely associated with neuroinflammatory responses in neurodegenerative diseases, and a contributor to neurotoxicity in in- vitro- models. This suppression, coupled with a decrease in inflammatory mediators such as NO, PGE_2, TNF-α, IL-1β, and IL-6,along with the inhibition of MAPK protein levels and the NF-κB signaling pathway, underscore TGN's potential therapeutic role in addressing neuroinflammation and neurodegenerative diseases associated with microglial activation [39].

Quercetin

Polyphenols such as quercetin and resveratrol have shown a reduction in proinflammatory genes with lipopolysaccharide-treated glial cells. Additionally, quercetin has demonstrated a decrease in inflammation-induced neuronal cell death. These findings suggest potential therapeutic benefits, particularly in the context of Parkinson's disease, and the promising utility of quercetin as an anti-inflammatory agent in the realm of neurodegenerative diseases [40].

Heptamethoxyflavone (HMF)

The polymethoxylated flavone (PMF) known as 3,5,6,7,8,3′,4′-Heptamethoxyflavone (HMF), primarily sourced from citrus fruits, has demonstrated neuroprotective properties in various experimental models. It has been observed to modulate the ERK/CREB cascade in cultured cortical neurons, potentially mitigating cognitive dysfunction. Moreover, it has exhibited anti-neuroinflammatory effects in models of lipopolysaccharide-induced neuroinflammation, and demonstrated antidepressive effects in models of stress-induced depression. Notably, HMF has induced BDNF expression in C6 cell cultures, highlighting its potential as a neurotrophic agent . Additionally , its analog, 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone (5-OH-HMF), has enhanced neurite outgrowth in PC12 cell cultures [41]. These collective findings collectively underscore the potential therapeutic significance of HMF in managing neurodegenerative diseases.

Rutin

Rutin, a flavonoid antioxidant, has emerged as a protective agent against neurodegeneration.

Recent research has unveiled a connection between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD), where amylin, a hormone, and β-amyloid (Aβ) share common pathological features and elicit similar neurotoxic effects. In this context, rutin has demonstrated the ability to inhibit amylin aggregation, thereby reducing its neurotoxicity. Rutin's capacity to reduce oxidative stress and pro-inflammatory cytokines, preserve mitochondrial function, and enhance antioxidant enzyme activity all suggest its potential in preventing the onset of AD and maintaining brain health during the aging process or in the face of neurodegenerative conditions [42].

Furthermore, Rutin displayed promise in addressing prion disorders, which are progressive neurodegenerative diseases marked by neuronal loss and the abnormal accumulation of scrapie prion protein (PrP) . Rutin effectively suppresses reactive oxygen species and nitric oxide induced by PrP while also preserving neurotrophic factors that are typically depleted due to PrP accumulation. Notably, rutin's capacity to inhibit apoptotic pathways in neuronal cells highlights its potential therapeutic benefits for prion diseases and other neurodegenerative disorders [43].

Eriodictyol

Eriodictyol, a flavonoid found in citrus, has been shown to alleviate neuroinflammation through the modulation of the MAPKs and NF-κB pathways (which are regulated by reactive oxygen species), restore cell viability, and reduce oxidative stress by engaging the Nrf2/Keap1 pathway. Additionally, eriodictyol increases the expression of silent information regulator 1 (Sirt1), thereby countering synaptic dysfunction [44]. Consequently , these findings underscore the potential of eriodicytol in promoting and preserving neurological health.

Didymin

The citrus flavonoid Didymin has demonstrated antioxidant activity and neuroprotective potential against oxidative damage induced by hydrogen peroxide. It effectively improves cell viability, lowers intracellular levels of reactive oxygen species (ROS), and enhances the activity of antioxidant enzymes [45]. Additionally, Didymin safeguards against mitochondrial dysfunction and inhibits caspase-3 activation and the phosphorylation of c-Jun N-terminal kinase – pathways that play crucial roles in apoptosis. These findings underscore the neuroprotective capabilities of Didymin particularly in the context of mitigating oxidative damage, which enhances its potential for utilization in the management of neurodegenerative diseases.

8B. Animal studies

The empirical evidence derived from animal studies provides valuable insights into the impact of lemon's phytochemicals, including those present in lemon pickle, on neurodegenerative diseases. These studies contribute to our understanding of the potential beneficial effects of these compounds and their role in mitigating neurodegeneration **(Table 3)**.

Phytochemical	Experimental Type/ Animals	Neurodegenerative Model	Possible Mechanisms/Pathways	Ref Number
Nobiletin	AD, PD and cerebral ischemia models	Alzheimer's disease (AD), Parkinson's disease (PD), Cerebral ischemia	Preserving cholinergic innervation, decreasing Aβ accumulation, activating ERK, reducing oxidative stress	[46-51]
Hesperidin	AD, PD, MS, EAE models	Alzheimer's disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Experimental autoimmune encephalomyelitis (EAE)	Promoting neural stem cell proliferation via AMPK/CREB signaling, reducing Aβ accumulation, modulating pro-inflammatory mediators, antioxidant effects	[52-58]
Hesperetin	Various animal models	Various neurodegenerative diseases	Modulating PI3-Akt and MAPK signaling pathways, controlling apoptotic effector proteins	[59,60]
Naringin	PD and AD models	Parkinson's disease (PD), Alzheimer's disease (AD)	Enhancing mitochondrial function, diminishing apoptosis via Nrf pathway, elevating GDNF levels in neurons, triggering mTORC1, reducing TNF-α levels	[61-67]
Heptamethoxyflavone (HMF)	Animal models of cerebral ischemia	Memory disorders, cerebral ischemia	Triggering ERK1/2, provoking CREB phosphorylation, increasing BDNF expression	[68,69]
Naringenin	AD model	Alzheimer's disease (AD)	Enhancing cognitive function, decreasing oxidative stress, preserving ChAT-positive neurons, diminishing hippocampal neuron damage	[70]
Rutin	Animal models of trimethyltin-induced hippocampal damage and HD	Alzheimer's disease (AD), Huntington's disease (HD)	Mitigating hippocampal damage, preserving pyramidal neurons, inhibiting microglia and pro-inflammatory cytokines, enhancing spatial memory and synapse formation, reducing beta-amyloid aggregation	[71-73]

Tangeretin (TGN)	PD, cerebral ischemia-reperfusion injury, and epilepsy models	Parkinson's disease (PD), Cerebral ischemia, Epilepsy	Mitigating 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dementia, improving motor function, reducing memory deficits, downregulating inflammatory cytokines, activating PI3K/Akt pathway	[74-76]
Quercetin	Rat	Aluminum-induced oxidative stress	Mitigates ROS, improves mitochondrial functionality and biogenesis, anti-inflammatory and anti-apoptotic properties, and cholesterol transport	[77-82]
Limonene	Stroke-prone hypertensive rats	Ischemic cerebral injury	Lowers blood pressure, enhances cognitive function, reduces inflammation, affects gene expression related to oxidative stress	[83]
Eriodictyol	Mouse	Alzheimer's disease model	Reduces amyloid-beta aggregation, inhibits Tau hyperphosphorylation, antiferroptotic effect through Nrf2/HO-1 signaling pathway via the vitamin D receptor	[84]
Isoimperatorin (IMP)	Mouse	Aluminum chloride-induced neurotoxicity	Reduces inflammation, oxidative stress, and diminished neurotransmitter levels, regulation of antioxidant responses and inflammation via Nrf2 and MAPK pathways	[85]
Apigenin	Mouse	Alzheimer's disease model	Anti-inflammatory, anticarcinogenic, and antioxidant properties, enhances learning and memory, and cerebral blood flow	[86]
Luteolin	Mouse	Obesity-related neuroinflammation and cognitive impairment, Alzheimer's disease model	Mitigates neuroinflammation and neuronal insulin resistance, improves cognitive performance, reduces amyloid beta deposition	[87,88]
Vitamin C (Vit C)	Animal model of Parkinson's Disease	Parkinson's Disease (PD)	Antioxidant and anti-inflammatory properties, reduces loss of dopaminergic neurons, improves locomotor activity, modulates inflammation	[89]

Table 3: Phytochemicals in Lemons which demonstrate protective properties against neurodegeneration in Animal models.

