**Scholars Academic Journal of Biosciences**
Abbreviated Key Title: Sch Acad J Biosci
ISSN 2347-9515 (Print) | ISSN 2321-6883 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

**General Surgery**

# Paan – A Mouthful of Betel Leaf Packaged Ambrosia for Good Health

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**DOI:** https://doi.org/10.36347/sajb.2025.v13i01.012 | **Received:** 06.12.2024 | **Accepted:** 14.01.2025 | **Published:** 16.01.2025

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## 1. Abstract

**Review Article**

The chewing of sachet-like betel leaf quids, packing various spicy and flavoured ingredients in a folded betel leaf, is a customary practise in a number of nations of South Asia. The betel leaf munchie (*paan*), most popularly chewed after meals, has been much berated and unfairly scorned, as it is thought to produce detrimental effects on the body. This dogma about the harmful effects of *paan* has been upended by recent studies demonstrating the beneficial impact of betel phytochemicals on several body functions, as well as on the gut microbiota. Moreover, the advantageous effects of the health-promoting phytochemicals contained in catechu heartwood extract (*kattha*), slaked lime, betel nut (*supari*), and the other condiments added to the quid according to individual preferences, have also been documented in a large number of studies conducted over the past decade. In the reconsidered position, the betel leaf quid can be regarded as a delectable munchie loaded with phytoactives possessing multifarious health benefits.

**Keywords:** Betel Leaf, Areca Nut, Paan Quid, Mouth Freshener, Munchie Dessert, Phytochemicals.



## 2. INTRODUCTION

Evidence from archaeological excavations suggests that both the areca nut and the betel leaves have been chewed since ancient times. The earliest archaeological affirmation for Betel nut use in humans, comes from Spirit Cave in Thailand, dating to the terminal Pleistocene, around 10,000 years ago [1, 2]. Evidence of betel leaf use in prehistoric times has been found in caves located in eastern Timor, where remains of the Piper betel vine and Areca nut have been found in deposits dating between 13,000 to 4,000 years ago [3,4]. Remains of Areca nut have also been discovered at Kuala Selingsing in Peninsular Malaysia [5]. In the Indian sub-continent, the betel leaf (BL) and nut have played an essential part in the popular culture, since days of yore. It is not known when these two distinct stimulant botanicals, betel leaf and nut, were used together for the first time, but the religious *pooja* rituals in India utilize both together, wherein the *pongi phalam* (intact oval betel nut) is placed on the *tamboolam* (betel leaf). The first recorded usage in India dates to about 400 BC, and there is mention of chewing betel leaves in the ancient Ayurvedic text, the Charak Samhita [6]. The custom of chewing betel leaf (BL) after meals became widespread between the years 75 AD and 300 AD. Marco Polo, a European explorer, observed that monarchs and nobles in India chewed betel during the time that he was here in the 13th century AD [7].

The way that humans chew their food has evolved throughout time. The areca nut, mineral slaked lime, and betel leaves are often chewed together as a wrapped packet (quid) made by folding over the betel leaf three times at some stage in evolution, catechu (also known as kattha, derived from Acacia catechu) and other flavouring compounds including spices were introduced as well. Over the course of many decades, tobacco was also included in the BL package. It is now increasingly more common to find chewing of *gutkha*, which is a ready-to-eat alternative, made from tobacco, areca nuts, and slaked lime, as opposed to the traditional habit of chewing BL quid, which has been steadily declining in popularity.

Betel leaf chewing is looked upon with disdain in the present times, primarily because of its purported link with oral cancer. But the evidence is contrary, and sometimes confounding. Several studies that have evaluated the effects of BL, have indicated that it has no carcinogenic effects when ingested alone. The effect of aqueous BL extract was studied by Bhide *et al*., and Shirname *et al*., who found that administration of betel leaf extract in Swiss and C17 mice did not result in development of any tumours [8, 9]. In animal tumour models, BL extract has even shown a positive impact in the form of a lowered tumour development rate. In their study, Rao and colleagues showed that the extract of

betel leaves prevented the development of DMBA-induced mammary carcinomas in rats [10].

A large number of studies have been conducted to determine the pharmaceutical actions of BL, and the results of these studies have shown that the leaf extract, fractions, and purified compounds all have various beneficial properties, including antidiabetic, cardioprotective, antiinflammatory/immunomodulatory, antiulcer, hepatoprotective and antiinfective actions. Patents have also been granted for some of the extracted phytochemicals which exert biological actions such as anti-inflammatory, anticancer, and immunomodulatory [11]. The various ingredients and delectables used in making the paan quid, namely slaked lime, catechu, betel nut, minced coconut, flavours and spices also confer a variety of therapeutic effects, as have been described below. Additionally, the leaf extract has been found to play a role in oral hygiene. In view of these benefits, replacing routine sweet desserts with the "sweet *paan*" may be the best idea for the Western World.

## 3. METHOD OF PREPARING THE BETEL LEAF QUID (*PAAN)*

The preliminary step in crafting the multi-component packaged betel leaf quid, is the application of a thin layer of slaked lime (*chuuna*) over one surface of the betel leaf. Over this layer of lime, another thin layer of *Kattha* (paste of Acacia catechu heartwood in water) is applied (Figure 1).

**Figure 1: The first step in preparing the Paan quid consists of applying thin layers of lime (top figure) and catechu paste (*kattha*) as shown in lower figure.**

After applying these two layers of lime and catechu, the other herbs and spices are placed, one after the other, on the betel leaf. The most important component is diced areca nut. The diced areca nut pieces are usually soaked in water for some time before use. After adding areca nut pieces, a dash of peppermint paste is applied, followed by minced coconut, sliced dates, rose petal jam (gulkand), fennel seeds, tuti fruity and cardamom, according to individual preferences. The betel leaf is now folded obliquely two or three times to create an envelope like quid, and a clove is pierced through all the layers of betel leaf (like a rivet) to hold the folds in place (Figures 2 & 3). The betel quid is now ready to be eaten.

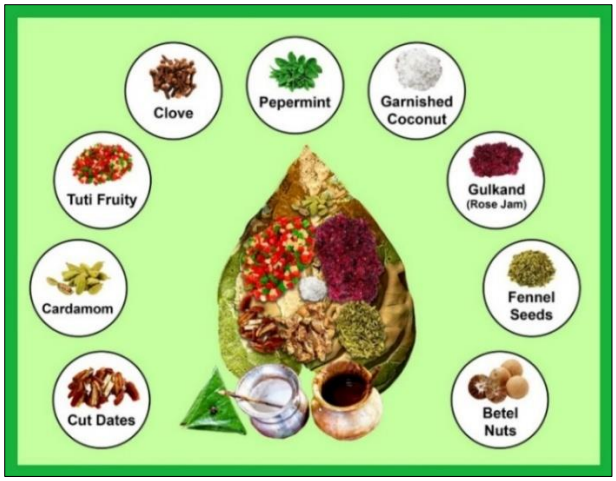


**Figure 2: The various constituents of the Betel leaf quid are shown, including slaked lime and catechu suspensions shown at the centre bottom in metal pots. The readied betel quid is exhibited on the left side of the pots, demonstrating how a clove is utilized as rivet**

## 4. PHARMACOLOGICAL PROPERTIES AND HEALTH BENEFITS OF PHYTOCHEMICALS CONTAINED IN *PAAN* QUID CONSTITUENTS

### 4A. Bioactive Compounds in Piper Betel Leaf and Their Pharmacological Effects

A broad range of bioactive compounds have been identified from the extracts and essential oil (EO) of betel leaves. These include polyphenols, alkaloids, steroids, saponins, tannins, glycosides, fatty acids, amino acids and flavonoids. Also, coumarin compounds such as 3-ρ-coumaroylquinic acid, 4-ρ-coumaroylquinic acid, as also diastase and catalase enzymes have been identified. Volatile compounds such as propenylphenols, allylpyrocatechol diacetate, chavibetol, chavicol and hydroxychavicol are also present [12-14].

