OPEN ACCESS

Current Research in Complementary & Alternative Medicine

Bali S. Curr Res Complement Altern Med 7: 179.

www.doi.org/10.29011/2577-2201.100079

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Research Article

The Indian Delicacy Nimbu Achar: Your Lemony Pathway to Brain Health

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Citation: Bali S (2023) The Indian Delicacy Nimbu Achar: Your Lemony Pathway to Brain Health. Curr Res Cmpl Alt Med 7: 179. DOI: 10.29011/2577-2201.100079

Received Date: 8 May 2023; **Accepted Date:** 11 May 2023; **Published Date:** 15 May 2023

Abstract

Lemon pickle has been made and consumed in India since times immemorial. Though the pickle is made in many different ways, using different ingredients, the basic pickle contains very few ingredients. These include lemons, red chillies, carom seeds and salt. All these ingredients have been found to have numerous health benefits, including promotive effects on the brain. These beneficial actions include anti-inflammatory, anti-oxidant, anti-dementia, anti-anxiety and anti-depressive effects. Several human studies have also ascertained that regular consumption of lemons and other citrus fruits improves cognition, mood and sleep patterns. Besides the direct effect of the lemon phytochemicals on the brain, lemon peel has also been found to boost the gut-brain axis via prebiotic effects.

Abbreviations: Ach- Acetyl choline; nAchR- nicotinic acetylcholine receptor; PMF- Poly methoxy flavonoids; CNS- Central nervous system; TC- Total cholesterol; LDL- Low density lipoprotein; Ox- LDL- Oxidized LDL; BBB- Blood brain barrier; PUFA- Poly unsaturated fatty acids; GABA- gamma-Aminobutyric acid; AD- Alzheimer's disease; RC- Red chilli; T2DM- Type 2 diabetes mellitus; GSH- Glutathione; Brain- derived neurotrophic factor (BDNF).

Introduction

Improved life expectancies have greatly increased the aging population, leading to a surge in metabolic disease burden, and a rising incidence of age-associated neurodegenerative diseases such as Alzheimer's Disease (AD). The pathology of AD comprises neurological dysfunction due to amyloid-β accumulation, tau hyperphosphorylation, oxidative stress, and neuroinflammation in the brain. In addition, lifestyle-related diseases such as dyslipidemia, diabetes mellitus, obesity, and cardio-vascular dysfunction increase the risk of developing dementia. This has brought to the fore the great need to develop new strategies to maintain brain health and prevent the onset of dementia in the older population.

Citrus fruits contain bioactives such as polyphenolic compounds which have shown potential in ameliorating the metabolic disease processes [1], and preventing cardiovascular disease [2]. Citrus fruits including lemons are abundant in polymethoxylated flavones (PMF)and flavanones such as nobiletin, hesperidin and narirutin. Preclinical studies reported that these compounds have neuroprotective effects in models of dementia such as AD, showing beneficial effects on cognition and related functions. These studies suggest that it would be worthwhile to include lemon and other citrus fruit in our daily diet. A simple and economical way to partake of all the benefits of lemons is by regular inclusion of lemon pickle in the meals.

The Indian Lemon Pickle

Lemon pickle is commonly made in most Indian homes, especially in rural areas. Though there are several recipes for the pickle, the

most simple and popular one utilizes very few ingredients. These include, Tachyspermum ammi (carom or Ajwain seeds), Capsicum annuum (red chillies), rock salt, sugar and of course, lemons (Figure 1). The process of preparing is quite simple, and involves no cooking. After mixing all the ingredients, the pickle is kept for few days in sun, and then indoors before using. This time lapse allows for softening of the peel, a process that involves disintegration of the cell walls (of the lemon peel), and release of precious phytochemicals packed inside the cells, along with the fermentation of pectin (which forms a major part of the cell wall).