Nobiletin

Nobiletin, a flavonoid derived from citrus fruits, exhibits significant therapeutic potential in various animal models of neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and cerebral ischemia. In AD models, Nobiletin has demonstrated notable neuroprotective and memory-enhancing properties. These benefits are attributed to several mechanisms, including the preservation of cholinergic innervation, reduction of amyloid-beta (Aβ) accumulation, activation of the extracellular signal-regulated kinase (ERK), and mitigation of oxidative stress [46]. In PD animal models, Nobiletin has been shown to ameliorate motor and cognitive deficits by stimulating intracellular pathways related to dopamine synthesis and by inhibiting neuroinflammation . It restores dopamine levels by enhancing tyrosine hydroxylase (TH) activity and partially protects dopaminergic neurons from MPP^+-induced toxicity [46].

In models of cerebral ischemia, Nobiletin has proven effective in reducing neuronal death and brain damage, diminishing memory

impairment and motor deficits by mitigating ischemia-reperfusion injury [46]. Further, recent studies have suggested Nobiletin's role as a clock-modulatory agent, influencing circadian rhythms, and promoting healthy aging by enhancing cellular energy metabolism [47]. It has also demonstrated potential in treating neurodegenerative conditions characterized by dysregulated CRE (cAMP response element)-dependent transcription by enhancing CRE- dependent transcription, and promoting neurite outgrowth [48]. Interestingly, Nobiletin's impact on memory enhancement appears selective, showing improvements in emotional and novelty recognition memory, but not in spatial memory [49]. Recent studies have shown Nobiletin's ability to preserve neuronal integrity, reduce oxidative stress and inflammation in the hippocampus, and improve cognitive function in rats injected with Aβ1-40, an AD model [50]. Furthermore, it has displayed potent effects in regulating mitochondrial function, decreasing mitochondrial ROS production, enhancing ATP production, and restoring neuronal viability [51]. These collective findings suggest the potential of Nobiletin as a therapeutic agent for neurodegenerative disorders [46-51].

Hesperidin

Hesperidin (HSP), a bioflavonoid primarily found in citrus fruits, possesses significant neuroprotective, anti-inflammatory, and antioxidant properties. In an Alzheimer disease model, HSP notably promoted neural stem cell proliferation through the activation of the AMPK/CREB signaling pathway, without affecting neuronal and astrocyte differentiation **(Figure 1)**. It also reduced the accumulation of amyloid-beta and improved memory dysfunction in 5xFAD mice, achieved through the AMPK/BDNF/TrkB/CREB signaling pathway [52]. In another study, co-administration of HSP and AlCl3 exhibited a protective effect against cognitive impairment, oxidative stress, and apoptosis induced by AlCl3 in male Wistar rats, suggesting potential therapeutic benefits in neurodegenerative diseases associated with oxidative stress and apoptosis [53]. In a Parkinson's disease (PD) animal model induced by 6-OHDA, HSP effectively prevented memory impairment, depressive-like behavior, and oxidative stress. It achieved this by mitigating the reduction in glutathione peroxidase (GPx) and catalase (CAT) activity, total reactive antioxidant potential, and dopamine levels in the striatum of aged mice. Furthermore, HSP reduced ROS levels and glutathione reductase activity [54]. In an AD study using transgenic APP/PS1 mice, oral administration of HSP improved non-cognitive behaviors, reduced β-amyloid deposition, and attenuated neuroinflammatory reactions, indicating the behavioral improvements may be attributed to a reduction in Aβ deposition and neuroinflammation [55,56].

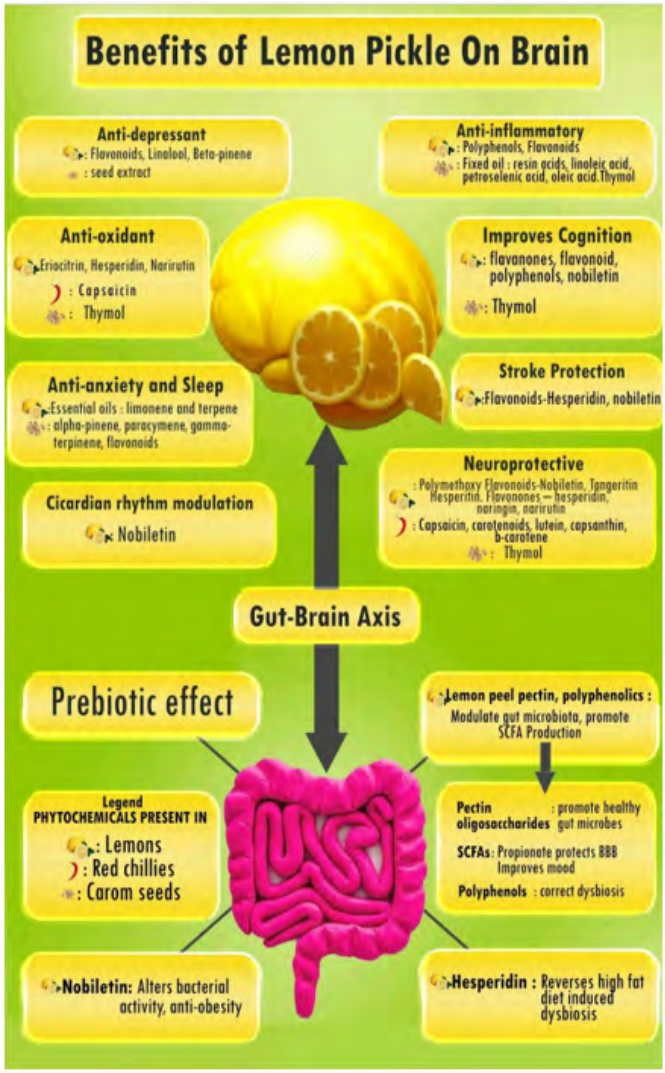

Figure 1: Beneficial effects of lemon pickle on the brain. The actions of the different phytochemicals present in lemons, red chili and carom seeds are shown, along with the prebiotic effects of lemon peel (from Bali S (2023) The Indian Delicacy Nimbu Achar: Your Lemony Pathway to Brain Health. Curr Res Cmpl Alt Med 7: 179.).

Additionally, HSP has demonstrated its ability to restrict microglial activation in AD models, reduce the production of pro-inflammatory mediators and suppress inflammation-related signaling pathways [45,46]. In demyelinating diseases of the central nervous system (CNS), such as multiple sclerosis (MS) and experimental autoimmune encephalomyelitis, hesperidin (HSP) has shown benefits. It suppresses T-cell proliferation, activates regulatory T cells, reduces microglial cells, and decreases demyelination. Moreover, it exhibits cytoprotective and antioxidant effects in CNS tissues, promoting myelin repair and reducing myelin loss [57,58].