### 4A1. Antimicrobial Activity of *Paan* Leaf

Due to the presence of alkaloids, tannins, phenolic substances, sterols, chavicol acetate, eugenol and glycosides, betel leaf extracts show antibacterial activity against the gram-positive bacteria Bacillus subtilis, Staphylococcus aureus, Streptococcus pyogenes and Micrococcus luteus, and gram-negative bacteria Escherichia coli, Proteus vulgaris and Pseudomonas aeruginosa [15-17]. Taukoorah et al demonstrated that Piper betel leaf extracts containing high amounts of phenols and flavonoids exhibit antibacterial activity against Propionibacterium acnes and Staphylococcus epidermidis [18]. The volatile compounds in betel leaf have shown a significant fungicidal effect against Candida albicans and Candida glabrata. This latter effect is particularly useful for treating topical infections, and as gargle mouthwash against oral Candida infections [19]. Eugenol also exhibits strong antifungal activity against Aspergillus fIavus [20].

The compound 4-allylpyrocatechol (APC) extracted from Piper betel inhibits the growth and biofilm formation of oral Streptococcus and Candida spp. by different mechanisms of action and at differing killing rates. Phumat *et al*., considered APC as a promising agent for preventing and treating dental disorders caused by S. intermedius, S. mutans, and C. albicans [21]. Antibacterial activity of Allylpyrocatechol against oral bacteria was also demonstrared by Ramji *et al*., 2002, in an “in vitro” saliva chip model. These researchers found that APC reduced the production of volatile sulphur compounds, such as methyl mercaptan and hydrogen sulphide by oral anaerobic bacteria, and prevented halitosis and periodontal infection [22].

Some compounds derived from Piper betel plants, namely piperidine, chlorogenic acid, and eugenyl acetate, exhibit bactericidal effects against various strains of Vibrio species. Vibrio is a genus of pathogenic bacteria that can cause diseases in humans such as gastroenteritis, wound infections, and septicemia. Piperidine exhibited the best anti-Vibrio effect against the five Vibrio species tested. Combinations of sub-inhibitory concentrations of the three compounds also showed inhibitory effects against Vibrio strains. These findings suggest that compounds derived from Piper betel plants could potentially be used as broad-spectrum antibiotics against Vibrio species [23].

### 4A2. Antioxidant Activity of Betel Leaf

Eugenol, a marker compound IN PBLE, shows moderate antioxidant activity [24]. Piper betel leaf extract (PBLE) contains flavonoids and polyphenols which provide anti-oxidative activity [25, 26]. The Piper betel phenolics, allylpyrocatechol (APC) and chavibetol (CHV), were found to effectively protect photosensitization-mediated lipid peroxidation (LPO) of rat liver mitochondria, APC being significantly more potent. The results suggest that APC may play an important role in protecting biological systems against damage, by eliminating reactive radicals generated from certain endogenous photosensitizers [27].

Hydroxychavicol (HC), also found in PBLE, is a potent COX-1/COX-2 inhibitor, ROS (Reactive Oxygen Species) scavenger and inhibits platelet calcium signalling, TXB(2) production and platelet aggregation. HC could thus be a potential therapeutic agent for prevention and treatment of atherosclerosis and other cardiovascular diseases through its anti-inflammatory and antiplatelet effects, without affecting haemostatic functions [28].

Paridhi *et al*., found that Piper betel essential oil possesses effective antibacterial, antioxidant and anti-inflammatory potential and could be used effectively in the formulation of oral health care product [29]. Leaf essential oil was evaluated for its anti-inflammatory activity, using the detection of MMP-2 (metalloproteinase-2) and MMP-9 (metalloproteinase-9) using the gelatin zymography method in vitro. An effective anti-inflammatory activity with 85% inhibition was observed. Piper betel essential oil also showed effective antibacterial activity against the tested periodontal pathogens alongside antioxidant and anti-inflammatory actions [29].

### 4A3. Anticholinesterase Activity and Neuro-Protective Effect

Betel leaf methanol extract, containing hydroxychavicol was assessed for its anti-acetylcholinesterase (AChE) and butyrylcholinesterase (BchE) inhibitory activity, as compared to chlorogenic acid. Hydroxychavicol was found to have a more potent cholinergic effect than chlorogenic acid, but a combination of both (1:1) showed the highest inhibitory activity against AchE and BchE [30]. AchE inhibitors are used to treat Alzheimer's disease.

### 4A4. Anti-Ulcer Activity

The ethanol extract of betel leaves and the isolated compound allylpyrocatechol were found to have excellent healing properties against indomethacin-induced stomach ulceration in Sprague-Dawley rats. The

extract reduced the ulcer index by 93.4%, accelerated ulcer healing, improved the mucin content of gastric tissues, restored normal levels of protein and malondialdehyde (MDA), and also increased levels of SOD and Catalase, which are anti-oxidant enzymes that protect against ulceration [31].

**4A5. Lipid Lowering and Hepato-Protective Effect**

Venkadeswaran in 2014 demonstrated that 7 days of administration of betel leaf ethanol extract and its constituent eugenol decreased high levels of Total cholesterol, Triglycerides, LDL and VLDL in serum and liver tissue, and increased the levels of enzymatic and non-enzymatic antioxidants in rats. These results were significantly better in Eugenol treated rats as compared to the extract. In another study by Venkadeswaran *et al*., in 2016, the extract and eugenol also reduced raised liver enzymes, such as AST, alkaline phosphatase, ALT, and decreased lipid metabolizing enzymes such as lipoprotein lipase, and lactate dehydrogenase in serum, and decreased malondialdehyde (a biomarker of oxidative stress) in liver tissue and hemolysate [32].

**4A6. Anticancer Potential of Phytochemicals in Betel Leaf Extract**

The formation of tumours in the buccal mucosa was studied by Rao and colleagues [33] in Syrian golden hamsters, in which the carcinogen benzo(a) pyrene (BaP) was applied topically, alongwith aqueous extracts of tobacco, areca nut, or BL extract, to the buccal pouch mucosa. Animals that were treated with BaP alongwith tobacco and areca nut had a tumour formation rate of 15 and 10 percent, respectively, but animals who were treated with BL extract alongwith BaP, and animals that were treated with vehicle (control) did not develop any tumours. Rao *et al*., concluded that Betel leaf extract, in both short-term and long-term studies, expressed its inhibitory influence on B(a)P-induced tumorigenesis [33].

The chemopreventive action of betel leaves was further proven by Bhide *et al*., who demonstrated that a few constituents of betel leaf, namely hydroxychavicol, α-tocopherol, eugenol and β-carotene, exhibited effects against benzo[a]pyrene-induced neoplasia in the stomach of Swiss male mice. The extract of betel leaf and its constituents were able to decrease the number of stomach papillomas, and the highest protection was shown by α-tocopherol and β-carotene [8]. Betel-leaf extract and hydroxychavicol suppressed the mutagenicity of 4-(methyl- nitrosamino)- I-(3-pyridyl)-1 -butanone (NNK) in both the Ames and the micronucleus test. In other studies in mice, betel-leaf extract reduced the tumorigenic effects of NNK (a potent tobacco-specific nitrosamine) by 25%. Concurrent treatment with the extract also inhibited the NNK-induced decrease in the levels of vitamin A in liver and blood. Betel leaf thus has protective effects against the mutagenic, carcinogenic and adverse metabolic effects of NNK in mice [34].