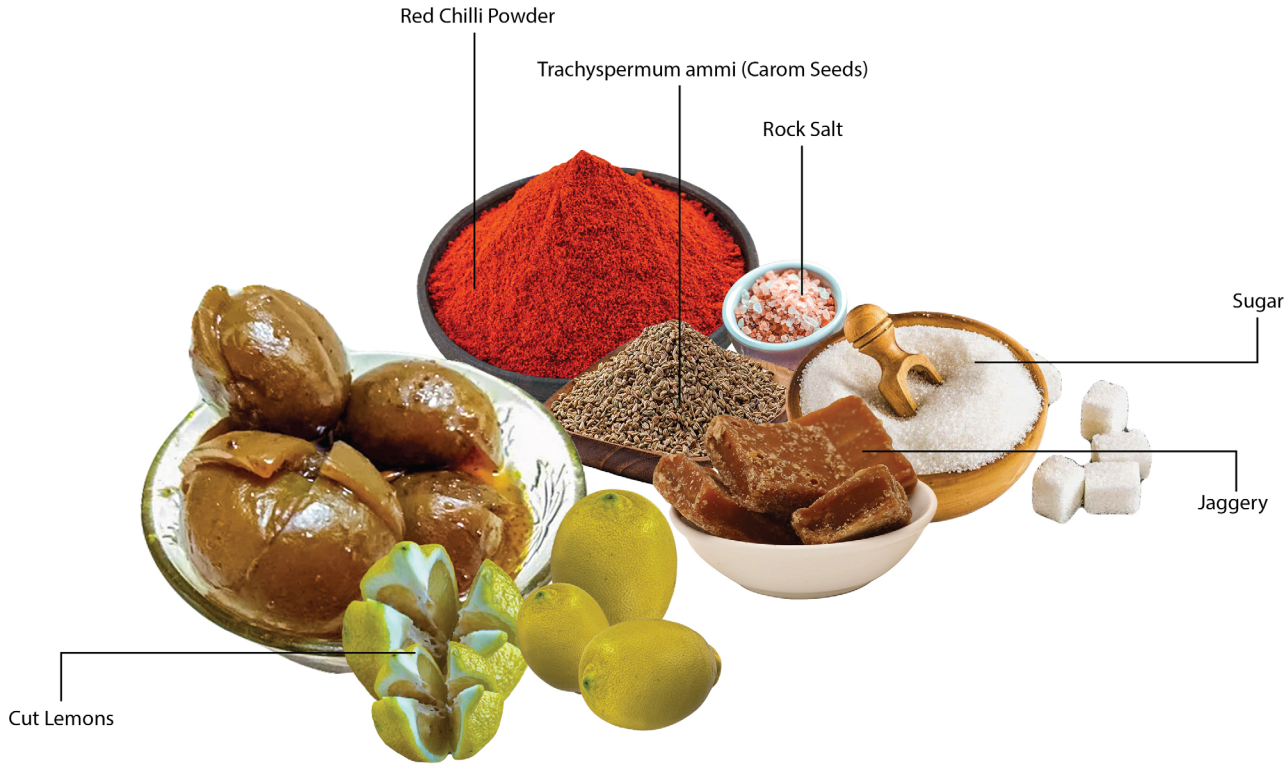

Figure 1: Ingredients used in lemon pickle. The main ingredients are sliced lemon, carom seeds, red chili powder and rock salt. Jaggery and sugar may be used for sweeter taste. The prepared pickle is seen on the left.

The softening of the cut lemon pieces thus, not just makes the pickle more palatable, but also much more nutritious. All the ingredients used in making the pickle have several health benefits, and contribute towards well-being and longevity. Lemon peels are known anti-cancer agents, with their anti-mitotic effects being several folds more than many chemotherapeutic drugs [3,4]. It may be noted that there are very limited ways in which citrus and lemon peels are eaten, since after extraction of juice the peels are usually discarded. This is probably because the peels are bitter and hence not palatable. In their pickled form, the lemon peels are delicious, and are a delicacy.

Phytochemical Composition of Lemons

Lemon (Citrus limon) is very rich in important natural compounds, including citric acid, ascorbic acid, minerals, polyphenols, and essential oils. Polyphenols are compounds with a chemical structure having one or more phenolic rings; Flavonoids are the largest polyphenolic constituents of citrus fruits [5]. These phytochemicals are believed to be responsible for many lemon related biological actions, although several other compounds are also present in various lemon fruit and juice sources (e.g., anthocyanins, flavonols, carotenoids, pectins), and are therefore likely to also possess bioactive properties [5]. Lemon also contains polymethoxy flavonoids (PMFs), such as nobiletin [6].

Lemon juice contains significant amounts of the flavanones' hesperidin and eriocitrin, besides being quite rich in flavones, especially diosmin and di-C-glucosyl flavones. C. limon juice is also abundant in diosmetin 6,8-di-C-glucoside and contains some amount of apigenin di-C-glucoside [7].

Lemon peel contains Phenolics, Flavonoids, Flavonol, and Tannins [8]. Among the flavonoids, lemon peel contains large amounts of eriocitrin and hesperidin, and some amount of narirutin, diosmin, DGD and GD. (DGD – 6,8-di-C-b-glucosyl-diosmin. GD – 6-C-b-glucosyldiosmin) [9]. Bao in 2020, using HPLC analysis, showed that Lemon peel flavonoids consisted of isomangiferin, rutin, astragalin, naringin, and quercetin; the content of isomangiferin was highest, followed by rutin [10].

Lemon peel essential oil contains: Limonene, sabinene, b-pinene, neral, borneol, linalool, cineole, geranial and myrcene [11]. **All the flavonoid compounds were found to be more abundant in the peel than in the edible par**t and juice [12]. Flavonoid glycosides were present primarily in the peel of lemon fruit.

