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Review Article

Memory in a Drop: Harnessing the Distillation Principle for Enhancing Cognition

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Abstract

Emerging evidence supports the potential role of *Citrus limon* (lemon), pomegranate (*Punica granatum*) and Piper betle (betel leaf), in enhancing cognitive functions and offering therapeutic benefits. On the other hand, distillation of natural medicinal substances extracts the essence of these substances, creating a low volume-high efficacy liquid. Distillates of herbs have been used in India for ages, especially in the Siddha and Unani medical systems, to provide the beneficial effects of the herbs in a few drops, circumventing the need to partake large volumes of decoctions. This review explores how the distillates of lemon, pomegranate and betel leaf, when combined, may bestow amplified neuroprotective and cognition-enhancing effects. *Citrus limon* is recognized for its rich phytochemical profile having potent antioxidant and anti-inflammatory properties that benefit cognitive health. Pomegranate, renowned for its health-promoting capabilities, has also shown promise in enhancing memory and cognitive functions, due to its content of myriad bioactive phytochemicals such as Ellagitannins and Punicalagin. Piper betle, an important herb in traditional Southeast Asian medicine, has been studied for its neuroprotective properties, and contains bioactive constituents like eugenol and chavibetol, which inhibit key enzymes associated with Alzheimer's disease. Both preclinical and human studies have reported encouraging outcomes from each of these botanical extracts, prompting interest in a combined distillate form.

Keywords: *Citrus limon* (lemon); Pomegranate; Piper Betle (Betel Leaf); Neuroprotective Phytochemicals; Cognition-Enhancing; Distillates; Neuropharmacology

Introduction

In recent years, there has been an increase in demand for phytotherapeutic agents useful in the enhancement of cognitive function and the treatment of neurodegenerative conditions. In this regard, a number of research studies have focused on the potential neuroprotective properties of lemon and pomegranate fruits, and betel leaf. Individually, these plant parts are rich sources of bioactive compounds with promising neuroprotective and cognitive-enhancing properties. For example, *Citrus limon* is rich in polyphenols that demonstrate significant antioxidant and anti-inflammatory activities, which are beneficial for cognitive health. Pomegranate too, is a powerhouse of bioactive phytochemicals like ellagitannins and punicalagin, known for their ability to boost memory and cognitive functions. The Piper betle leaf, a staple in traditional Southeast Asian medicine, is rich in neuroprotective constituents like eugenol and chavibetol. While each of these botanical extracts offers individual benefits for memory and cognitive enhancement, the synergy between lemon, pomegranate, and betel leaf holds particular promise. Studies indicate that combined administration of the distillates of these three could

amplify the therapeutic effects, offering a multi-targeted approach to cognitive health and therapy (Figure 1). This review aims to consolidate the current evidence on the unique neuroprotective advantages for a dosage form that combines the distillates of lemon, pomegranate, and betel leaf.

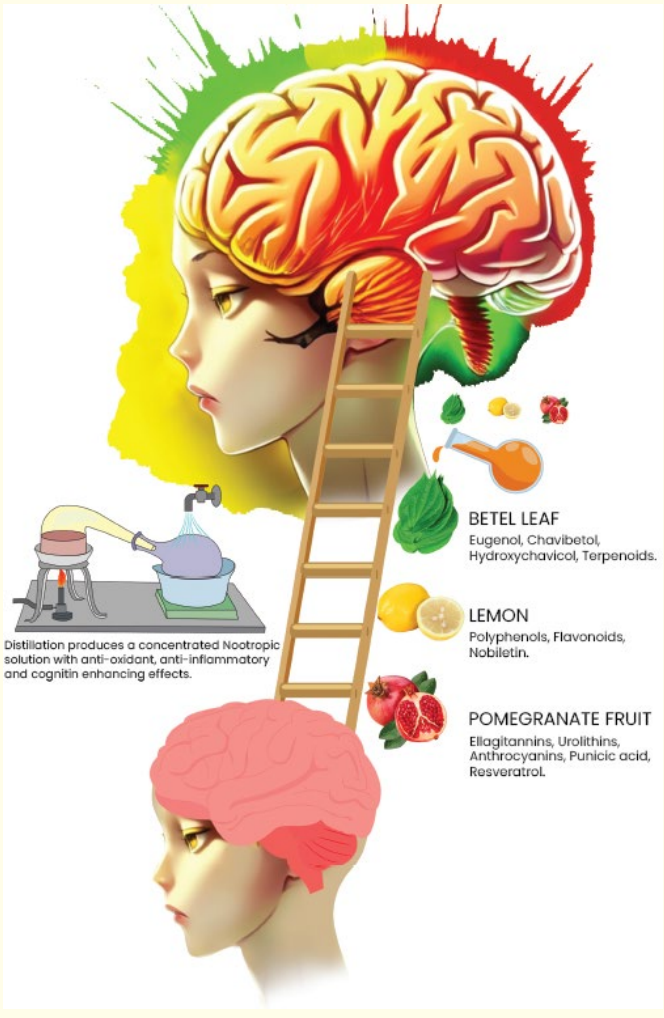

Figure 1: The important phytochemicals contained in distillate of Lemon, Pomegranate and Betel leaf enhance cognition and memory, while fending off neuro-degeneration.