Azuine *et al*., 1992, in a study on hamsters, concluded that beta-carotene and a-tocopherol of betel leaf extract caused prolonged latency, regression of established tumours, and decrease in tumour incidence and tumour size. When combined with turmeric, the inhibitory effect of betel-leaf extract and its constituents was higher than that of the individual constituents. The study suggests that betel-leaf extract could be developed as a potential chemopreventive agent for human oral cancer [35]. Chlorogenic acid (ChA), another active ingredient isolated from betel leaves, has been reported to eliminate cancerous cells without harming normal cells, unlike most conventional chemotherapeutics [36]. Hydroxychavicol also inhibits inflammatory response molecules like inducible nitric oxide synthase and COX-2 (cyclooxygenase), which are known to enhance tumor growth by downregulation of the NF-kB pathway. Chavibetol (CHV), along with hydroxychavicol, acts as a radioprotectant, and exhibits substantial immunomodulatory and free radical scavenging activities. CHV synergizes with hydroxychavicol to exert antiproliferative activity against human prostate cancer PC-3 cells [36]. Betel leaf contains large amounts of safrole, which is rapidly degraded in the human body into dihydroxychavicol and eugenol, which are antimutagenic agents.

Several other studies have re-enforced the view of hydroxychavicol being an antimutagenic agent [36]. Gundala *et al*., have also identified Eugenol, hydroxychavicol, b-carotene, and a-tocopherol as key players in suppressing benzo[a]pyrene-induced neoplasms of the gut in mice, when betel leaf extract was mixed with drinking water. Eugenol in the betel leaves exhibited specific antiproliferative activity while partially triggering apoptosis along with eliciting radical scavenging activity, thus illustrating its antioxidant effects. Eugenol was also shown to hinder the upstream signalling molecule NF-kB, a key player in regulating the expression of genes controlling cell proliferation and survival [36].

**4B. Pharmacological Properties and Health Benefits of Phytochemicals in Areca Nut (*supari*)**

Areca nut (Areca catechu) contains a number of beneficial phytoconstituents, notable among them being arecoline, catechins, isorhamnetin , chrysoeriol , luteolin, arecaidine, phenolics and flavonoids. Hamsar *et al*., 2011, determined that the methanol extract of unripe areca nut seeds possessed high concentration of phenolics and total flavonoids [37]. Phenolics and flavanoids are well recognized for their highly beneficial effects on various body systems and functions [38-41]. The phytochemical arecoline, is also present in significant amounts in the water extract of areca nut and is pharmacologically very active. It has been found to be active against tapeworms, and the mechanism of action is considered to be due to the paralyzing effect caused by arecoline [42]. Arecoline has a significant synergetic effect with pentachlorophenol sodium and esculentoside

against Oncomelania, which are very small fresh water snails that are vectors for two serious human diseases: they can carry the schistosomiasis blood fluke parasite, and the paragonimus lung fluke parasites. The mechanism of the anti-oncomelania action is the ability of arecoline to bind well with protein PcRoo, which then leads to dropping of the gill cilia of the snail, affecting respiratory metabolism, since the gills take part in respiration. Loss of gill cilia accelerates the entry of arecoline into hemolymph, and then through the vasculature into the nervous system of the snail, inhibiting AChE and finally leading to the death of the parasite [43]. Arecoline is also reported to be an active agent against Bacillus proteus, Candida albicans and Bacillus anthracis [44].

The water extract of areca nut containing 0.06% arecoline has been demonstrated to increase the contraction of gastric smooth muscle and muscle strips of the duodenum, ileum, and colon [45]. Further, Arecoline was found to significantly increase sobriety and improve hangover symptoms in ethanol-exposed mice [46]. In addition, arecoline can bind with the GABA receptors, making people happy, and improving cognitive function and memory in patients having Alzheimer's disease [47]. Xiao *et al*., in their study showed that the total alkaloids of Areca catechu, especially arecoline could improve the mood of patients suffering from schizophrenia and depression [47]. Arecaidine and guvacine isolated from the A. catechu are also effective antagonists of GABA, with the ability to improve mood [48].

Arecoline also inhibits the release of the peripheral catecholamines via activation of cholinergic receptors [49]. This action has a blood pressure lowering effect. Some compounds isolated from the areca nut have been reported to possess notable DPPH radical-scavenging activities [50]. Arecoline hydrobromide, an alkaloid contained in the betel nut, inhibits the activity of the enzyme ACAT1 (acetyl-CoA acetyltransferase) which leads to attenuated cancer cell proliferation and tumour growth in mice [51].

The catechins isolated from the areca nut demonstrate a clear antiplatelet effect in the study of Ghayur *et al*., where the experimental platelet aggregation was induced by AA (arachidonic acid), ADP (adenosine diphosphate), PAF, epinephrine, and Ca2+ -ionophore [52]. Acetyl ursonic acid, ursonic acid and sitosterol extracted from the areca nut also possess antiplatelet effects on AA, ADP and PAF-induced platelet aggregation [53]. Administration of polyphenols isolated from the areca nut via the drinking water can decrease ovalbumin-induced allergic responses (including diarrhoea and infiltration and degranulation of mast cells in the duodenum); moreover, the serum ovalbumin-specific IgE and interleukin-4 (IL-4) levels in the duodenum are reduced by treatment with the polyphenols [54]. Areca nut chewing has also been shown to increase salivation, decreasing the chances of calculi forming in the ducts of the salivary glands.

### 4C. Pharmacological properties and Health Benefits of Phytochemicals Contained in Acacia Catechu (*kattha*)

#### 4C1. Acacia Catechu Heartwood Extract (*Kattha*)

Acacia catechu heartwood extract (ACHE), known in India as *Kattha*, has been used traditionally since a long time in the preparation of betel quid (and, in recent decades, *paan masala*). ACHE mixed with water, has also been a popular "thirst quencher" beverage in peninsular India for ages [55]. The coating or smearing of the Piper betel leaves with slaked lime and *kattha* is the initiating step in preparing the betel quid. Apart from lime and *kattha*, the other essential component of betel quid is areca nut. After placing some pieces of diced areca nut on the betel leaf smeared with lime and catechu paste , the betel leaf may be folded to make the basic *paan* quid. The other ingredients may be added as per convenience and preference (Figure 3). These include various spices, rose jam and flavoured condiments such as peppermint paste. Acacia catechu heartwood extract is obtained in paste form by boiling the heartwood with water and evaporating the solution to prepare the extract [56].

#### 4C2. Phytochemicals Contained in *Kattha*

The chemical analysis of the extract obtained from the heartwood and leaves of A. catechu (AC) has shown that the primary constituents are catechins (tannins), which by definition are gallic acid (polyhydroxylated benzoic acid) derivatives and polymers [56]. The predominant catechins in A. catechu include catechin, epicatechin, epicatechin-3-O-gallate, and epigallocatechin-3-O-gallate. Other major secondary metabolites present in the extracts include flavonol glycosides, flavonal dimers, and caffeine [56]. Also, extracts of A. catechu include rhamnetin, 4-hydroxyphenol, 3,3′,5,5′,7-pentahydroxyflavane, fisetinidol, 5-hydroxy-2-[2-(4-hydroxyphenyl)acetyl]-3-methoxybenzoic acid, and (2S,3S)-3,7,8,3′,4′ pentahydroxyflavane [56].

The presence of high amounts of gallic acid-derived compounds is primarily responsible for the astringent, tanning, and antioxidant properties of the extracts. The extract also contains alkaloids, ascorbic acid, and carbohydrates, and has also tested positive for terpenoids and triterpenoids as well as glycosides [56].

#### 4C3. Antioxidant and Neuroprotective Effects

In human neuroblastoma SH-SY5Y cells treated with hydrogen peroxide, Acacia catechu heartwood extract (ACHE) has been demonstrated to prevent a decrease in viability (as assessed by DAPI labelling), reduce ROS formation, and recover the mitochondrial potential and caspase-3 activation [57]. AC also demonstrated neuroprotective effects in rat brain slices exposed to hydrogen peroxide, by preventing the

expression of the main proteins involved in apoptosis, and the signalling pathways related to calcium homeostasis following oxidative stress-mediated injury [58]. Additionally, assessment done by quantitative mass spectrometry showed that AC.