Antioxidative flavonoid compounds in lemon fruit**:** Miyake found Six flavanon glycosides: eriocitrin, neoeriocitrin, narirutin, naringin, hesperidin, and neohesperidin, and three flavone glycosides: diosmin, 6~-di- C-p-glucosyldiosmin (DGD), and 6- C-p-glucosyldiosmin (GD). Neoeriocitrin, naringin, and neohesperidin were present only in trace amounts. The antioxidative activity of eriocitrin, neoeriocitrin and DGD was stronger than that of the others [9].

Bioavailability, Stability and Access to Brain

The flavonoids in lemon are reasonably stable to heat [9]. Bioavailability of the flavonoids is improved when these are ingested along with cereals. In a randomized study conducted by Egert et al, six healthy females (aged 22–28yrs) consumed 130 mg quercetin either in the form of quercetin-enriched cereal bars or quercetin powder filled capsules. Systemic availability in terms of plasma concentration-time curves was five times higher after quercetin-enriched cereal bar ingestion [13]. These findings suggest that carbohydrate composition of the food matrix is an important determinant of the total flavonoid absorption in the small intestine [14]. It is thus better to consume lemon pickle along with meals, rather than alone, to get maximum benefit.

To have an effect on the brain, the lemon phytochemicals must be able to cross the blood- brain barrier (BBB). Available evidence indicates that citrus flavonoids, namely hesperetin, naringenin, as well as their relevant metabolites, are able to reach the brain; though the extent to which citrus polyphenols cross the BBB remains to be fully determined [15-19]. Since PMF has been seen to be loaded onto chylomicron lipoproteins (in the intestines, after absorption), it is also possible for these flavonoids to reach the brain through the lymphatic route [20].

CNS Effects of Phytochemicals Present in Lemon

As given above, Lemons are a considerably rich source of bioactive compounds, particularly flavanones (such as hesperidin and narirutin), which are a sub-set of the flavonoid group. Preclinical studies have shown convincingly the neuroprotective effects of citrus flavonoids. Several animal studies have also demonstrated their anti-inflammatory and anti-oxidative properties. Newly emerging evidence indicates their actions upon blood-brain barrier function/integrity, and this may be the mechanism by which these neurological effects are mediated.

Besides animal and in-vitro studies, results from human studies, although limited in number, have demonstrated improvements in cognitive performance. The various actions of bio actives present in lemon fruit juice, pulp and peels are explained below.

Anti-oxidative Actions

The high metabolic activity of the brain leaves the brain susceptible to oxidative damage. Along with their ability to scavenge free radicles [21], citrus polyphenols have also demonstrated their ability to stimulate the endogenous antioxidant defense machinery. A number of studies have shown the activation of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), glutathione S-transferases (GST), glutathione reductase (GR) and glutathione peroxidase (GPx) by all the citrus polyphenols. Activation coincided with subsequent reduction of reactive oxygen species (ROS) and other oxidative markers [5].

Experimental studies have shown that upregulation of the transcription factor NRF2 occurs and is probably key to this polyphenol mediated anti-oxidative system through the activation of the antioxidant response element [22-24]. Hesperidin and hesperetin have also been shown to upregulate Haem-oxygenase (HO-1) and downregulate the superoxide radical generating enzyme Xanthine Oxidase (XO) respectively [25].

Anti-inflammatory Effects

Neuro-inflammatory modulation is inherent across all citrus flavonoids, and the immunomodulatory capabilities of citrus polyphenols within the brain have also been demonstrated [5]. The molecular targets which citrus polyphenols interact with appear to reduce pro-inflammatory cytokines IL-1β, IL-2, IL-6, IFN-γ, and TNF-α. This is likely mediated through the mitigation of hyperactive immune cells as is suggested by the reduction of NF-κB which governs chemokine and inflammatory mediator

transcription [26,27].

Bioenergetic Actions

In experimental studies, Citrus flavonoids appear to ameliorate mitochondrial damage caused by exogenous factors which can predispose individuals to certain neurodegenerative conditions. The impact was consistent, resulting in an increase of mitochondrial respiratory chain complexes (I–IV) function [5]. Mitochondria function disturbance impacts mitochondrial enzyme bioenergetics, reducing ATP production, while simultaneously leading to substantial increases in ROS production. In addition to mitochondrial function, citrus flavonoids in general led to a reduction in acetylcholinesterase activity, accompanied by increased acetylcholine levels and cholinergic transmission [25,28-33].

Proteinopathy and Dementia

Lemon phytochemicals may have beneficial effect in Alzheimer's disease, with reports revealing improvements in Tau phosphorylation [16,34,27], and Aβ deposition [16,35,27]. A reduction of α-synuclein, the protein implicated in parkinopathy has also been described [36]. A report by Shagirtha in 2017, in which hesperetin was administered demonstrated restoration of brain proteolytic enzyme levels [37]. Studies on involvement of cathepsin D in proteinopathies, have linked citrus flavonoids to lysosomal degradation processes [38].