Hesperidin has also proven beneficial for hippocampal dysfunction associated with cognitive impairments in conditions like MS and EAE. It protects neurons from cell death, promotes the survival of neuronal progenitor cells, and suppresses microglial cell activation. Additionally, hesperidin has exhibited potential benefits in depressive-like behaviors in various models [57,58]. In summary , the neuroprotective effects of hesperidin, its antioxidant and anti-inflammatory properties, and its potential benefits for depressive-like behaviors underscore its therapeutic value in neurodegenerative and demyelinating disorders.

Hesperetin

Derived from hesperidin, hesperetin is a flavanone that possesses neuroprotective attributes, effectively mitigating oxidative stress, inflammation, and neurotoxicity. These factors are critical in the context of neurodegenerative diseases. Hesperitin achieves this neuroprotection by influencing signaling pathways, including PI3-Akt and MAPK and by modulating apoptotic effector proteins [59]. Moreover, hesperetin has been shown to promote neuronal survival, reduce proinflammatory cytokines, lower oxidative stress markers, and enhance cognitive function in animal models. Hence it holds promise for the treatment of central nervous system disorders due to its anti-inflammatory, antioxidative, and potential autophagy-modulating effects [60].

Naringin

Naringin is a flavonoid found in citrus fruits. In a study involving rats exhibiting Parkinson's disease (PD)-like symptoms, Naringin was found to alleviate behavioral abnormalities, enhance mitochondrial function, and reduce apoptosis through the Nrf pathway [61]. Utilizing a mouse model of PD, researchers demonstrated that Naringin preserved dopaminergic projections, activated mTORC1, and suppressed microglial activation [62]. In another rodent study, Naringin was found to elevate glial cell line-derived neurotrophic factor (GDNF) levels in neurons, trigger mTORC1, and reduce tumor necrosis factor-alpha (TNF-α) levels in microglia [63]. Additionally, in a Caenorhabditis elegans model, Naringin extended lifespan, enhanced stress tolerance, reduced lipofuscin accumulation, and delayed PD progression through the activation of the transcription factor DAF-16 [64]. These findings suggest that Naringin has the potential to play a neuroprotective role in PD models, by enhancing neurotrophic factors in dopaminergic neurons, regulating cellular growth pathways, curtailing lipofuscin accumulation and decreasing inflammatory cytokines in glial cells.

In a rat model of Alzheimer's disease (AD) Naringin demonstrated its ability to protect against cognitive impairment and oxidative damage induced by colchicine [65]. Further, in another study using aluminum chloride-induced AD rats, Naringin improved memory performance, ameliorated neurochemical changes, and modulated tau, iNOS, and LC3 protein expressions. These effects countered oxidative and autophagic stress [66,67]. This evidence reinforces Naringin's potential in addressing neurodegenerative disorders, as it can improve cognitive abilities, regulate neurochemical alterations, and manage oxidative and autophagic stress in the brain.

Heptamethoxyflavone (HMF)

HMF, a compound derived from Citrus peels, activates the extracellular signal-regulated kinases 1/2 (ERK1/2) within the mitogen-activated protein kinase (MAPK) signaling cascade, a pathway associated with synaptic plasticity. HMF significantly stimulates the phosphorylation of the cAMP response element-binding protein (CREB), a vital step in the signaling pathway leading to structural modifications associated with long-term potentiation, crucial for long-term memory formation. Notably, when administered to mice treated with the NMDA receptor antagonist MK-801, HMF successfully alleviated the decline in spatial learning performance induced by MK-801 [68]. These findings underscore HMF's role as a neurotrophic agent, highlighting its potential in the treatment of memory disorders.

In mouse models of cerebral ischemia, HMF has demonstrated its ability to stimulate the phosphorylation of ERK1/2 and CREB in the hippocampus. This activation leads to an increase in the expression of brain-derived neurotrophic factor (BDNF) in the hippocampal dentate gyrus [69]. These findings suggest that HMF has the potential to enhance BDNF production in astrocytes, potentially promoting neurogenesis following brain ischemia. This could have significant implications for the treatment and recovery of individuals who have experienced cerebral ischemia [69].

Naringenin

In a rat model of Alzheimer's disease(AD), pretreatment with Naringenin (NAR), a polyphenolic compound, led to preservation of choline acetyltransferase (ChAT)-positive neurons, improved cognitive function, reduced oxidative stress, and decreased hippocampal neuron damage [70]. These findings highlight the potential utility of NAR as a neuroprotective agent for neurodegenerative conditions, particularly in the context of AD [70].

Rutin

Rutin, a flavonoid found in citrus fruits and green tea, has displayed notable neuroprotective potential in various studies. In rat studies, Rutin alleviated hippocampal damage caused by trimethyltin. It effectively preserved pyramidal neurons, suppressed microglial activation, and reduced pro-inflammatory cytokines. These effects correlated with enhancements in spatial memory and synapse formation, underscoring Rutin's potential for protection against neurodegenerative conditions [71]. In a rat model of Huntington's disease (HD), Rutin pretreatment counteracted the detrimental effects produced by 3-Nitropropionic acid (3-NP), a neurotoxic agent used to induce HD-like symptoms. This suggests Rutin's capacity to mitigate oxidative/nitrosative damage in the brain, indicating its therapeutic potential in managing HD [72].

In transgenic mice models of Alzheimer's disease, Rutin inhibited beta-amyloid aggregation and reduced nitric oxide production as well as pro-inflammatory cytokines. It also restored antioxidant levels by enhancing superoxide dismutase activity and improving the balance of glutathione and glutathione disulfide. Additionally, Rutin reduced microgliosis and astrocytosis while lowering the levels of interleukin-1β and interleukin-6 in the brain. These findings lend credence to Rutin's potential role in neurodegenerative disease therapies, particularly in the context of Alzheimer's disease [73].

Tangeretin (TGN)

TGN, a potent flavonoid with antioxidant and anti-inflammatory properties, has shown significant therapeutic promise in animal studies focused on neurodegenerative disorders. In a rodent model of Parkinson's Disease (PD), TGN effectively mitigated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dementia, improved motor function, and reduced memory deficits. The neuroprotective action was suggested to occur through the downregulation of inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and IL-2, and suppression of TNF-α, COX-2, and iNOS signaling pathways, which are implicated in neuroinflammation [74].

Another study underscored TGN's extensive neuroprotective effects. These effects ranged from enhancing dopamine content and reducing oxidative stress in a PD model to attenuating brain damage in a cerebral ischemia-reperfusion injury model. Furthermore, TGN demonstrated potential benefits in an epilepsy model by reducing seizure severity, possibly through the activation of the PI3K/Akt pathway and the regulation of matrix metalloproteinases [75]. This diverse range of neuroprotective effects highlights the potential of TGN as a versatile therapeutic agent in the treatment of neurodegenerative diseases. In a dementia model of Parkinson's disease , TGN was found to reduce MPTP-induced dopaminergic degeneration, hippocampal neuronal loss, and the expression of inflammatory mediators like COX-2 and iNOS. These findings suggest that TGN may have the potential to prevent neuroinflammation and dementia associated with PD [76].