Distillation

Classical distillation of medicinal plant parts involves the process of separating the volatile components called essential oils (EO), from an aqueous mixture by using boiling and condensation, usually inside an apparatus known as a still. Distillation of medicinal plant parts can be carried out in a number of ways. The most common technique of obtaining a distillate is Hydro distillation, which is the simplest and oldest method of essential oil extraction [1]. The apparatus includes a heating source, vessel, condenser, and a decanter to collect the condensate. The essential oil is released from the plant tissue under the influence of heat, and is converted into vapour. Indirect cooling with water condenses the vapour, which is a mixture of water and volatile compounds. The main advantage of this technique is that the required material is distilled at a temperature less than 100 °C. Some important EOs, such as rosemary, geranium, oregano, lemon, lavender, sage cumin, clove, thyme, basil, and garden mint are extracted using this method [2]. There are mainly two types of hydro-distillation techniques for extracting EOs: water distillation and steam distillation [3]. In the process of water distillation, the plant material is immersed in boiling water and then the mixture is subjected to distillation [4]. In steam distillation, the process is carried out by passing steam through the material until it starts volatilizing EOs in the biomass and then the mixture of hot vapours is collected and condensed [5].

Nootropic effects of the distillate of lemon, pomegranate, and betel leaf

Lemon

(*Citrus limon*) is a well-studied citrus fruit recognized for its rich nutritional profile, including essential micronutrients like vitamin C, folate, and potassium. Recent empirical evidence has revealed its potential cognitive benefits. A 2021 meta-analysis by Pontifex., *et al*. concluded that citrus polyphenols, including those in lemon, are advantageous for cognitive function due to their antioxidant and anti-inflammatory properties [6]. Investigative work by Riaz., *et al*. (2014) supported the cognition enhancing effects of both lemon and pomegranate together. The researchers found that administration of the botanical extracts of these two together resulted in notable improvements in the memory performance of rodents, which was ascribed to the high content of bioactive compounds like flavonoids, anthocyanins, flavonols, carotenoids, punicalgin and several others present in these fruits [7].

Additionally, the therapeutic potential of lemon in neurodegenerative conditions has been substantiated by several studies. A 2018 study by Falls., *et al*. demonstrated that the administration of lemon oil to mice led to memory enhancement, comparable to the effects of donepezil, a medication approved for

Alzheimer's treatment. The mechanisms of action of lemon oil includes reduction of acetylcholinesterase activity in the brain, enhancement of antioxidant defense mechanisms, and lowered levels of plasma corticosterone and oxidative stress markers [8]. Animal studies have repeatedly shown the neuroprotective attributes of citrus flavonoids, extending to improvements in motor functions, even in extreme models of brain injury [9,10].

Human studies have also begun to explore this relationship. A Norwegian study conducted by Nurk., *et al*. (2010) in elderly subjects revealed a strong association between citrus fruit (among other plant foods) consumption and multiple dimensions of cognitive function, including episodic memory, executive function, perceptual speed, and visuospatial abilities [11]. Another key study by Kean., *et al*. (2015) investigated the effects of chronic consumption of flavanone-rich orange juice on cognitive function in adults. Remarkably, their findings indicated that high flavanone intake led to improvements in global cognition and recall abilities. Importantly, these cognitive benefits were not influenced by alterations in mood or blood pressure, which remained constant throughout the study [12].

Further, clinical trials have also begun exploring citrus compounds in the context of Alzheimer's disease (AD). A study by Seki., *et al*. (2013) evaluated the anti-dementia effects of nobiletin-rich Citrus reticulata peel extract on AD patients already on donepezil therapy. After one year of thrice-daily administration of the extract, results indicated a suppression in cognitive decline, without discernable side effects [13]. The proposed mechanistic pathway for these cognitive benefits centers on the antioxidant and anti-inflammatory activities of nobiletin, which is present in significant amounts in lemons. Nobiletin appears to activate memory-related signaling pathways such as the cAMP/PKA/CREB/BDNF pathway, consequently enhancing synaptic plasticity in the cortex and hippocampus [14-16]. Taken together, these findings suggest that citrus fruits and their bioactive compounds could offer significant neuroprotective and cognitive-enhancing benefits.