Citrus polymethoxy flavonoids (PMFs), such as nobiletin (present in lemon) and tangeretin exerted beneficial effects on cognitive function in numerous experimental models—e.g., AD, Parkinson's disease, and dementia [39] — by modulating pathological features such as Aβ/tau pathology, oxidative stress, and neuroinflammation. PMFs also improved synaptic plasticity in many ex perimental models [40-43]. Flavanones such as hesperidin, naringin, and narirutin were found to exert neuroprotection in several neurodegenerative disorder models [44-46]. Essential oil of lemon was found to inhibit acetylcholineesterase, helping AD, besides having anti-oxidant activity [11].

Despite the above preclinical evidence pointing to the beneficial effect of citrus flavonoids in models of Alzheimer's and Parkinson's diseases, etc. there remains very limited evaluation at the human level. In a retrospective cohort study by Zhang et al., 2017, the association between daily citrus intake and dementia incidence in 13,373 participants (age 65 years) was assessed over a 5.7year period. In general, an inverse dose-response relationship was noted between weekly citrus fruit intake and incident dementia [47].

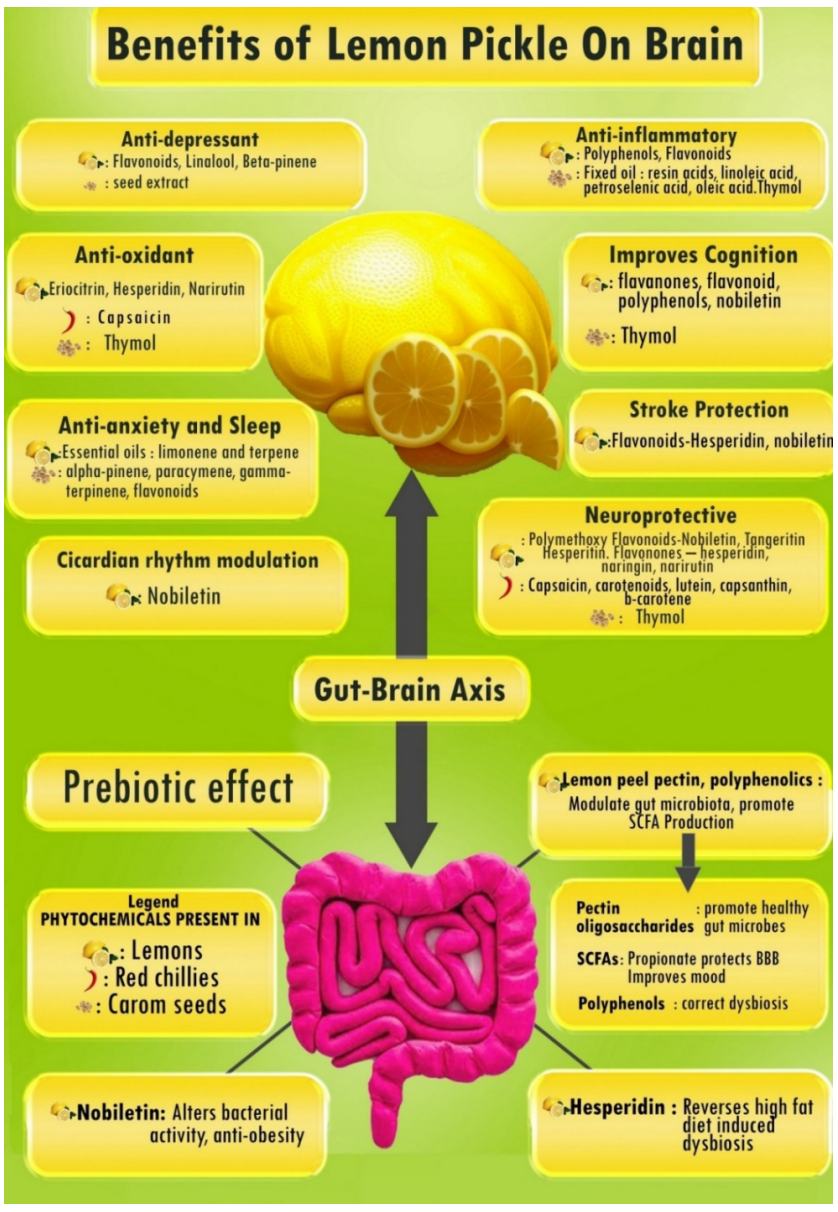

Figure 2: Beneficial effects of lemon pickle on the brain. The actions of the different phytochemicals present in lemons, red chili and carom seeds are shown, along with the prebiotic effects of lemon peel.