Quercetin

Quercetin has show effectiveness against aluminum-induced oxidative stress in rat brains. It reduces ROS levels and enhances mitochondrial functionality and biogenesis by upregulating key biomarkers such as PGC-1α, NRF-1, NRF-2, and Tfam [77]. These findings highlight the potential therapeutic value of quercetin in neurodegenerative diseases characterized by mitochondrial dysfunction. In a rat model of intracerebral hemorrhage (ICH), treatment with quercetin resulted in a reduction in inflammatory markers and the number of apoptotic cells , suggesting its potential therapeutic use in mitigating ICH-induced brain injuries [78]. Quercetin has also been observed to increase apoE levels, which

are crucial for cholesterol transport and lipid homeostasis in the central nervous system. The observed decrease in insoluble Aβ levels in the cortex of amyloid model mice indicates the therapeutic potential of quercitin for Alzheimer's disease [79].

Interestingly, quercetin displayed a dual role in mice, depending on dietary conditions. It reduced oxidative stress and improved cognition under high-fat dietary conditions, but exerted pro-oxidant effects and impaired cognition under balanced conditions [80]. Additionally, the compound mitigated high-cholesterol-induced neurotoxicity in aged mice by reducing oxidative damage reduction and activating AMP-activated protein kinase (AMPK), indicating its potential therapeutic role in neurodegenerative diseases associated with cholesterol dysregulation [81]. Quercetin has also exhibited neuroprotective properties against aluminum-induced neuronal death. It achieved this by reducing ROS production, increasing mitochondrial SOD activity, and circumventing apoptotic cell death mechanisms [82]. These findings highlight quercetin's therapeutic potential in addressing aluminum-induced neurodegeneration.

Limonene

Limonene has demonstrated potential therapeutic properties in mitigating ischemic cerebral injury, a common occurrence observed in stroke cases. Its observed effects include lowered blood pressure, enhanced cognitive function, reduced inflammatory markers, and decreased cerebral infarct size in stroke-prone hypertensive rats. The compound's antioxidant attributes and its influence on the expression of genes related to inflammation and oxidative stress suggest that plants rich in limonene may serve as promising therapeutic agents for addressing cerebral and vascular damage caused by stroke [83].

Eriodictyol

Eriodictyol has demonstrated potential in mitigating cognitive deficits, reducing amyloid-beta (Aβ) aggregation, and inhibiting Tau hyperphosphorylation and neurotoxicity induced by Aβ1-42 oligomers in an Alzheimer's disease mouse model. Notably, it also displayed an antiferroptotic effect through the activation of the Nrf2/HO-1 signaling pathway via the vitamin D receptor (VDR). Consequently, eriodictyol may provide a potential treatment approach for AD by ameliorating memory impairment and pathological changes through the Nrf2/HO-1 signaling pathway [84].

Isoimperatorin

Isoimperatorin (IMP) has demonstrated neuroprotective effects in mice exposed to neurotoxic levels of aluminum chloride (AlCl3), that typically induces inflammation, oxidative stress, and diminished neurotransmitter levels. The mechanism underlying this protective effect is believed to involve the regulation of antioxidant responses and inflammation, with a particular focus on key pathways such as Nrf2 and MAPK [85].

Apigenin

Apigenin, a flavonoid known for its anti-inflammatory, anticarcinogenic, and antioxidant properties, has displayed promising outcomes in countering amyloid-β (Aβ)-induced neurotoxicity, a significant factor in AD. When administered orally to mice apigenin led to improved learning and memory, reduced oxidative damage, and enhanced regional cerebral blood flow among other beneficial effects. These findings highlight the potential therapeutic value of apigenin in the management of Alzheimer's disease [86].

Luteolin

Luteolin, another flavonoid, has been studied for its potential in alleviating obesity-related neuroinflammation and cognitive impairment. Supplementation with luteolin has shown several beneficial effects, including reduced weight gain, improved glucose metabolism, and mitigation of neuroinflammation and neuronal insulin resistance in mice fed a high-fat diet. Increased levels of BDNF, SYP, and PSD-95 have been associated with improved cognitive performance. These findings suggest that luteolin may have therapeutic value in managing cognitive impairment induced by obesity [87].

In another study, luteolin was found to be effective in alleviating cognitive dysfunction associated with chronic cerebral hypoperfusion, a condition contributing to cognitive deficits in Alzheimer's disease. Luteolin's antioxidant and anti-inflammatory properties, along with the downregulation of NF-**κB** and BACE1 expression, led to a reduction in amyloid beta (Aβ) deposition. These findings underscore its potential therapeutic role in Alzheimer's disease [88].

Vitamin C

Vitamin C (Vit C) has been investigated for its potential role in neurodegenerative diseases, such as Parkinson's Disease (PD), due to its antioxidant and anti-inflammatory properties. A study by De Nuccio., *et al*. using an animal model of PD found that Vit C reduced the loss of dopaminergic neurons, mitigated microglial cell activation and astrogliosis, and improved gait and locomotor activity. Vit C also downregulated inflammatory cytokines and upregulated anti-inflammatory proteins. Additionally, Vit C inhibited the activation of the NLRP3 inflammasome. These findings suggest that Vit C modulates inflammation and may provide neuroprotective effects in PD [89].

8C. Human studies

Despite limited human studies on phytochemicals contained in lemons, recent research indicates neuroprotective properties of bioactive compounds found in lemons and other citrus fruits. These phytochemicals, such as flavonoids and polyphenols found in citrus fruits, are being recognized for their potential in managing and preventing neurodegenerative conditions. Preliminary studies suggest these citrus-derived compounds may help ameliorate neurodegenerative conditions by various mechanisms **(Table 4).**

Author (s)	Experiment Type/No. of Participants	Intervention	Findings	Possible Mechanism	Ref. No.
Hashimoto., *et al*. (2022)	Randomized, double-blind, parallel-armed design; healthy elderly Japanese individuals	Perilla seed oil and nobiletin-rich ponkan powder	Higher cognitive index scores in the group receiving the combined intervention compared to those only receiving Perilla seed oil	Enhances serum BDNF levels and antioxidant potential, increases levels of ω-3 fatty acids in red blood cells	[90]
Yamada., *et al*. (2021)	Randomized, double-blind, placebo-controlled study; elderly Japanese participants	Nobiletin-rich extract from C. depressa peel in a test food called Nobilex®	Improvement in memory functions in the group receiving the nobiletin-containing test food	Not specified	[91]
Seki., *et al*. (2013)	Pilot clinical study; Alzheimer's disease patients already receiving donepezil	Nobiletin-rich Chinpi (NChinpi) in conjunction with donepezil	Potential prevention of cognitive decline in AD patients already receiving donepezil	Not specified	[92]
Neshatdoust., *et al*. (2016)	Two randomized controlled trials; adults aged 26-70 and older adults aged 62-75	High-flavonoid or low-flavonoid fruit and vegetables; high-flavanol or low-flavanol cocoa drinks	Improvements in cognitive performance and increased serum BDNF levels	Changes in BDNF expression and signaling pathways may play a role	[93]
Nakamura., *et al*. (2022)	Randomized, double-blind, placebo-controlled study; adults aged 60 to 75 years	Beverages containing quercetin glycoside	Improvement in reaction time and potential protection against decreased cerebral blood flow and amyloid β accumulation	Not specified	[95]
De Luca, P., *et al*.	Longitudinal Study with 69 patients	Palmitoylethanolamide and Luteolin (PEA-LUT) treatment with or without olfactory training	Significant improvement in odor identification scores, reduction in parosmia prevalence and mental clouding severity over three months	The anti-inflammatory and neuroprotective properties of PEA-LUT may play a role	[97]

Table 4: Citrus's phytochemicals with protective properties against neurodegenerative conditions in human trials.