Pomegranate

(*Punica granatum*), has been extolled for its health-promoting properties for centuries, and recent scientific investigations have also highlighted its potential to enhance memory and cognitive function. Pomegranate is a rich source of various phytochemicals offering a plethora of health advantages. These bioactive compounds include polyphenolic constituents such as Ellagitannins (ETs), Gallotannin, Ellagic Acid (EA), Urolithins, Anthocyanin derivatives, Punicic Acid, Gallagic Acid, Ursodeoxycholic Acid (UDCA), Castalagin, Punicalagin (PUN), and Resveratrol [17]. Investigations conducted on these isolated compounds have reported encouraging outcomes related to neuroprotection, memory enhancement, antioxidative, and anti-inflammatory capabilities.

A recent study by Chen., *et al*. (2023) examined the efficacy of Punicalagin (PU), a potent antioxidant polyphenol from pomegranate. This study demonstrated improvements in memory, learning capabilities, and redox balance in aged murine models. These results posit Punicalagin as a viable therapeutic agent for Alzheimer's disease [18]. Further, Ellagic acid, a polyphenol derived from pomegranate, was researched by Mansouri., *et al*. in 2016. They discovered that ellagic acid effectively reversed drug-induced amnesia in animal models. This suggests its promise as an agent for enhancing memory functions [19]. In another study by Hajipour., *et al*. (2014), the benefits of Pomegranate Seed Extracts (PGSE) were examined in rats suffering from Cerebral Hypoperfusion Ischemia. The study concluded that PGSE improved both memory and motor coordination in affected rats, with its antioxidative properties believed to be a contributing factor [20]. Furthermore, Ridzwan., *et al*. (2020) focused on pomegranate-derived anthocyanins in their study, administering them to rats. The treatment led to improved cognitive performance, further fortifying the argument for pomegranate's therapeutic potential in cognitive ailments [21].

A systematic review by Sahebkar., *et al*. evaluated randomized controlled trials focusing on the influence of pomegranate juice on cognitive faculties. The meta-analysis encompassed five studies with a cumulative total of 122 participants and concluded that pomegranate juice had a positive, significant impact on cognitive function, including memory and attention [22]. Bookheimer., *et al*. (2013) conducted a study involving older adults who reported memory complaints. Upon consumption of pomegranate juice, participants exhibited noticeable improvements in verbal memory tests along with increased neural activity during tasks associated with memory [23]. Further supporting the cognitive-enhancing potential of pomegranate in older adults, Hosseini., *et al*. (2016) conducted a randomized, double-blind, placebo-controlled trial to

investigate the impact of pomegranate juice on memory function [24]. The subjects were administered 237 ml of pomegranate juice daily for a four-week duration. The results showcased a significant improvement in verbal memory among those who consumed pomegranate juice, when compared to the placebo group.

In another controlled-designed study, Asgary., *et al*. (2014) examined the influence of pomegranate seed oil on cognitive performance *in patients with coronary artery disease.* Employing a randomized, double-blind, placebo-controlled methodology, the participants ingested a daily dose of 400 mg of pomegranate seed oil for an eight-week period. The data revealed a significant enhancement in cognitive function post-intervention [25]. Additionally, A longitudinal study by Siddarth., *et al*. (2020) spanning one year investigated the cognitive impact of pomegranate juice on middle-aged and older adults. The study's results pointed towards the juice's efficacy in sustaining visual learning abilities over an extended time frame [26].

Betel leaf

Betel leaf or Piper betle, has been an important herb of traditional medicine in Southeast Asia for centuries. Recent scientific explorations have aimed to substantiate its traditional uses, particularly concerning neurological health. A comprehensive review by Prasanna., *et al*. (2019) discussed the potential therapeutic applications of Piper betle leaf in the treatment of neurological disorders [27]. Bioactive compounds in the plant, including eugenol, chavibetol, and Hydroxychavicol, were identified for their neuroprotective properties, suggesting their possible utility as agents in the treatment of various neurological conditions. Earlier, Ferreres., *et al*. (2014) had employed high-performance liquid chromatography coupled with diode-array detection and electrospray ionization mass spectrometry (HPLC/DAD-ESI/MS) to profile phenolic compounds in Piper betle leaves [28]. Their analysis had revealed the presence of numerous phenolic compounds, some of which exhibited significant acetylcholinesterase inhibitory activity, thereby offering a promising avenue for the treatment of cognitive deficits.