**Figure 3: The various spices and condiments comprising the ingredients employed in preparing the betel leaf quid. Few, or all of these may be used, depending on user preferences. The ready-to-eat betel quids are shown at bottom.**

Partially prevented the hydrogen peroxide-induced altered proteome, including proteins belonging to the synaptic vesicle fusion apparatus. Defects in the latter are known to be a causative factor in Alzheimer disease [59]. Prevention of damage to the proteome suggests the possibility that ACHE is a nutraceutical useful in preventing neurodegenerative diseases [58].

**4C4. Anticancer Potential**

Administration of catechin-rich aqueous extract of Acacia catechu heartwood (AQCE) showed a dose-dependent growth inhibition response and DNA fragmentation in cells of the human breast adenocarcinoma cell line (MCF-7). Tumour multiplicity was significantly decreased with AQCE when compared with 7,12-dimethylbenz[a]anthracene (DMBA)–induced mammary carcinoma in Balb/c mice. AQCE treatment restored tumour marker levels, and also significantly reduced elevated levels of nitrite and malondialdehyde in DMBA-treated animals [60]. In such DMBA-treated animals, AQCE increased the activities of antioxidant enzymes, such as catalase, superoxide dismutase and total thiol, while it reduced levels of glutathione, protein thiol, glutathione peroxidase, glutathione reductase, and glutathione-S-transferase in mammary and liver tissue. AQCE also significantly improved body weight and maintained the architecture of mammary tissue in normal range. In a similar study, AQCE demonstrated chemopreventive activity against DMBA/TPA induced squamous cell carcinoma in Balb/c mice. The results suggest that AQCE may exert its chemopreventive activity by acting as an antioxidant [61].

In another study conducted on human colorectal adenocarcinoma HT-29 cells, AC extract irreversibly decreased cell viability in a concentration-dependent fashion. Cytotoxicity was accompanied by increases in apoptotic cells and ROS, a reduction in Mitochondrial Membrane Potential and increases in caspase-9 and 3 activities. AC did not affect the viability and functionality of rat ileum and colon rings, suggesting a safe profile toward healthy tissue. This study furnishes findings that indicate the potential of AC for colon cancer prevention and treatment [57].

**4C5. Immunomodulatory Activity**

The immunomodulatory effect of *Kattha* (AQCE) was studied by Ismail *et al*., in 2009. They found that AC extract engendered an increase in neutrophil adhesion to nylon fibres, increased the phagocytic index and provided significant protection against cyclophosphamide induced neutropenia. All these effects indicate that AQCE enhances cell mediated immunity [62]. AC extract also produced a significant increase in the quantum of serum immunoglobulins, demonstrating its beneficial actions on humoral immunity [62].

Sunil *et al*., 2019, demonstrated that ACHE provoked an enhancement in the number of antibody producing cells in the spleen of mice. Peritoneal macrophages also showed an increased phagocytic response [63]. The extracts also inhibited the production of NO and the release of TNF-α, while Interleukin-10 production was significantly increased after treatment with butanol fraction. The study suggests the possible use of A. catechu for its immunostimulatory actions [63].

**4C6. Antipyretic, Antidiarrhoeal and Hepatoprotective Properties**

An ethyl acetate extract of A. catechu heartwood given orally showed significant antipyretic activity in albino rats [64]. The antipyretic effect is presumably due to the flavonoid content, since many flavonoid compounds are known to be inhibitors of cyclooxygenase and lipooxygenase [65]. AC extract was also found to possess highly significant antidiarrhoeal property in respect of latent period of onset of diarrhoea, average number of stools passed and purging index. This effect is due to the tannins and polyphenols contained in AC, that impart astringent activity.

Highly significant hepatoprotective activity was also observed by Ray *et al*., when the extract of Acacia catechu was administered prophylactically for seven days [64]. AQCE treatment was also shown to prevent liver injury and significantly reduce elevated levels of nitrite and hepatic malondialdehyde (MDA) in DMBA-treated animals [60]. This liver protective effect is attributed to the phytochemical Cyanidanol, present in AC. Monga *et al*., 2012, also found that, in DMBA treated animals, AQCE maintained the liver cellular architecture within the normal range, and promoted the enzymatic and non-enzymatic antioxidant defence system [60].

**4C7. Antihyperglycemic Potential**

Bark extract of A. catechu exhibited significant anti-hyperglycaemic activity and produced dose-dependent hypoglycemia in fasting normal rats, while treatment of diabetic rats with ethanolic extract of AC restored the elevated biochemical parameters to the normal level [66]. Significant reduction of blood glucose level was also observed in nondiabetic albino rats following single dose treatment with the test drug [64]. The wood extract of Acacia catechu showed maximum anti-hyperglycemic activity [67].

**4C8. Miscellaneous Beneficial Effects**

In antinociceptive activity tests conducted by Rahmatullah, 2013, AC extract demonstrated a dose-dependent significant reduction in the writhing induced in mice through intraperitoneal administration of acetic acid, a strong peritoneal irritant [67]. These findings validate the folk medicinal use of the plant in Bangladesh for alleviation of pain.

ACHE has exhibited antimicrobial activity against B. subtilis, S. aureus, Klebsiella pneumonia, Shigella species, Sal. typhi, Escherichia coli, P. aeruginosa, and Candida albicans [68-70].

Treatment with different doses of *Katha* (ACHE) showed dose-dependent reduction in liver iron, lipid peroxidation, protein oxidation, liver fibrosis and ferritin [71]. The antioxidant enzymes levels were enhanced and the reductive release of ferritin iron increased significantly [71]. These results indicate that *Katha* has a potent hepatoprotective action against hepatic damage induced by iron overload in mice, probably by restoring the levels of antioxidant enzymes and reducing serum ferritin levels [71].

A study by Hazra provided evidence that 70% methanol extract of *kattha* acts as an antioxidant, iron chelator and DNA protector which is partly due to the phenolic and flavonoid compounds present in it [72]. Jagannathan *et al*., 2020, demonstrated that Katha extracts can be used to disinfect removable orthodontic appliances because of their good antimicrobial activity [73].

**4D. Pharmacological Properties and Health Benefits of Phytochemicals Contained in Cloves (Syzygium Aromaticum)**

**4D1. Phytochemicals Contained in Cloves**

Extracts of clove contain phenols, flavonoids, alkaloids, tannins, and saponins along with carbohydrates, terpenoids, steroids, sterols, phenolic compounds, cardiac glycosides, and fixed oil [74]. Sixteen volatile compounds are also present, with eugenol (71.56%) and eugenol acetate (8.99%) as the major ones; others are limonin, ferulic aldehyde,

tamarixetin 3-O-b-D-glucopyranoside, ombuin 3-O-b-D-glucopyranoside and quercetin [74].

Clove bud essential oil (EO) has been found to contain several bioactive components, the most abundant being eugenol (87%), chavibetal (19.7%), and β-caryophyllene (13%), and eugenyl acetate. Other bioactives present in clove are kaempferol, quercetin and its derivatives, caffeic, ferulic, elagic, and salicylic acids, as well as other minor constituents like α-humulene, β-humulene, methyl salicylate, crategolic acid, benzaldehyde, and six sesquiterpenes [74].

**4D2. Anti- Microbial Activity**

Extracts of clove exhibit antibacterial activity against Escherichia coli, Salmonella typhi, Staphylococcus aureus and Methicillin-resistant Staphylococcus aureus (MRSA) [75]. Eugenol, the major component of clove oil was shown to have bactericidal action against Proteus mirabilis [76].

Syzygium aromaticum (clove) extract (containing eugenol (58.88%), eugenyl acetate (23.86%), trans-caryophyllene (14.44%) and α-humulene (1.88%) exhibited the highest antifungal activity against C. tropicalis, C. albicans, and C. glabrata [77]. Encapsulated clove oil also exhibited strong antifungal action against Fusarium oxysporum and antiseptic effects on meat products [78].