Cognitive and Behavioral Effects

In animal studies, where cognitive and behavioral assessments were carried out, citrus flavonoid supplementation led to improvements in cognitive performance. These studies have demonstrated the neuroprotective properties associated with citrus flavonoids. Anxiolytic and anti-depressant actions are particularly prominent across the literature, suggesting modulatory effects on a fundamental anxiety and depression related process. Similarly, citrus polyphenol supplementation has been shown to improve deficits in learning and spatial memory, which may indicate protection of medial temporal lobe (Figure 2). The latter lobe is particularly vulnerable in Alzheimer's like neurodegenerative diseases. Improvements in motor functions and locomotion were also apparent, even in most severe models such as middle cerebral artery occlusion [48], and traumatic brain injury [49].

In a human study conducted on healthy individuals in Norway, exploring the impact of different plant foods on cognitive performance in elderly, a very strong association was found between citrus fruits and cognition [50]. The tested individuals showed better episodic memory, executive function, perceptual speed, and visuospatial skills. A similar study by Kean et al. (2015), on the chronic consumption of flavanone-rich orange juice in adults, showed an increase in global cognition. In addition, high flavanone intake significantly improved recall [51]. These effects were independent of mood and blood pressure which both remained unchanged. A clinical trial evaluated the anti-dementia effect of nobiletin-rich Citrus reticulata peel extract on AD patients taking donepezil [52]. The intervention group ingested extract three times daily for one year, after which cognitive function was again evaluated. The results showed that long-term intake of citrus peel extract suppressed cognitive decline in AD patients. Moreover, long-term citrus peel ingestion caused no apparent side effects. These results suggest that long-term intake of nobiletin-rich citrus peel extract prevents AD progression [52]. The proposed mechanism by which Nobiletin-rich citrus peel extracts may improve cognitive function in the elderly and AD patients is by antioxidant and anti-inflammatory effects. Nobiletin may be involved in activating signaling pathways related to memory formation (i.e., the cAMP/PKA/CREB/BDNF pathway) and improving synaptic plasticity in the cortex and hippocampus [53-55].

Acute neurological responses to citrus flavonoids in healthy adults have also been investigated [56,57]. In a randomized trial, Alharbi et al. (2016) explored the cognitive benefits associated with Flavonoid rich orange juice (hesperidin, narirutin, and others); consumption of the juice led to higher non-significant global cognitive performance, as well as an increase in subjective alertness at 6 hours post consumption. Interestingly, this higher performance coincided with a peak in flavanone metabolites at 5-7 h [58].

Lamport et al. (2016) also assessed acute neurological response to a commercially available high flavanone beverage (hesperidin, naringin, narirutin, and caffeic acid) in healthy young adults [57]. They utilized an additional measure of cerebral blood flow (CBF). Participants underwent either cognitive testing 2 h post consumption or completed an fMRI assessment of CBF 2 and 5 h post consumption. High flavanone beverage intake significantly increased cerebral perfusion in the inferior frontal and middle right frontal gyrus in the right hemisphere at 2 h. Similarly, at 2 h, improvement in digit symbol substitution test (a measure of executive function) was seen, correlating with the increased regional perfusion of the inferior frontal gyrus, known to be involved in executive function [59]. Thus, both chronic and acute flavanone-rich beverage intake improved neurological function.

Depression is a common mental illness and complex mood disorder [60]. People with dementia often suffer from depression [61,62]. In a prospective NHS cohort study over 10 years, following 82,643 women with no previous diagnosis of depression, an inverse association between incident depression and citrus intake was found. It was observed that higher intakes of all flavonoid subclasses resulted in a significant reduction in incident depression risk [63]. Thus, high flavonoid intake may reduce the risk of depression, especially among older women [63]. The anti-depressant effects of flavonoids are usually attributable to their antioxidant and anti-inflammatory actions, as also the inhibition of monoamine oxidases [64]. Brain-derived neurotrophic factor (BDNF), an important serological marker observed to be significantly lower in patients with major depressive disorder, is often increased in response to flavonoid consumption [65]. BDNF plays an important role in neuronal survival and growth, serves as a neurotransmitter modulator, and participates in neuronal plasticity, which is essential for learning and memory. It is widely expressed in the CNS, gut and other tissues. The anti-depressant effects of citrus flavonoids were recently re-tested by Park et al. (2020), in a single blind, randomized control study examining the effects of daily flavonoid rich orange juice consumption on depressive symptoms and gut microbiota for an 8-week period in young adults. Compared with baseline, the results suggested potential improvement in BDNF and depression [66].

Effects on Vascular Function and Stroke Protection

Older individuals, who are at higher risk of dementia, can also suffer from stroke as a result of systemic hypertension. Stroke can then become a cause of dementia. Dietary interventions that reduce systemic blood pressure can be helpful in reducing incidence of stroke, and lemon pickle can be one such intervention. The lemon flavonoids hesperidin and nobiletin have been shown to induce PPARγ signaling and reduce diastolic pressure and mean arterial pressure in diabetic rats [67-69]. The lemon flavonoids also seem to exert a protective effect on stroke [67-69]. Eating flavonoid containing lemon pickle regularly can thus have a beneficial effect on blood pressure and vascular function, reducing the incidence of stroke.