Figure 2: Lemon juice and peel contain powerful anti-oxidants, anti-apoptic and anti Acetyl cholinesterase (which increase the neurotransmitter acetylcholine) phyto-compounds, that can prevent and even improve symptoms in neuro-degenerative disorders.

Nobiletin, a citrus flavonoid primarily found in lemon and other citrus fruits, has garnered attention in recent years for its potential benefits in treating neurodegenerative diseases. Specifically it has been identified as a possible therapeutic agent for conditions like Alzheimer's disease (AD). In a 12-month long study involving healthy elderly Japanese individuals, researchers investigated the effects of two interventions: Perilla seed oil (PO) and a combination of PO with nobiletin-rich ponkan powder (POPP). The study found that the group receiving the combination of PO and POPP demonstrated higher cognitive index scores at the end of the study compared to the group that received PO alone. Additionally, increased levels of ALA (alpha - linolenic acid) and DHA (docosahexaenoic acid) were observed in red blood cell plasma membranes and there were elevated serum levels of brain derived neurotrophic factor (BDNF). The findings suggest that the use of Perilla seed oil with nobiletin-rich ponkan powder may hold potential in improving cognitive function and addressing age-related cognitive impairment in healthy elderly individuals [90].

Indeed, there is growing evidence suggesting the potential benefits of nobiletin, which in citrus fruits is present mostly in the peels, in managing neurodegenerative diseases, particularly in the context of cognitive function. One study examined the effects of a combination food containing a nobiletin-rich extract from Citrus peel in elderly participants. Those who consumed this food once a day for 16 weeks showed significantly higher scores for both "general memory" and "visual memory" compared to the placebo group [91]. This study re-enforces the finding that nobiletin-containing food may be beneficial in alleviating memory dysfunction in healthy elderly individuals.

Further, a pilot clinical study tested the effects of nobiletin-rich Chinpi, a component of dried Citrus peels used in Kampo medicine, on dementia in patients already receiving donepezil. The patients treated with the nobiletin-rich Chinpi had their cognitive function preserved over a year, while the control group demonstrated cognitive decline. The study concluded that a year-long intervention with nobiletin-rich Chinpi prevented cognitive decline in Alzheimer's patients receiving donepezil [92]. The above studies show the potential role of citrus fruits, particularly the nobiletin-rich citrus peel, as a natural therapeutic agent in managing neurodegenerative diseases. It is important to recognize that the best way to ingest lemon peel is by way of lemon pickle.

The beneficial effects of various other citrus and lemon phytochemicals on cognitive function and neurodegenerative disorders are further supported by several human studies. For instance , the flavone group of flavonoids found in citrus fruits has been associated with cognitive improvements, as demonstrated in two randomized controlled trials. In one study, adults consuming high-flavonoid diets demonstrated increased levels of brain derived neurotrophic factor (BDNF) in serum, and experienced significant enhancements in cognitive performance [93]. In another study, Rutin, a flavonoid found in citrus fruits, exhibited positive effects on metabolic parameters and increased BDNF levels in a study involving patients with type 2 diabetes mellitus [94]. Beyond its influence on metabolic factors, rutin was also linked to a decrease in inflammatory and oxidative stress markers, implying its potential role in managing neurodegenerative conditions. Further, Quercetin, another citrus flavonoid, showed promise in improving cognitive function, reflected in reaction time, in older adults who consumed a quercetin glycoside beverage during the study period [95]. While the exact mechanisms are not fully understood, the study suggested that quercetin may help prevent the decline in

cerebral blood volume, flow, and brain activity associated with aging. These collective findings underscore the potential of citrus and lemon phytochemicals, such as flavones, rutin, and quercetin, to positively impact cognitive function and potentially contribute to the management of neurodegenerative conditions **(Figure 2).**

Interestingly, the potential benefits of citrus and lemon phytochemicals extend to various neurological applications. Notably, a dietary supplement containing three prominent citrus flavonoids, including rutin, luteolin, and quercetin led to significant improvements in communication, daily living skills, and overall behavior in children with autism spectrum disorders [96]. This suggests that these phytochemicals found in citrus may have a positive impact on neurodevelopmental disorders. Additionally, a combination of palmitoylethanolamide and luteolin demonstrated the ability to improve olfactory dysfunction and memory in patients with long COVID [97].

8D. Bioactive compounds in Citrus that improve brain functioning in humans in general

Auraptene, a citrus coumarin, has shown potential protective effects against cognitive decline. In a randomized controlled trial, consumption of auraptene was associated with a difference in the percentage change in cognitive function, indicating its potential role in preserving cognitive abilities [98]. These findings collectively suggest that various citrus and lemon phytochemicals, including flavones, rutin, quercetin, luteolin, and auraptene hold promising potential in the prevention and treatment of neurodegenerative conditions. Their mechanisms of action encompass modulating BDNF levels, improving metabolic parameters, reducing inflammation and oxidative stress, and potentially preserving cognitive function **(Table 5)**.

Author(s)	Experiment Type/No. of Participants	Intervention	Findings	Ref. No.
Bazyar., *et al*. (2023)	Double-blind, placebo-controlled trial; Type 2 diabetes mellitus (T2DM) patients	500 mg rutin flavonoid daily	Significant improvements in metabolic parameters, reduced inflammatory and oxidative stress markers, and increased BDNF levels	[94]
Taliou., *et al*. (2013)	Open-label pilot study; children aged 4-10 with autism spectrum disorders (ASD)	Dietary supplement containing luteolin, quercetin, and rutin	Significant improvements in communication, daily living skills, social domains, and overall behavior	[96]
Igase, M., *et al*.	Randomized, placebo-controlled, double-blind study with 84 cognitively normal adult volunteers	Consumption of auraptene-enriched test juice	No improvement in cognitive function compared to baseline, but significant difference in the percentage change in cognitive function between test and placebo groups	[98]
Kean, R. J., *et al*. (2015)	Double-blind, randomized crossover design with 37 healthy older adults	Daily consumption of high-flavanone (305 mg) 100% orange juice vs low-flavanone (37 mg) orange-flavored cordial for 8 weeks	Significant improvement in global cognitive function after consuming high-flavanone orange juice	[99]

Alharbi, M. H., *et al*. (2016)	Randomized, double-blind, counterbalanced order with middle-aged adult males consuming FR orange juice vs placebo	Consumption of 240-ml FR orange juice (272 mg of flavonoids) vs a calorie-matched placebo drink	Improved performance on tests of executive function and psychomotor speed, and higher subjective alertness	[100]
Lamport, D. J., *et al*. (2016)	Single-blind, randomized, crossover design with 24 healthy young adults consuming high-flavanone drink vs control drink	Consumption of high-flavanone (70.5 mg) drink vs a control drink matched for energy and vitamin C but devoid of flavanones	Significant increase in regional perfusion in the inferior and middle right frontal gyrus, and improved performance on the Digit Symbol Substitution Test	[101]
Zhang, S., *et al*. (2017)	Cohort study with 13,373 participants comparing frequency of citrus consumption	Regular consumption of citrus	Frequent citrus consumption associated with a lower risk of developing dementia	[102]
Bruno, A., *et al*. (2017)	Clinical trial with 20 outpatients with schizophrenia	Supplementation with bergamot polyphenolic fraction (BPF) at a daily dose of 1000 mg for 8 weeks	Significant improvement in perseverative errors and semantic fluency, and a trend towards improvement in other cognitive variables	[103]

Table 5: Bioactive compounds in Citrus that improve brain functioning in humans.