Extract of clove also exhibits a dose-dependent antiviral effect against Feline Calicivirus, used as a surrogate for Human Norovirus, a food-borne virus. Eugenol and Eugenin isolated from clove bud essential oil were shown to have potent inhibitory effect against herpes simplex virus (79 ,80].

**4D3. Anti-Inflammatory Action**

Han 2017 demonstrated that clove essential oil exerted strong anti-inflammatory action in a model of the human dermal fibroblast system [81]. The extract of clove and eugenol when used separately, were also seen to exert immunomodulatory and anti-inflammatory action in murine macrophages. While clove extract inhibited the production of IL-1β, IL-6, and IL-10, eugenol did not affect IL-1β production but inhibited IL-6 and IL-10 [82].

In an experimental study done by Nikoui *et al*., on dogs in 2017, a surgical incision was made over the abdomen, and the effect of clove oil on healing was evaluated. It was observed that the dogs injected intravenously with clove oil post-operatively, had significantly reduced wound oedema, blood white blood cell count, serum neutrophils, and rectal temperature compared to controls. Also, histopathological examination conducted on a small piece of tissue biopsy taken from the wound 10 days post-operatively, showed that clove oil reduced inflammation significantly in dogs [83].

**4D4. Anticancer Activity**

In a study carried out by Nirmala *et al*., 2019, the extract of clove and its essential oil showed significant cytotoxic potency against the thyroid cancer cell line (HTh-7) [84]. In another study carried out by Han *et al*., 2017, Clove essential oil exhibited anti-proliferative activity against human dermal fibroblasts, and significantly inhibited the production of pro-inflammatory biomarkers, including VCAM-1), IP-10), I-TAC, MIG and tissue remodelling protein molecules. It also altered signalling pathways critical in cancer signalling processes [81]. Liu *et al*., 2014, also tested Clove extract and its component oleanoic acid against human cancer cell lines. They found that treatment with clove extract selectively increased protein expression of p21WAF1/Cip1 and g-H2AX, proteins that are involved in cell-cycle arrest [85].

**4D5. Anti Diabetic Effects**

Milind *et al*., in 2011, reported that extracts of clove improve serum biomarkers, antioxidant status, and histopathological changes in kidneys of streptozotocin-induced diabetic rats by correcting glycaemic control, lipid profile and preventing kidney damage. Clove essential oil and extracts mimic the suppressive action of insulin on gene expression of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. The latter catalyses the first committed (rate-limiting) step in hepatic gluconeogenesis [79].

In another experimental study, Polyphenol-rich extracts from Clove buds inhibited the activity of carbohydrate hydrolyzing enzymes linked to type 2 diabetes and Fe2+-induced lipid peroxidation in rat pancreas. Alpha-glucosidase inhibition was significantly higher than that of alpha-amylase and could be the mechanism by which clove elicits exerts its ameliorative effect on type 2 diabetes [86].

**4D6. Metabolic Effects**

Shukri *et al*., 2010, found that dietary intake of clove in rats, led to reduced tissue and cardiac muscle damage, reduced blood sugar levels, decreased lipid peroxidation, and decreased hyperglycaemia-induced oxidative tissue damage and cataract formation in the eye lens [87]. In a later study, Rosarior *et al*., 2021, demonstrated that Clove essential oil and extract exhibited antiradical and antioxidant activity that is several times higher than butylated hydroxytoluene (BHT), a standard antioxidant used in food products [88]. Abtahi-Eivari, 2021 also confirmed that extracts of clove improved serum biomarkers, antioxidant status, and prevented kidney damage in streptozotocin-induced diabetic rats [89]. Dietary inclusion of Syzygium aromaticum for 4 weeks in the diet of alloxan-induced diabetic rats, caused significant decrease in serum glucose, total cholesterol, LDL-C, VLDL-C, triglyceride levels, AST, ALT, and ALP, as well as liver function and lipid profile [90]. Extract of clove (containing eugenol, acetyl eugenol, caryophyllene and humulene) was

reported to inhibit S-phase DNA replication of HepG2 cells and adipocyte differentiation and prevent obesity [91].

**4D7. Effects on the Brain**

Eugenol has been observed to cause depressive action on action potentials, mostly by blocking sodium channels. In animal models, treatment with eugenol has been demonstrated to decrease the duration and intensity of pilocarpine-induced seizures. Daily eugenol treatment in pilocarpine chronic epilepsy animal models was also shown to prevent neuronal loss in the hippocampus, and decrease seizure mortality [92].

**4E. Pharmacological Properties and Health Benefits of Rose**

**4E1. Anti Microbial Properties**

Rose absolute and essential oil contain high levels of Phenolics, Tocopherol and Carotene, and have demonstrated strong antibacterial activity against Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Chromobacterium violaceum and Erwinia carotovora strains [93]. Phenyl-ethyl alcohol (78.38%) is the main constituent of rose absolute, while Citrenellol and Geraniol are the major compounds (>55%) of rose essential oil and hydrosol.

Aridoğan *et al*., 2002, found that the volatile oils of rose showed activity against Staph aureus [94]. Talib & Mahasneh, 2010, demonstrated that the butanol extract of rose showed high inhibition against the bacteria Salmonella typhimurium and Bacillus cereus, and the fungus Candida albicans. The aqueous and butanol extracts also showed significant active against Methicillin-resistant Staphylococcus aureus [95]. Since flavonoids and terpenoids were the compounds identified in these extracts, the anti-microbial activity was attributed by the workers to these phytoconstituents.

**4E2. Immunomodulatory and Anti-Oxidant Effects**

Slavov *et al*., extracted a water-soluble polysaccharide named RP-1 from distilled rose petals of R. damascena. They demonstrated its potent immunomodulatory effect on cultured mice intestinal Peyer's patch cells and IL-6 producing activity in murine peritoneal macrophages [96]. Kalim *et al*., 2010, demonstrated that 50% methanolic extract of rose showed scavenging property against DPPH, ABTS, NO, OH, O2 and ONOO(−). The extract prevented oxidative DNA damage. The methanolic extract was found to be comprised of Phenolics and Flavonoids, and these phytochemical groups may be considered responsible for the potent antioxidant activity [97]. In an in-vitro study, Wedler *et al*., 2016, detected a significant decrease in inflammatory gene expression and cellular protein secretion of pro-inflammatory biomarkers by use of polyphenolic fractions of rose oil distillation waste water [98]. The above studies suggest there are several compounds in rose extract that exert anti-inflammatory effects.