Montesinos et al in 2021 conducted a study to evaluate the effectiveness of citrus flavonoids on LDL levels, in which the subjects having cardio-vascular risk factors consumed flavonoid-rich hydroethanolic extract for 90 days. The authors observed significantly lowered Ox-LDL levels and increased serum paraoxonase activity relative to controls [70]. In another clinical trial conducted by Macarro et al in 2020, healthy individuals were administered an eight-week supplementation with Citrus flavones. At the end of the study period, the subjects were found to have lowered blood pressure, better endothelial function (assessed by flow-mediated vasodilation) and improved lipid metabolism-

associated parameters (TC, LDL, LDL- oxidase, oxidized/reduced glutathione ratio) [71]. A similar clinical trial assessed the impacts of hesperidin supplementation on blood pressure and inflammatory markers in T2DM patients [72]. The results suggested that chronic hesperidin intake exerts antihypertensive and anti-inflammatory effects in T2DM patients [72]. All these studies attest to the efficacy of lemon flavonoids in improving vascular function; lemon pickle can be a relevant dietary supplement in neurodegenerative diseases.

Modulation of Circadian Rhythms

Circadian rhythms are bioactive rhythms inherent in many organ systems. These rhythms form the basic regulatory mechanism for several physiological functions [73], and disturbances in this biological clock are associated with the development of various disorders, including dyslipidemia, obesity, inflammation, and cognitive decline [74,75]. Also, circadian disruption is common in older adults and more prominent in individuals suffering from neurodegenerative diseases such as AD [74,75]. In the last decade, several preclinical studies have documented how citrus PMFs (e.g., nobiletin) physiologically benefit the biological clock [76-80]. Interestingly, nobiletin modulates circadian rhythms and improves metabolic disorder indices, neuroinflammation, and cognitive function in animal models [77,80,81]. The improvement of cognitive function by citrus flavonoids may be the result of the improved regulation of circadian rhythms.

Effect of Citrus Components on Anxiety and Sleep

Kwangjai et al., in 2021 investigated C. reticulata essential oil (EO) inhalation on electrical brain waves and sleep parameters in the rat model. The rats had electrodes implanted on the skull over the frontal and parietal areas and were given the citrus EO inhalation while Electroencephalography (EEG) signals were recorded. EEG data analysis revealed that citrus EO effects are comparable to diazepam. C. reticulata EO inhalation was associated with reduced REM sleep latency and improved sleep-wake patterns. There was significantly increased total time and episode numbers of REM sleep [82]. Thus, it can be concluded that clinical applications of C. reticulata essential oil can be helpful to improve sleep quality in various neurodegenerative conditions.

In behavioral studies, oral administration of C. reticulata EO was observed to reduce anxiety in mice using light/dark box and marble- burying tests. The citrus EO also prolonged sleeping time induced by ether inhalation [83]. Other studies have presented the beneficial effects of citrus essential oils as central nervous system (CNS) depressants, particularly in reducing stress severity. Anxiety symptoms were significantly reduced after Neroli (Citrus aurantium L.) EO inhalation in coronary artery disease [84]. Lemon peel oil is a rich source of Limonene [85], which has exhibited good anxiolytic effects [86]. Other monoterpenes present in lemon EO, such as linalool and β-pinene have demonstrated antidepressant-like activity by modulating brain monoamine levels via noradrenergic (a2 and β) receptors, dopamine (D1) receptors, and serotonin (5-HT1A) receptors [87].

Ueda et al. in 2023 demonstrated specific effects of lemon essential oils on the human brain. Instant high brain activation was observed after lemon essential oil inhalation, exhibiting effects on memory processing, task performance, and cognitive function [88]. Another study suggested that lemon essential oil inhalation can reduce memory impairment induced by the administration of scopolamine [89]. Furthermore, inhalation of lemon essential oil can lead to positive effects on mood and emotions [90]. Citrus EOs contain a high concentration of terpenes that are known for their anti-inflammatory properties by inhibiting pro-inflammatory cytokines such as TNF-α, NF-κB, and IL-1β [91]. It has also been found that orange EO inhalation can induce mood-enhancing effects by decreasing oxyhemoglobin concentration in the brain's right prefrontal cortex [92].