Furthermore, the intake of flavone-rich orange juice, as studied by Alharbi., *et al*. and Kean., *et al*. led to improvements in cognitive performance, particularly in the domains of working memory and executive function, in middle-aged adults [99,100]. Another research study by Lamport., *et al*. showed that consumption of a high-flavanone drink significantly increased regional perfusion in certain areas of the brain, resulting in improved performance on cognitive tests among healthy young adults [101]. Additionally, epidemiological studies have suggested that frequent consumption of citrus fruits may be linked to a reduced risk of dementia. For example, a cohort study by Zhang., *et al*. identified a negative correlation between citrus consumption and the incidence of dementia [102]. Additionally, beyond flavonoids, citrus fruits are rich in polyphenolic compounds, including those found in bergamot, which may have therapeutic benefits. In a pilot study, Bruno., *et al*. discovered that supplementation with bergamot (a type of orange) polyphenolic fraction improved cognitive outcomes in patients with schizophrenia, suggesting potential applicability in managing cognitive dysfunctions associated with this condition [103].

Moreover , citrus flavonoids may play a role in promoting mental health and well being by reducing depressive symptoms, possibly through modulation of the gut microbiome. A randomized controlled study conducted by Park., *et al*. discovered that the consumption of flavonoid-rich orange juice brought about changes in the gut microbiome, which could potentially lead to improvements in depressive symptoms [104]. Additionally, Chang., *et al*. (2016) observed a reduced risk of depression among midlife and older women with a higher intake of dietary flavonoids, including flavanones from citrus fruits [105].

9. Beneficial Effects of other Lemon pickle Ingredients in Neurodegenerative Conditions

9A. Black salt

Though called black salt, it actually looks purplish, is a component of lemon pickle. It is made by roasting crystalline salt along with the three myrobalans and Babool (*Acacia nilotica*) bark in powdered form. After firing in brick kilns for 12-14 hours, these herbs become incorporated into the “black”and salt. Thus

the beneficial effects of the myrobalans are transferred to the food products which contain black salt. The three myrobalans are *Phyllanthus emblica* (*Indian gooseberry* or Amla), Harad (*Terminalia chebula*) and *Terminalia bellerica* (Behera). Besides black salt, the other key ingredients of the lemon pickle are red chilies and carom seeds **(Figure 3)**.

9B. *Phyllanthus emblica* (PE, *Amla*)

Amla berry, a key component of black salt, demonstrates significant potential in the management of neurodegenerative conditions, particularly Alzheimer's disease (AD). Uddin., *et al*. (2016) evaluated the effects of ethanolic extracts from *Phyllanthus emblica* (PE) fruits on cognitive functions and various biochemical markers in Swiss albino male rats. Administered over 12 days at doses of 100 and 200 mg/kg body weight, these extracts notably improved memory retention and cognitive responses, evidenced through passive avoidance and rewarded alternation tests. Moreover, the biochemical assessments revealed significant enhancements in the activities of antioxidant enzymes—superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px)—and a reduction in acetylcholinesterase (AChE) activity, which is often elevated in AD patients [106]. Jang., *et al*. (2017) investigated the effects of Amla on retinal degeneration in an AD mouse model. The administration of Indian gooseberry extract for 21 days prior to amyloid beta (Aβ) injection markedly reduced oxidative stress within the retina and mitigated Aβ-induced histological damage. Interestingly, key neuronal markers such as neurofilament-L (NF-L), thymocyte differentiation antigen 1 (Thy-1), and sirtuin 1 (SIRT1) were preserved, indicating the extract's protective role against neurodegenerative changes [107]. Moreover, in 2015, Biswas., *et al*. demonstrated the significant inhibitory effects of a crude methanol extract (CME) from dried *P. emblica* fruits, on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), suggesting that the extract of *P. emblica* could enhance neurotransmitter levels and reduce oxidative stress and inflammation, key factors in AD pathology [108]. Additionally, Rajalakshmi., *et al*. (2019) assessed the neuroprotective properties of *P. emblica* extracts on human neural cell lines (PC12) exposed to glutamate-induced toxicity. Their results confirmed that *P. emblica* showed antioxidant activity, with notable improvements in cell viability and reductions in cytotoxicity [109]. A recent investigation by Chen., *et al*. (2023) examined the impact of a water extract of Indian gooseberry fruit (WEIG) and its bioactive compound gallic acid (GA) on cognitive decline induced by a high-fat diet (HFD) in rats. The study highlighted significant reductions in fat accumulation and improvements in learning and memory deficits. Both WEIG and GA were effective in decreasing brain levels of Methylglyoxal and advanced glycation end products, reducing insulin resistance, and lowering the production of inflammatory cytokines and malondialdehyde (MDA). Furthermore, they were shown to decrease Alzheimer's disease-related protein levels while enhancing antioxidant enzyme activities and increasing levels of anti-inflammatory cytokines. Notably, the study found that WEIG and GA mitigated pathways such as receptor for advanced glycation end products, MAPK, and NF-κB [110].

9C. Harad (*Terminalia chebula*)

Harad, also known as Haritaki, is another key component of black salt, that demonstrates significant neuroprotective properties against neurodegeneration. A study by Pugazhendhi., *et al*. (2018) investigated the effects of methanolic extracts from *T. chebula* fruit and *T. arjuna* bark and discovered their potent antioxidant activities, including radical scavenging and metal chelating capabilities. The extracts also exhibited significant anticholinesterase activity, inhibiting both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), important in managing AD symptoms. Additionally, they were found to inhibit Aβ (amyloid-β) aggregation and destabilize mature fibrils, indicating potential as therapeutic agents for AD treatment due to the bioactive compound 7-methyl gallic acid (7-MG) [111]. Another study by Shen., *et al*. (2017) focused on the neuroprotective effects of *T. chebula* extracts and ellagic acid on beta-amyloid 25-35 (Aβ25-35)-induced cell toxicity in PC12 cells. They confirmed that the extracts of *T. chebula*, as well as isolated ellagic acid, significantly reduced cell toxicity, reactive oxygen species (ROS), and calcium influx, which are associated with Aβ-induced damage. These findings suggest that components like ellagic acid contained within *T. chebula* can reduce oxidative stress and improve cell viability, suggesting a potential role in AD therapy [112]. Further, Zhao., *et al*. (2021) evaluated the effects of *T. chebula* water extract (TWE) on Alzheimer's disease (AD) pathology using transgenic Caenorhabditis elegans (worms) models that express Aβ, leading to Alzheimer's-like symptoms. The study observed significant reductions in Aβ-induced paralysis and Aβ aggregation in the worms treated with TWE., Moreover, TWE treatment was found

to enhance the nuclear localization of transcription factors DAF-16 and HSF-1, increasing the expression of the heat shock protein Hsp-16.2, which is known to inhibit Aβ aggregation. These findings indicate that TWE mitigates Aβ toxicity and delays Aβ-induced paralysis in C. elegans primarily through the DAF-16/HSF-1/Hsp-16.2 pathway, highlighting its potential as a neuroprotective agent for AD management [113].