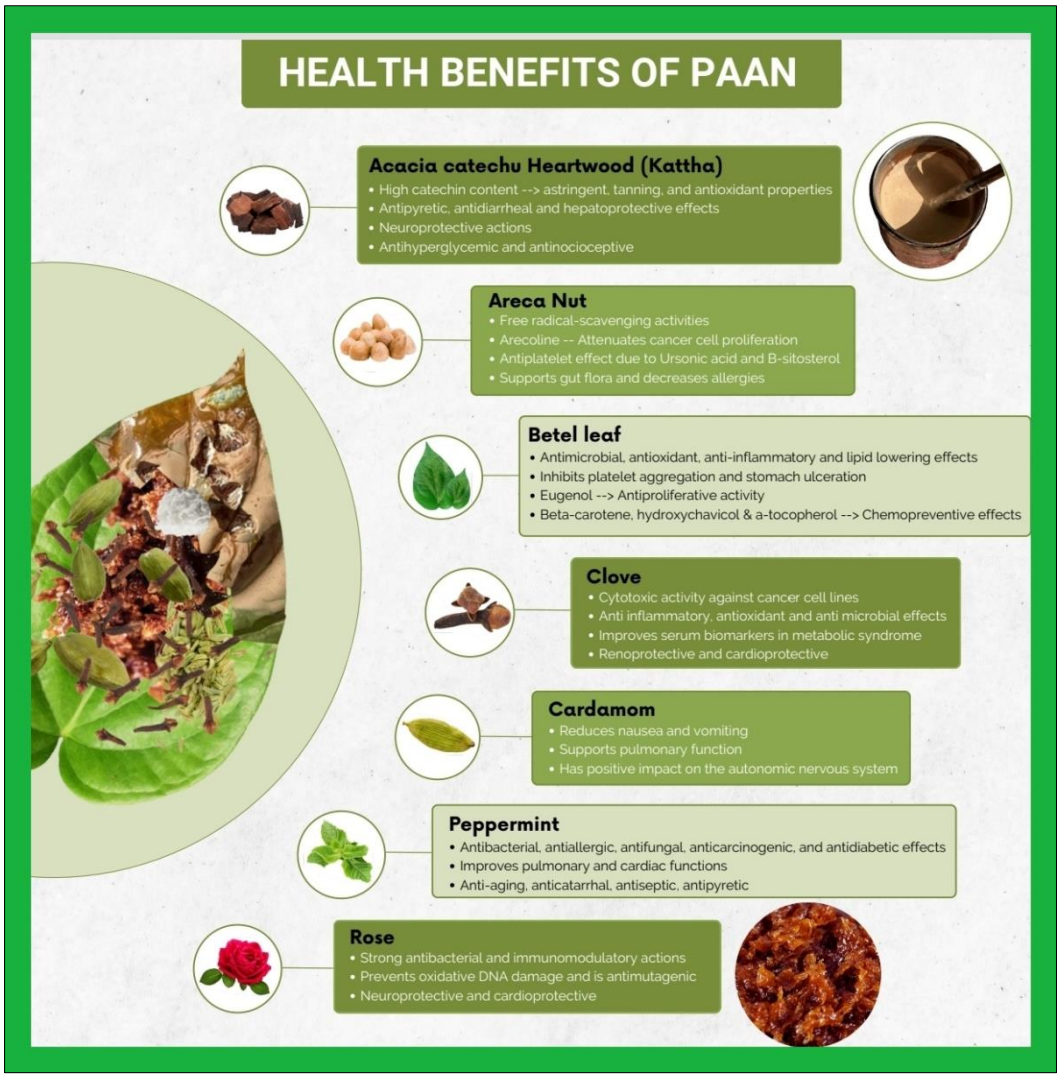


**Figure 4: A summary of the health benefits accruing from the different spices and condiments that are used to make the delicious Betel quid known as *Paan*.**

### 4E3. Neuro-Protective Actions

Awale *et al*., 2011 demonstrated that the extract of *Rosa damascena* buds significantly induced neurite outgrowth activity and inhibited the A*β*(25–35)-induced atrophy and cell death in cultured cortical neurons of rat embryos [99]. Further workup led the isolation of a very long polyunsaturated fatty acid having molecular formula $C_{37}H_{64}O_2$ as an active constituent. In another study, essential oil from rose reduced the H2O2-induced neuronal death and showed protective effects against aluminium-induced neurotoxicity, indicating a neuroprotective effect on immortalized GT1-7 mouse cell cultured hypothalamic neurons. Rose essential oil also demonstrated significant antioxidant properties and invoked increased viability of the neuronal cells against H2O2, probably due to the Citronellol content [100].

### 4E4. Cardio-Vascular and Metabolic Effects

A flavonoid glycoside named roxyloside A, alongwith isoquercitrin, afzelin, and quercetin gentiobioside, all isolated from rose buds, exhibited high levels of inhibitory activity against HMG-CoA reductase, the key enzyme in cholesterol biosynthesis. A separate compound, Cyanidin-3-O-beta-glucoside significantly suppressed angiotensin I-converting enzyme (ACE) activity, an enzyme involved in hypertension. These results indicate that R. damascena and its flavonoids may be effective in rectifying the functioning of the cardiovascular system, by decreasing blood cholesterol and reducing the systemic blood pressure [101].

### 4E5. Antimutagenic Activity

Hagag *et al*., 2014, in their study found that both rose concrete (orange-red waxy semi-solid material) and absolute oils showed significant antimutagenic and anti-cancer activity against human liver carcinoma cell line (HepG2) and breast carcinoma cell line (MCF7). Both extracts were also found to be cytotoxically and genotoxically safe on normal human blood lymphocytes. On analysis, the major aroma compounds in concrete oil were phenyl ethanol (37.83%), b-citronellol (8.2%), geraniol (4.04%), eugenol(1.48%), and in absolute oil were phenyl ethanol(33.31%), b-citronellol (12.45%),

geraniol (6.28%) and eugenol (2.03%). The workers noted that high level of phenyl ethanol may be one of the responsible constituents along with previously identified geraniol and eugenol for the anticancer properties [102].

**4E6. Other Beneficial Effects**

Sadraei *et al*., 2013 & 2016, found that hydroalcoholic extract of rose has inhibitory effect at higher concentration but stimulatory action at lower concentrations on ileal contractility. The isolated geraniol and citronellol were found to have much stronger ileum relaxation activity than the essential oil itself [103,104]. The difference in actions on ileal smooth muscle contractility, depending on the concentration of administered rose extracts, explains the benefits of rose extracts in both diarrhoea and constipation.

In Solimine's 2016 study, the workers studied the anti-tyrosinase activity of the polyphenol rich fraction which remained after the rose had been distilled, and found this polyphenolic fraction to be many times more potent than kojic acid. Substances with anti-tyrosinase activity are used as anti-hyperpigmentation agents. On analysing this polyphenolic fraction, Solimine *et al*., found it to be rich in quercetin, kaempferol and ellagic acid [105]. In a previous study, Wedler *et al*., had identified Ellagic acid as the compound being responsible for the potent tyrosinase inhibitory effects of rose [98].

**4F. Pharmacological Properties and Health Benefits of Peppermint**

Peppermint is derived from plants of the genus Mentha. Mentha derivatives are best known for their antimicrobial, antiallergic, antifungal and anticarcinogenic effects, and are widely used in the treatment of nausea, vomiting, obesity, and gastrointestinal problems [106,107]. Mentha piperita has also demonstrated anti-aging, anticatarrhal, antiseptic, antipyretic, antispasmodic, emmenagogue, and stimulant properties [108]. The composition of mint essential oil includes mainly menthol and menthone, along with other components such as 1,8-cineole, limonene, and beta-caryophyllene.

Oral Peppermint Essential Oil administration enhances memory and strengthens mental functioning in Wistar albino rats [109]. Peppermint oil has also been shown to help prevent mental fatigue and improve cognitive performance in humans after oral administration [110]. Antidepressant properties of peppermint oil were also observed in the ethanolic extract of peppermint after intra-peritoneal instillation in rats [111]. Abdelhalim in 2021 assessed the effects of oral administration of Mentha piperita (peppermint) on the mental health problems affecting university students. Study results demonstrated the beneficial effect of peppermint administration on memory, stress, and insomnia among participants [112].

Mentha plants are rich in bioactive compounds such as carvacrol, rosmarinic acid, quercetin, baicalein, and apigenin which have cardioprotective effects [113]. Menthol has been found to improve pulmonary functions, and is beneficial in the treatment of ischemic heart disease [114,115]. Carvacrol promotes the activity of antioxidant enzymes such as superoxide dismutase, glutathione, and glutathione peroxidase, as well as the Akt/eNOS pathway, facilitating cardio protection [116]. The extract of Mentha leaves shows considerable anti hyperlipidemic activity by reducing Fasting Blood Sugar (FBS), serum cholesterol, low-density lipoprotein (LDL), and triglyceride in experimental rats [117]. Significant Reno-protective effects were observed in rats, in which diabetic nephropathy was ameliorated [118]. Research studies also suggest that peppermint can also protect the liver, with excellent anti-hepatotoxicity effects observed against carbon tetrachloride-induced lipoperoxidation [119].