Effect of Lemon Pulp and Peel on the Gut Microbiota: The Gut - Brain Axis

The gut microbes have an important part to play in human health, including brain health. The trillions of intestinal bacteria help in metabolizing and breaking down foodstuffs and complex carbohydrates such as dietary fibres. Some of the derivative metabolites have been found to act as neurochemicals and possess neuromodulatory properties. Short-chain fatty acids (SCFA) are a relatively well-characterized example of this [93] and are produced via fermentation of dietary fibres like pectin. Low levels of SCFA have been found to be associated with conditions such as depression, AD and Parkinson's disease [93]. The SCFA propionate has been recently reported to protect the BBB from oxidative stress via NRF2 (NFE2L2) signaling [94]. The influence of metabolites such as SCFA produced by our gut microbiome on the gut-brain axis has been extensively reviewed by Teratani et al., 2020 [95] and Lv et al., 2019 [96]; Wang et al., 2019 [97]. Separate studies by Foti 2022 [98] and Miguez [99] concluded that lemon peel pectin oligosaccharides (POS) could be used as prebiotics due to their antimicrobial and microbiota modulating ability. Gómez 2016 elucidated the greater prebiotic activity of citrus POS, as compared to those available in the market. Better prebiotic activity translates into better performance in production of beneficial microbial strains, which in turn leads to a greater amount of SCFA produced in the gut [100].

The gut-brain axis can be considered as a bidirectional system that encompasses both neuro-immune and neuro-endocrine communication as well as a direct neuronal affect (vagus nerve) [101], where each mode of transmission undergoes microbial modulation. The fact that beneficial shifts could be achieved by

food stuff acting like prebiotics, makes it an attractive therapeutic target (Figure 2) The gut microbiota can be modulated by citrus polyphenolic compounds [102]. Moreover, the gut microbiota metabolizes citrus flavonoids—such as hesperidin, naringin, and nobiletin—into phenolic and aromatic splitting heterocompounds, enhancing their bioavailability [103]. The increased bioavailability enhanced the efficacy of citrus flavonoids in animal models [104,105].

In preclinical studies, long-term ingestion of nobiletin has been reported to have an anti-obesity effect by altering the activity of the intestinal microbiota [104]. Nobiletin has also been shown to promote thermogenesis of brown and beige adipose tissue and reduce body weight in mice fed a high-fat diet by affecting the formation of the gut microflora [105]. Hesperidin, a polyphenol found in lemons, has recently been shown to reverse high-fat-diet-induced intestinal dysbiosis by increasing general microbial diversity as well as specific beneficial bacterial strains including Bacteroidetes and Firmicutes [106]. The beneficial hesperidin mediated metabolic effects were also detailed in an earlier experiment by Estruel-Amades et al., 2019, which reported upon the concomitant immunomodulatory actions [107]. Another interventional study showed that consuming 300 mL of orange juice for 60 days modulated the gut microbiota and simultaneously improved blood glucose and lipid profiles [108].

Protective Effect of Red Chillies on Brain

Red chillies (RC) contain several bioactive phytochemicals, such as capsaicinoids and carotenoid pigments. The capsaicinoids include capsaicin, dihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, and nordihydrocapsaicin [109], while the carotenoid pigments present are capsanthin, cryptocapsin, and capsorubin.

Anti-inflammatory and Anti- oxidant Actions

The antioxidant activity of capsaicin was reported in the oxidation of methyl linoleate (ML) and also of soybean phosphatidylcholine liposomal membrane. This anti-oxidant activity was comparable to that of alpha-tocopherol which is one of the most important antioxidants in vivo [110]. The antioxidant property of capsaicin can even prevent cardiovascular diseases. Kim et al found capsaicin showed significant inhibition of the production of inflammatory molecule PGE2 in lipopolysaccharide (LPS)-stimulated murine peritoneal macrophages. They also noted that Capsaicin inhibited the enzyme activity of COX-2 and the expression of the iNOS protein [111].

Metabolic activity

Capsaicin has also been found to reduce glucose intolerance and fasting glucose levels in experimental mice, demonstrating antihyperglycemic and antidiabetic activities [112]. Concentration-dependent reduction in LDL and cholesterol was observed when RC powder and standard diet were taken together, thus confirming the anti-atherogenic potential of red chilli powder. Red chilli consumption has been linked to reduced blood glucose in rabbit models [113]. Chilli pepper has demonstrated the potential to inhibit key enzymes of glucose metabolism such as α-glucosidase and α-amylase, which increase blood glucose by degrading carbohydrates [114].

Anti-Alzheimer disease. Capsicum annuum extracts have been found to be effective in suppressing major Alzheimer's associated enzymes such as butyrylcholinesterase, acetylcholinesterase, and β-secretase [115]. Capsaicin exhibits high free radical scavenging capacity [116], and also helps regulate the mitochondrial enzymes which are beneficial in minimizing the risk of lung carcinoma [117]. This finding holds significance for degenerative brain disorders, since increase of Mitochondrial Lipid peroxidase (LPO) levels are associated with damage to brain cells [118,119]. The carotenoids, lutein and β-carotene have demonstrated a positive effect on memory [120]. Additionally, red paprika contains capsanthin, which, alongwith b-carotene, protects against deteriorative diseases caused by the mechanisms of oxidative stress [121].