Furthermore, another study by Kim., *et al*. (2018) investigated the potential anti-amnesic effects of TWE in mice with scopolamine-induced amnesia. The study explored the impact of TCE on the cholinergic system and oxidative stress markers. Mice received TCE orally at doses of 100 or 200 mg/kg for fourteen days, with scopolamine administered intraperitoneally during the last seven days to induce memory impairment. TCE treatment reversed the learning and memory deficits caused by scopolamine, reduced AChE activity, and increased levels of ACh and choline acetyltransferase. Furthermore, TCE exhibited strong antioxidative effects by reducing ROS, NO, and MDA levels, which are associated with oxidative stress and neurodegeneration in AD. These results suggest that TCE can effectively ameliorate amnesia, and could be helpful in neurodegenerative disease that affect memory and cognitive function [114]. Similarly, Lakshmi., *et al*. (2018) also examined the effects of TCE on scopolamine-induced amnesia in an experimental rat model for AD, and obtained similar results. Their study confirmed the neuroprotective potential and memory-enhancing properties of TCE, as it improved cognitive functions and learning [115].

9D. *Terminalia bellerica* (Behera)

Terminalia bellerica (TB), found in black salt, demonstrates significant neuroprotective properties against neurodegenerative diseases. Goud and Shabnamkumari (2020), studied the methanol extract of *Terminalia bellerica* (METB) for its neuroprotective properties, particularly against aluminum chloride and haloperidol-induced amnesia in mice. METB demonstrated potent AChE inhibition, which is a valuable therapeutic action for Alzheimer's disease treatment. Also, the antioxidant activity assays indicated high efficacy in reducing oxidative stress and lipid peroxidation. Additionally, *in vivo*, METB improved cognitive impairments in passive avoidance and plus maze tasks and reduced catalepsy in the rota rod apparatus and bar test. The anti-amnesic effects and cognitive enhancement potential of METB seen in mice, indicate the potential use of TB to improve the symptoms of neurodegenerative conditions such as AD [116].

Further, numerous studies have also investigated the combined use of *Emblica officinalis, Terminalia chebula* and *Terminalia bellirica* (called *Triphala,* three myrobalans) against neurodegenerative conditions, including Parkinson's disease and AD. One study in 2020 investigated the effect of methanolic extracts from the three fruits of *Triphala* for their anti-Parkinson's activities in male Wistar rats, induced with Parkinson's-like symptoms using haloperidol. Pre treatment with PE and TB at a dose of 300 mg/kg administered orally significantly reduced catalepsy and reversed haloperidol-induced biochemical changes such as increased lipid peroxidation and depletion of antioxidants like superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). These findings suggest that PE and TB can mitigate Parkinson's disease symptoms and protect against oxidative stress [117]. Another previous study by Sukma., *et al*. 2012, had found the neuroprotective potential of the three myrobalans. The researchers used the methanol extracts of the three myrobalans in a hydrogen peroxide (H2O2)-induced neuroblastoma NG108-15 cell death model. The study demonstrated that these extracts protected cells from H2O2-induced damage and exhibited significant hydroxyl radical scavenging and ion chelating activities. Specifically, PE and TB showed anti-COX-2 activity, supporting their use in managing oxidative stress and inflammation, which are prominently seen in neurodegenerative diseases [118]. The above studies highlight the potential of these traditional herbal medicines (three myrobalans), in the treatment and management of neurodegenerative diseases through their various neuroprotective properties.

9E. *Capsicum annuum* (red hot pepper)

Capsicum annuum (red hot pepper), a component of lemon pickle, shows significant neuroprotective potential in research studies, against neurodegenerative disorders such as AD. A study conducted by Abdel-Salam., *et al*. (2023) evaluated the effects of *C. annuum* methanolic extract on AD induced by aluminum chloride (AlCl3) in male rats. The study measured brain levels of oxidative stress markers (GSH, NO, MDA), paraoxonase-1 (PON-1) activity, interleukin-6 (IL-6), Aβ-peptide, and AChE concentrations, alongside behavioral assessments for neuromuscular strength and memory performance. The outcomes showed that Capsicum extract significantly mitigated the adverse effects of AlCl3 by reducing oxidative stress, Aβ-peptide, and IL-6 levels, enhancing

grip strength, improving memory function, and preventing neuronal degeneration in critical brain areas such as the cerebral cortex, hippocampus, and substantia nigra. These findings suggest that *C. annuum* extract has potential therapeutic properties against neurodegenerative changes linked to Alzheimer's disease [119].

Another study conducted by Wang., *et al*. (2020) reported significant potential of capsaicin, the active component in chili peppers, against Alzheimer's disease (AD) in humans. They found that a diet high in capsaicin was linked to improved cognitive function and reduced serum Amyloid-beta (Aβ) levels in people over 40. Further experiments on APP/PS1 mice revealed that capsaicin significantly lowered the brain's Aβ burden and mitigated cognitive decline. Mechanistically, capsaicin favored the α-cleavage of Amyloid Precursor Protein (APP), reducing Aβ production and promoting the maturation of a disintegrin and metalloproteinase 10 (ADAM10), which is a key enzyme in the non-amyloidogenic pathway of APP processing. In addition, capsaicin alleviated other AD-related pathologies such as tau hyperphosphorylation, neuroinflammation, and neurodegeneration [120].

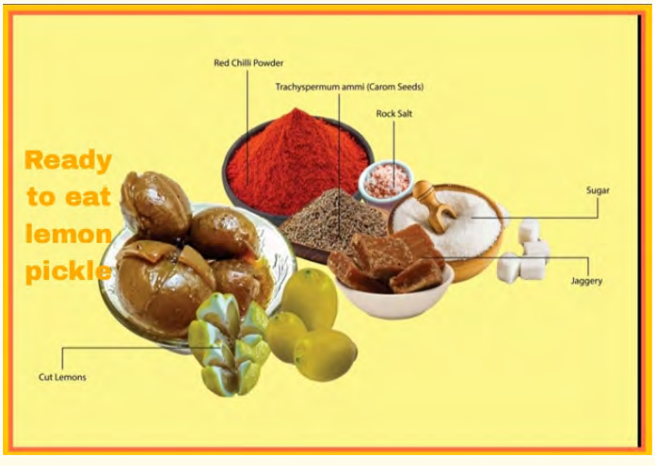

Figure 3: Lemon pickle is prepared using very few ingredients, with carom seeds and red chili powder being mandatory.

9F. *Trachyspermum ammi* (Carom Seeds)

Trachyspermum ammi (commonly known as Ajwain), a mandatory ingredient in the lemon pickle, has exhibited significant potential against neurodegenerative conditions. A research study by Sharma., *et al*. 2023, examined the neuroprotective effects of *T. ammi* (also known as Carom Seeds) in neurodegenerative diseases, particularly in AD. Extracts from *T. ammi*, containing bioactive compounds such as Carvacrol, identified through GC/MS analysis, were tested for their neuroprotective properties using cell-based assays. The outcomes showed that Carom extracts exhibited significant neuroprotection by modulating pathways involved in neurodegeneration. They also alleviated oxidative stress**,** improved mitochondrial membrane potential, and inhibited acetylcholinesterase activity, which are key factors in treating neurodegenerative conditions. Furthermore, the extracts displayed anti-Aβ1-42 fibrilization/oligomerization and anti-glycation activities, both essential in preventing the progression of AD and other neurodegenerative diseases [121].