Chumpitazi *et al*., in 2018 reviewed the effects of peppermint oil on gastrointestinal physiology [120]. They noted that in several studies, Peppermint oil helped reverse serotonin-induced and acetylcholine-induced contraction through the blockage of calcium channels in pig colon and rabbit smooth muscle of jejunum [121,122]. This smooth muscle relaxation effect has been utilized to facilitate completion of clinical procedures such as colonoscopy and endoscopic retrograde cholangio- pancreatography (ERCP) [120]. Peppermint oil (menthol) has also shown strong anti-inflammatory effects [123]. Research studies have demonstrated that oral administration of peppermint oil can help prevent acetic acid-induced colitis and xylene-induced gut inflammation in experimented rats [124]. Human trials have revealed peppermint oil to be effective in irritable bowel syndrome [125], childhood functional abdominal pain [126], and functional dyspepsia [127]. These beneficial effects are probably due to the combined smooth muscle relaxant and anti-inflammatory effects.

Brown *et al*., in 2019 analyzed the antioxidant potential of polyphenols present in mint leaves [128]. Their study results showed that the total phenolic content of mint extracts is positively associated with antioxidant activity. The major phenolic compounds in mint are rosmarinic acid, eriocitrin, luteolin 7-O-rutinoside, hesperidin, apigenin, pebrellin, and gardenin B [129]. Other polyphenols found in mint include caffeic acid, eugenol, and ferulic acid [130]. Mentha extracts protect against oxidative damage by eliminating iron (II) ions, thus preventing metal-catalyzed hydroperoxide decomposition or hydroxyl radical-generating reactions [131]. Phenolics found in mint extracts were also seen to inhibit LDL cholesterol oxidation through the scavenging of peroxyl radicals and the chelation of cupric ions. LDL oxidation is now considered the key trigger for atherosclerosis; thus, inhibition of this process would result in delaying the normal process of arterial narrowing caused by atherosclerosis. The mint

polyphenols also act as anti-inflammatory agents, since they are inhibitors of Cyclo-oxygenase-2 [128].

Chakraborty *et al*., in 2022 reviewed the pharmacological benefits of Mentha piperita L. in various disease conditions [132]. Peppermint has shown good tumour inhibitory activity which can be attributed to the presence of menthol that inhibits cancer cells by various mechanisms, including inhibition of tumor angiogenesis, induction of apoptosis and cell cycle arrest [133]. Flavonoids found in peppermint such as luteolin7-O-rutinoside can prevent antigen-mediated nasal allergies [134]. Yucharoen *et al*., (2012) showed the antiviral activity of peppermint extract consisting of dichloromethane and methanol, against HSV-1 and HSV-2 [135]. Rosmarinic acid has also demonstrated significant anti-helminthic and antiviral activity, particularly against Herpes simplex virus [136]. Phytochemicals contained in Mentha piperita can also play an effective role in reducing SARS-CoV-2 infections by directly inhibiting the virus and minimizing its replication [137].

Menthol, due to its anti-inflammatory properties, is effective in the amelioration of chronic obstructive pulmonary disease (COPD) by modulation of transient receptor potential (TRP) channels, and helps to alleviate associated symptoms, such as fever and cough [138]. In an interesting study, Meamarbashi in 2014 investigated the effects of peppermint ingestion on exercise performance and physiological parameters among healthy male university students. After peppermint essential oil administration, the subjects showed significant improvements in grip strength, jump performance, spirometric parameters, reaction times, and vital signs, including blood pressure, heart rate, and breath rate [139]. These findings suggest that peppermint essential oil could potentially enhance athletic performance and respiratory parameters, thereby opening new avenues for sports nutrition and athletic training.

## 5. AROMA EFFECTS OF PEPPERMINT AND CARDAMOM

The condiments comprising the mixture piled upon the betel leaf, while preparing the betel quid munchie, include some aromatic substances, such as cardamom and peppermint paste. These aromatic ingredients impart a very salubrious flavour to the delectable betel quid. Besides the refreshing odour that pleases the senses, these two aromatic condiments also impart beneficial effects due to the olfactory actions of their odorant molecules. These physiological actions occur either through the sensory olfactory nerves which reach the olfactory tract in the forebrain, or through direct entry of aroma molecules into the frontal areas of the brain through the cribriform (perforated) bony plate which forms the roof of the nasal cavity [140]. These health enhancing physiological actions are described below.

**Cardamom (Elettaria Cardamomum) Aroma Benefits**

Cardamom is part of the Zingiberaceae family, thereby closely related to ginger and turmeric. The essential oil of cardamom, which is primarily derived from the seeds of the plant, is endowed with a distinctively sweet and spicy aroma, reflecting the true essence of the plant itself. Cardamom oil comprises several components, with 1,8-cineole, alpha-terpinyl acetate, linalool, and limonene standing out as the most prominent.

In several studies, Cardamom aromatherapy has shown potential for alleviating symptoms of nausea and vomiting. Two randomized studies demonstrated that use of cardamom aroma significantly decreased the severity of nausea in cancer patients undergoing chemotherapy [141,142]. Similarly, cardamom aromatherapy demonstrated a reduction in postoperative nausea (PON) and vomiting in women undergoing cesarean sections [143]. Another study on PON also revealed that a blend of essential oils, which included cardamom, significantly reduced nausea in patients undergoing ambulatory surgery [144].

A possible mechanism of action of cardamom EO aromatherapy, is the significant physiological impact seen on the autonomic nervous system, as indicated by changes in heart rate variability and improved aerobic fitness when combined with exercise [145]. The results obtained by Patil *et al*., in their study, provide support for the stimulatory effects of cardamom aroma, as indicated by a shift of the autonomic balance towards sympathetic predominance. They concluded that performing exercise alongwith use of cardamom aroma is not only enjoyable because of its effects on the mood, but also promotes physiological excitation, resulting in enhanced physical activation.

**Peppermint Aroma Benefits**

Research studies on human subjects suggest that the scent of peppermint improves mood and alertness, and reduces frustration and anxiety [146]. Sniffing peppermint oil was associated with reduced mental fatigue in the mouse model [147]. Peppermint essential oil aromatherapy demonstrated significant fatigue-reducing effects in cardiac and cancer patients [148]. Clinical trials conducted by Mogharab *et al*., 2017, and Akbari *et al*., (2019) suggested that the inhalation of peppermint essence could effectively alleviate the pain and anxiety experienced by patients undergoing intravenous catheterization and other invasive procedures [149,150]. A clinical trial conducted by Soleimani *et al*., in 2022 concluded that peppermint EO inhalation can significantly alleviate anxiety in patients suffering from acute coronary syndrome in the emergency department [151].

Two comprehensive reviews conducted by Sari *et al*., in 2023, and Bali S. in 2023, evaluated the

therapeutic benefits of peppermint aromatherapy in cardiovascular disease patients [152,153]. The researchers found that peppermint scent, recognized for its refreshing aroma, exhibited analgesic, anxiolytic, and sedative properties. This comprehensive range of effects helps to alleviate symptoms such as anxiety, stress, and poor sleep quality, which are common complaints among cardiovascular disease patients. A randomized placebo-controlled trial by Baraka and Hassan in 2022, conducted in conscious patients on mechanical ventilation, demonstrated that pain scores were significantly reduced in patients who inhaled peppermint EO aroma compared to those who inhaled the placebo, almond oil [154]. Kim *et al*., (2005) observed that aromatherapy massage by a blend of essential oils (rosemary, lemon, and peppermint) significantly alleviated constipation in the study subjects [155]. Sembiring *et al*., (2021) studied the use of topical peppermint aromatherapy in reducing uremic pruritus, a common and bothersome symptom among chronic renal failure patients [156].