Contribution of Trachyspermum ammi towards Brain Health

Carom (Tachyspermum ammi) seeds, also called Carum copticum and ajwain seeds, have been shown to affect serum lipids and the cardio-vascular system in various beneficial ways. Considering the importance of metabolic and vascular disorders in causation of neuro-degenerative diseases, these effects are of significance. Javed et al in 2002 demonstrated the anti hyperlipidaemic potential of carom seeds; his study demonstrated that carom seed extract reduced total cholesterol, LDL-cholesterol, total lipids, and triglycerides in albino rabbits [122]. In a study conducted by Aftab and Usmanghani, C. copticum showed significant cardiovascular effects, reducing heart rate and blood pressure [123]. Gilani et al also in 2005 showed that T. ammi seed extract exhibited hypotensive activity and significantly reduced mean arterial blood pressure [124].

T. ammi seeds fixed oil contains palmitic acid, resin acids, petroselenic acid, linoleic acid, and oleic acid [125]. Extracts from Carum copticum seeds were found to affect kinnin, prostaglandin, lysozyme, and bradykinin synthesis, inhibiting inflammation in animal models [126]. Ajwain plant extracts exhibited the effects as a natural antioxidant on scavenging nitric oxide, hydroxyl, and superoxide radicals [127]. Soni and Parle in 2017 explored the positive effects of T. ammi seed powder on **amnesia** induced in mice. A 10-day administration led to an increase in brain

gtutathione (GSH) level while decreasing AChE activity, brain nitrite level, brain MDA level, and oxidative damage [128].

Rahman et al., in 2018 evaluated the **antidepressant**-like potential of T. ammi seed methanolic extract in neurological disorders by conducting a Forced Swimming Test (FST), Tail Suspension Test (TST), and Measurement of Locomotor Activity Test (MLAT). The results showed that T. ammi had similar efficacy to Imipramine hydrochloride (standard antidepressant) [129]. The oral administration of the extracts of T. ammi reduced the immobility time in the TST and FST and increased locomotion in albino mice. Studies have confirmed the adaptogenic effect of Trachyspermum ammi extract on the regulation of monoaminergic levels and stress parameters [130]. These findings support the antidepressant-like potential of the methanolic extract of Trachysperum ammi in the treatment of stress and depressive disorders. The phytoconstituent compounds present in Trachyspermum ammi such as alpha-pinene, paracymene, gamma-terpinene, and flavonoids are responsible for delivering **anxiolytic** effects that are highly comparable to standard medication diazepam [131].

The main phenolic compound in ajwain is thymol [132]. **Thymol** has demonstrated the potential to balance neurotransmitters and suppress proinflammatory cytokine expression in many types of depression models [133]. Thymol also has nociceptive actions, and this could be due to its action in increasing the spontaneous release of L-glutamate in substantia gelatinosa (SG) neurons by activating TRPA1 channels [134]. Rajput et al. in 2013 found that stimulation of GABA responses by thymol resulted in a significantly increased delay in the onset of convulsions, which indicates the potential application of Trachyspermum ammi in epileptic conditions [135]. Thymol inhibited cognitive impairments in scopolamine-treated rats, demonstrating its antioxidant, anticholineesterase, and anti-inflammatory actions [131]. Additionally, thymol decreased H2O2-induced oxidative stress in the PC12 cell line (embryonic neural crest cells) [136]. These results exhibit therapeutic potential in the treatment of Alzheimer's Disease (AD). Thymol supplementation also improved endogenous antioxidants and specific PUFA and phosholipid proportions in the aging brain of rats [137]. Thymol enhanced acetyl choline (Ach) synaptic levels and nAchR responsiveness, demonstrating beneficial effects in cholinergic dysfunction, which is observed in a range of neurodegenerative and psychiatric disorders such as Alzheimer's and Parkinson's disease [138]. All these effects testify to the great therapeutic potential of T ammi in prevention and amelioration of degenerative brain disorders.

Conclusion

All the ingredients used in making the Indian lemon pickle have been found to have beneficial effects on the functional abilities of the brain. Lemons particularly contain bioactives that are effective in promoting better cognition, memory and mood. It may be noted that eating lemon pickle is probably one of the very few ways in which the bitter peel can be eaten. This is significant because the majority of lemon flavonoids are present in the peel. The protective effects of lemon are probably linked with the anti-oxidative and anti-inflammatory action of the phytochemicals contained. A great advantage of lemon phytochemicals is their safety profile [52,139-143].

The complex mixtures of phytochemicals present in lemon fruits, red pepper and carom seeds and their bioactive nuances likely exert greater benefit than one purified compound, accumulatively acting upon multiple targets, and producing synergistic effects. Given the multifactorial nature of neurodegenerative diseases, it can be hypothesized that this complex form offers greater efficacy. Eating lemon pickle regularly may be a safe and delicious way to ward off neurodegenerative diseases and the cognitive decline associated with old age. In any case, lemon pickle can prove a useful adjunct to therapeutic agents against various diseases such as AD.

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