Another research study conducted by Timalsina., *et al*. (2023) investigated the neuroprotective properties of *T. ammi* seed extract (TASE) and its key component thymol in a scopolamine-induced Alzheimer's disease (AD) mouse model. TASE significantly reduced brain levels of oxidative stress markers, such as glutathione, hydrogen peroxide, and malondialdehyde. Importantly, the carom seed extract down-regulated pro-inflammatory cytokines like tumor necrosis factor-alpha and upregulated neuroprotective factors, such as brain-derived neurotrophic factor. The extract also increases phosphorylation of glycogen synthase kinase-3 beta (GSK-3 beta), leading to its inactivation. GSK-3 beta is implicated in the pathogenesis of AD. These molecular alterations are vital as they enhance memory and learning capabilities. Moreover, a notable reduction in Aβ 1–42 peptide accumulation, a hallmark of Alzheimer's pathology, was observed. The study also reported a significant promotion of adult neurogenesis, evidenced by an increase in double cortin-positive neurons in the hippocampus, a key area for memory formation and highly vulnerable in neurodegenerative diseases like AD. These outcomes suggest that TASE and thymol are promising natural therapeutic agents for neurodegenerative disorders by targeting oxidative stress, inflammation and amyloid-beta accumulation, along with supporting neurogenesis [122].

Moreover, in another investigation by Sharma., *et al*. (2023), the researchers reported the neuroprotective effects of *T. ammi* essential oil (TAEO) against glutamate excitotoxicity, induced by monosodium glutamate in rats. This study evaluated the effects of TAEO at doses of 250 and 500 mg/kg on motor and cognitive functions, oxidative stress, and acetylcholinesterase activity in an excitotoxicity rat model. Additionally, β-amyloid deposition was assessed. The results demonstrated that TAEO significantly improved motor and cognitive functions, reduced oxidative stress and AChE activity, and decreased β-amyloid deposition in the

brain. The study findings indicate that TAEO's protective effects are mediated through its interaction with the N-methyl-Daspartate (NMDA) receptor (a glutamate receptor) pathway. The results also highlight the potential of Ajwain as a therapeutic agent for conditions characterized by glutamate excitotoxicity, such as neurodegenerative diseases [123]. Additionally, an animal study found that the hydro-alcoholic extract of *T. ammi* significantly improved the enzyme levels, including butyrylcholinesterase (BChE), catalase (CAT), and glutathione (GSH), and also reduced ROS. These outcomes suggest that antioxidants and anticholinesterase inhibitors found in Ajwain could be effective in ameliorating oxidative stress and cognitive decline associated with neurodegenerative diseases [124].

10. Discussion

Citrus limon, colloquially referred to as lemon, is a perennial tree belonging to the Rutaceae family. It is characterized by its evergreen foliage and visually appealing, edible yellow fruits. The nomenclature for *C. limon* varies across languages, including 'Zitrone' in German, 'le citron' in French, 'limón' in Spanish, and 'níngméng' in Chinese [1]. *C. limon* is a highly important crop in the realm of fruit production. Its distinctive tart flavor makes it a versatile ingredient for various culinary and beverage purposes, including its incorporation into desserts and ice creams, and as an essential component in cooking. Despite the substantial nutritional and bioactive component of the by-products generated from the industrial processing of lemons, these resources often go underutilized [2,3]. These by-products, abundant in polyphenols, carotenoids, vitamins, essential oils (EOs), and dietary fibers, including pectin, cellulose, hemicellulose, and lignin, possess significant potential for applications within the food industry.

Lemon pickle, as a dietary inclusion, offers a convenient means of consuming the neuroprotective compounds contained within lemon juice, pulp and peel. For instance, hesperidin and its metabolite, hesperetin effectively counteract oxidative stress, inflammation, and neurotoxicity, key factors implicated in the pathogenesis of neurodegenerative diseases [28]. Lemon pickle provides a concentrated source of naringin and naringenin, both of which have demonstrated neuroprotective effects. These compounds exhibit promising capabilities in mitigating cognitive dysfunction, oxidative stress, and hippocampal neuron injury commonly observed in Alzheimer's disease. By preserving and potentially enhancing the bioavailability of naringin and naringenin, (because of softening and degradation of cell walls over time, the phytocompounds contained inside become free), lemon pickle consumption enables the realization of synergistic neuroprotective benefits against neurodegenerative conditions [24-27].

Rutin is another flavonoid naturally occurring in lemons, which contributes to neuroprotection when consumed through lemon pickle. Rutin has exhibited notable potential in mitigating hippocampal damage, improving spatial memory, and promoting synapse formation. Furthermore, it exerts inhibitory effects on beta-amyloid aggregation and diminishes the production of nitric oxide and pro-inflammatory cytokines, thus increasing its therapeutic potential in neurodegenerative disease management [42]. Heptamethoxyflavone (HMF), a constituent found in citrus fruits, facilitates the induction of long-term memory formation, while Tangeretin (TGN) has exhibited considerable neuroprotective capabilities in animal studies [39].

Numerous human studies have also demonstrated the cognitive benefits of citrus-derived compounds such as nobiletin. Healthy elderly individuals, as well as Alzheimer's patients, have shown potential cognitive improvement or prevention of cognitive decline following supplementation with nobiletin-rich substances [21]. Additionally, a diet supplemented with high-flavonoid fruits, vegetables, and cocoa drinks has been shown to improve cognitive performance in middle-aged and elderly adults, highlighting the potential of flavonoids, abundant in lemons, for cognitive health. Moreover, consumption of flavonoid-rich orange juice led to significant cognitive improvements in healthy older adults and middle-aged men. Similarly, younger adults consuming high-flavanone drinks showed increased regional brain perfusion and improved cognitive performance, indicating the neuroprotective potential of citrus flavonoids. These findings collectively highlight the potential of citrus-derived compounds for neuroprotection and cognitive enhancement, underscoring the possible benefits of lemon pickle consumption.

It is also clear from the above animal and human studies that the consumption of lemon pickle, rich in neuroprotective

phytochemicals, contributes to the prevention of neuroinflammation and dementia associated with neurodegenerative disorders. Given the heterogeneous nature of neurodegenerative diseases, the collective intake of these phytochemicals through lemon pickle consumption holds potential for synergistic neuroprotective effects. The pickling process serves to preserve and enhance the bioavailability of these compounds, thereby rendering lemon pickle a valuable dietary adjunct in promoting brain health.

11. Conclusion

In conclusion, lemon pickle, a traditional Indian condiment made from *Citrus limon*, emerges as a promising vehicle for delivering a myriad of neuroprotective phytochemicals. By incorporating lemon pickle into the diet, individuals can access and potentially enhance the availability of compounds such as nobiletin, hesperidin, hesperetin, naringin, naringenin, rutin, heptamethoxyflavone (HMF), tangeretin (TGN), quercetin, limonene, eriodictyol, isoimperatorin (IMP), apigenin, luteolin, and vitamin C—each of which exhibits unique mechanisms for safeguarding against neurodegenerative processes.

The collective intake of these phytochemicals through lemon pickle consumption holds promise in combating oxidative stress, inflammation, neurotoxicity, and cognitive dysfunction, while promoting neuronal survival, reducing neuroinflammation, and enhancing brain health. Future studies exploring the specific potential synergies between the various neuroprotective phytochemicals in lemon pickle can further elucidate their efficacy in prevention and management of neurodegenerative disease With its rich composition of beneficial compounds, lemon pickle presents an intriguing avenue for integrating traditional culinary practices with modern neuroprotective strategies.

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