Piper betel leaf is also enriched with bioactive constituents such as flavonoids and terpenoids, which have been implicated in a range of biological activities. Kumar., *et al*. (2010) conducted a study that offered a broader view of Piper betle's pharmacological capabilities [29]. The plant was found to have multiple pharmacological actions, including anti-inflammatory, antioxidant, and antimicrobial activities, thereby suggesting its multifaceted role in enhancing neurological and overall health. Upadhyaya., *et al*. (2019) employed both passive avoidance and Morris water maze tests to assess the effects of Piper betel leaf extract on Wistar rats that were subjected to Alzheimer's disease conditions via induction by aluminum chloride (AlCl3). The study demonstrated that rats treated with the Piper betel leaf extract exhibited significant improvements in memory retention and learning capabilities. Moreover, this group exhibited diminished escape latency times as acquisition trials advanced, relative to the AlCl3-treated group [30].

Furthermore, Dalai., *et al*. (2014) demonstrated that the hydroxychavicol and chlorogenic acid contained in Piper betel leaf extract, inhibit key enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) [31]. These enzymes are critical players in cholinergic dysfunction in Alzheimer's disease (AD) as they reduce levels of acetylcholine (ACh), a neurotransmitter essential for memory and cognition. The study by Dalai., *et al*. further revealed that the memory-retentive and latency-reducing effects of Piper betel were analogous to those seen in mice treated with rivastigmine, a known anti-Alzheimer's drug. This implies that Piper betel leaf extract may be a potential source of therapeutic agents that could ameliorate cognitive decline. This could be due to the presence of flavonoids and phenolic compounds such as eugenol, chavibetol and chavicol. Eugenol, in particular, has demonstrated notable neuroprotective effects. Its mechanism involves countering the neurotoxic effects of amyloid-beta peptides (Aβ), which are hallmarks of Alzheimer's disease [32]. Moreover, a separate study provided evidence that an aqueous extract of Piper betel leaf exhibited therapeutic effects against scopolamine-induced amnesia in albino rats [33]. The study confirms the leaf extract's promising role in mitigating cognitive deficits and memory disorders. These findings support that Piper betel leaf appears to offer significant prospects for the treatment of memory impairments and cognitive dysfunctions.

Synergism among phytochemicals

Recent research has demonstrated that a combination of different phytochemicals can have a more significant impact on health outcomes than the individual compounds themselves. It

has been found that when certain phytochemicals are consumed together, they enhance the pharmacological effects of each other. For instance, a recent study has reported the potential synergy of apple extracts and quercetin 3-beta-D-glucoside (Q3G) against cell proliferation. The study demonstrated a significant inhibitory effect on MCF-7 human breast cancer cell proliferation when these compounds are combined [34].

Curcumin, found in turmeric, and resveratrol found in several herbs, have together been shown to exhibit synergistic antioxidant effect, significantly greater than their individual effects [35]. Similarly, the combination of antioxidant compounds found in Osmanthus fragrans flowers and green tea has been shown to exhibit a synergistic effect, with acteoside and gallic acid noted as the primary contributors to the synergistic potential against oxidative stress [36]. The combination of ginkgetin and resveratrol has also been found to synergistically inhibit vascular endothelial growth factor (VEGF), offering a therapeutic strategy in cancer spread by suppressing VEGF-mediated angiogenesis [37]. Similarly, another study of various combinations of five phenolic compounds, including quercetin dihydrate, showed that some combinations, especially rutin hydrate, and resveratrol, exhibited synergistic antioxidant effects in specific ratios [38].

Synergism between betel leaf, pomegranate and lemon

Several phytochemicals found in betel leaf have been found to have synergistic effects when given alongwith some other phytochemicals. Two such major bioactive compounds present in Piper betel are eugenol and hydroxy-chavicol (HC). Yousefizadeh., *et al*. 2022 found that eugenol and thymoquinone synergistically exert anti-oxidant and anti-microbial effects [39]. Zhao., *et al*. 2019, in their study concluded that Eugenol had a synergistic neuro-protective effect when used in combination with rivastigmine, against Aluminium chloride induced dementia of AD type in rats and modulated the neuro inflammation produced by AlCl3 [40].

In vitro studies by Rahman., *et al*. 2014, have demonstrated that Gamma-tocotrienol (GTT), an isomer of vitamin E, when combined with hydroxy-chavicol, synergistically induced anticancer response in human glioma cancer cells [41]. The synergism between the GTT and HC is postulated to be due to these two bioactives acting in concert to reach different targets of the caspase-3 signaling pathway controlling apoptosis, thus accelerating the cell death process. Significantly, both tocotrienols and HC have been reported to be capable of crossing the blood–brain barrier [42,43]. Similarly, the strong inhibition of migration, invasion and colony formation in Epigallocatechin-3-Gallate (EGCG)+ HC treated cells indicated enhanced efficacy of combined EGCG and HC compared to single treatments [44]. All these studies point towards the synergistic potential of phytochemicals contained in betel leaf.

A seminal study by Riaz., *et al*. (2014) explored the synergistic effects of pomegranate and citrus lemon on memory enhancement. Utilizing a murine model, the authors demonstrated that the combination of pomegranate and lemon significantly bolstered memory performance. This outcome was attributed to the antioxidant and anti-inflammatory activities inherent in the fruits [7]. The results suggest that pomegranate, often in synergy with other plant parts like lemons, exhibits potential in enhancing cognitive and memory functions. The studies presented above indicate a synergistic potential when combining the neuroprotective and cognitive-enhancing properties of lemon, pomegranate, and Piper betle leaf. Thus, a combined distillate of lemon, pomegranate and betel leaf could serve as a promising candidate for cognitive enhancement.

Discussion

Distillates are concentrated yet gentle pharmaceutical preparations, suitable for use in infants, small children and frail individuals, who otherwise cannot partake of tablets and large amounts of decoction. The therapeutic power of a few drops of distillate roughly equals the therapeutic effects contained in half a cup of decoction or juice. Based on this postulate, a few drops of the formulation described above, when taken regularly, would be sufficient to boost the memory, mood and cognition. The origin of the science of distillation in India can be traced back to the Ravana Samhita, an ancient text narrated by the Lanka king Ravana thousands of years back. One of the sections in this exhaustive text is titled “Arq Prakash”, a treatise on distilled medicinal products. As narrated by Ravana to his wife Mandodri, the knowledge of distillation and its immense therapeutic application, was imparted to him by none other than Parvati, the spouse of Mahadeva [45]. The compendium Arq Prakash describes the distillates useful for the treatment of almost all medical conditions known today, utilizing unique herbal combinations.

In present day India, the use of distilled herbal formulations is prevalent in only a few regions of southern Karnataka and Kerala, where Siddha practitioners have kept this science alive over the millennia. This region of India is geographically close to Sri Lanka, where the Lanka king Ravana had his kingdom. In the Unani system of medicine also, some distillates are in use, mainly for the amelioration of indigestion and intestinal colic. The use of distillates as a therapeutic modality is almost absent in the Ayurvedic texts, except in the case of alcoholic medicinal preparations. In Arq Prakash, the technique of distillation and the equipment required is explained in detail. A significant dictum stated in this ancient scripture, is the utilization of betel leaf (Piper betel) in almost all distillation products, in order to enhance the benefits and flavour of the distillate. Phytochemicals contained in Piper betel are now known to synergistically act with several other phytochemicals and drugs, as described above. The cognitive and neuro-therapeutic advantages of plant-based substances are today the center of attention, and the potential synergy between lemon, pomegranate, and betel leaf distillates offers a novel frontier in phyto-neuropharmacology.

Conclusion and Future Perspectives

The presented evidence on *Citrus limon* (lemon), pomegranate (*Punica granatum*), and Piper betle (betel leaf) elucidates their potential as powerful neuroprotective and cognition-enhancing agents. While individually, each plant extract shows promising outcomes for promoting cognitive function, the synergy between their botanical extracts when administered in the form of a combined distillate, could offer a significant multi-targeted approach to cognitive health and therapy. This could be particularly useful in complex, multifactorial conditions like Alzheimer's disease. While lemon polyphenols have been shown to offer antioxidant and anti-inflammatory activities beneficial to cognitive health, pomegranate's extensive phytochemical profile, including ellagitannins and punicalagin, has demonstrated promise in memory enhancement and cognitive function. Piper betle leaf, rich in bioactive constituents like eugenol and chavibetol, offers neuroprotective effects especially relevant to Alzheimer's disease, such as inhibition of key enzymes related to the condition. Both preclinical and human studies have provided encouraging initial findings on the cognitive and therapeutic potentials of the extracts of these three substances. Nevertheless, the compounded benefits of a combined distillate are still largely unexplored. Future research should aim to fill this gap, focusing on identifying the underlying mechanisms that contribute to their synergistic effects and establishing optimal dosages for clinical applications. Such research could pave the way for novel, more effective therapeutic approaches in the domain of cognitive health and neurodegenerative disease treatment.

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