A study by Moss *et al*., in 2008 uncovered that peppermint aroma significantly boosted memory and alertness levels in healthy individuals [157]. Deivanayagame *et al*., in 2020 recorded a significant enhancement in visual and auditory reaction times with peppermint aroma exposure, suggesting that short exposure to peppermint aroma can significantly improve cognitive function and reaction times [158]. Another study by Mahachandra and Garnaby in 2015 showed that peppermint fragrance improved alertness in drivers, suggesting its application as an in-vehicle fragrance [159]. A noteworthy semi-experimental study conducted by Ghods and Valian in 2013 on critical care nurses in ICUs, showed a statistically significant improvement in accuracy in the group that received the peppermint essence [160].

Study participants exposed to peppermint aroma by Toda and Morimoto, 2011 showed significant reductions in salivary cortisol levels. Cortisol is often referred to as the "stress hormone," and its reduction is associated with lowered stress levels [161]. In 2013, Varney and Buckle found that inhaling a mixture of essential oils, including peppermint oil, had a positive impact on individuals suffering from mental exhaustion or moderate burnout [162]. A study led by Moss *et al*., (2023) showed that the presence of peppermint aroma in a simulated driving environment resulted in significant reductions in aggressive driving behaviors [163]. Hamzeh *et al*., in a 2020 study demonstrated a significant improvement in sleep quality after using lavender and peppermint essential oils [164]. All these benefits can accrue from the pleasing aroma of a well prepared Betel quid, and since chewing the quid takes some time, the olfactory receptors located in the nasal cavity and the nasal pharynx are able to perceive these aromas for a reasonable amount of time.

## 6. EFFECTS OF BETEL QUID ROUGHAGE CONTAINING CHLOROPHYLL ON CARCINOGENESIS AND THE GUT MICROBIOME

The betel quid can be made with various ingredients, and can be either plain or sweetened with rose jam. After placing the quid in the mouth, it is chewed for some length of time, crushing the ingredients and turning the mixture into pulp. One of the main ingredients of sweetened betel quid is rose jam, made from rose petals. Kamijo *et al*., 2008, investigated the effects of crushed rose petals on the growth of 10 species of intestinal and pathogenic bacteria. Their results suggested that the soluble phyto-constituents in the rose petals suppressed the growth of four pathogenic intestinal bacteria in plate culture, without affecting the growth of beneficial bifidobacteria or lactobacilli [165]. The latter two genera of bacteria are known to enhance the human immune system and to produce short-chain fatty acids. This selective antibacterial activity of the pulverized petals on intestinal and pathogenic bacteria resembles that of prebiotics such as oligosaccharides and dietary fibre. The investigators proposed that the active constituents in rose petals responsible for this beneficial activity, were the hydrolyzable tannins, such as rugosin D and tellimagradin II.

Betel leaf, the main constituent of betel quid, contains a significant amount of Chlorophyll. Chlorophyll, which is of several types, including Chlorophyll a, b, c, d and e, has recently been found to exert certain types of bioactivity in the human body, including the ability to act as antioxidant, antimutagen, and anticarcinogen [166]. This is because chlorophylls possess a unique chemical structure that enables them to scavenge harmful free radicals, limit DNA damage, and modulate other cellular processes. Also, their hydrophobic (lipophylic) side chains enable interactions with biological membranes (since cell walls/membranes are composed primarily of lipids), influencing uptake of compounds by cells and impacting signalling pathways [167].

Chlorophyll derivatives also exhibit dose-dependent antimutagenic activity. For example, topical application of “pheophorbide a” was demonstrated to inhibit skin tumour cell proliferation induced by carcinogens DMBA and TPA in mice [168]. The anticarcinogenic activity of chlorophylls is presumed to occur through various mechanisms, including the creation of a molecular complex with aromatic carcinogens, which results in reduced carcinogen uptake and bioavailability, thus inhibiting activation of the carcinogen. This protective effect through formation of molecular complex mainly occurs when chlorophylls are administered simultaneously with the carcinogen, highlighting the importance of regularly consuming chlorophyll containing foods in order to combat dietary carcinogens. Hence, daily consumption of paan after

meals provides a simple way to consume chlorophyll in an easy and delicious manner.

The above protective effect was further demonstrated in a rodent study carried out by by Simonich *et al*., in rats who were administered chlorophylls derived from spinach, the chlorophyll was found to protect the animals against biochemical and pathophysiologic biomarkers of Aflatoxin-B1 induced carcinogenesis in the liver and colon. This protective effect was thought to occur through the inhibition of intestinal uptake of AFB1 [169]. Mishra *et al*., 2011, found that chlorophyll intake also helps induce apoptosis in cancer cells [170]. Moreover, recent studies have reported that supplementation with chlorophyll-rich spinach extract significantly reduced body weight gain, low-grade inflammation, and improved glucose tolerance in mice fed a high fat diet [167]. Furthermore, use of this chlorophyll-rich extract also alleviated gut dysbiosis induced by the HFD.

Chlorophyllin (CHL) is a water soluble semisynthetic derivative of chlorophyll, which is used as a food additive, and has been found to confer a wide range of health benefits. These health benefits of CHL include potent antigenotoxic, anti-oxidant, and anticancer effects [171]. Several experimental and epidemiological studies have demonstrated that dietary supplementation by CHL lowers the risk of cancer. The modulatory effects of CHL on cancer initiation and progression appear to be mediated via abrogation of key oncogenic signal transduction pathways such as nuclear factor kappa B, Wnt/b-catenin, and phosphatidylinositol-3-kinase/Akt signalling. These pathways are involved in carcinogen metabolism, cell cycle progression, cancer cell invasion, and angiogenesis in tumours.

Zheng *et al*., also explored the effects of oral chlorophyllin on gut microbiota, intestinal inflammation and hepatic fibrosis in mice. Their findings indicated that chlorophyllin speedily rebalanced the gut microbiota, causing down-regulation of the phylum Firmicutes and up-regulation of the phylum Bacteroidetes [172]. Further, employing in vitro experiments on intestinal epithelial cells, they demonstrated that chlorophyllin could inhibit NF-κB pathway via suppression of IKK-phosphorylation. They concluded that their study highlighted the potential application of chlorophyllin in regulating the intestinal microbiota and inhibiting intestinal inflammation, thus ameliorating hepatic fibrosis.

Ying *et al*., studied the gut microbiota in human subjects who chewed betel nut. The gut microbiome profiles of the betel nut users suggested an increase in the abundance of beneficial microbes and a reduction in the numbers of disease-related microbes [173]. Zhao *et al*., studied the diversity and abundance of the intestinal microbiota in both male and female Kumming mice fed various areca preparations to mimic different areca nut chewing habits. They found that the gut microbiome was more myriad and abundant in the experimental groups as compared to the control groups [174]. The researchers also found that different areca preparations had disparate effects on the diversity, abundance, and composition of the intestinal flora in the mice.

Yi *et al*., studied the effects and molecular mechanisms of areca nut and its major ingredients in a rodent model of HFD (high fat diet) induced dyslipidemia [175]. Analysis of gut microbiota revealed that Areca nut polyphenols (ANP) increased the abundance of beneficial bacterium Akkermansias and diminished the numbers of the pathogenic bacterium Ruminococcus, while arecoline exhibited results opposite to ANP. The results indicated that areca nut polyphenols ameliorated Western diet-induced dyslipidemia by increasing the abundance of beneficial bacteria in the gut microbiota and reducing the expressions of SREBP2 and HMGCR, the proteins involved in synthesis of sterols and fatty acids.

## 7. DISCUSSION

The ancient Ayurvedic texts, such as the Charaka Samhitas, Sushruta Samhita, and Ashtang samgrah, recommend the chewing of betel leaf after bathing and meals [176]. These Ayurvedic texts extol the therapeutic virtues of betel leaf (BL), stating that it is especially beneficial for the heart [177]. These ancient texts also recommend taking betel leaf alongwith lime, catechu, clove, arecanut etc [176]. All of the latter are still employed as ingredients in preparing the *Paan* quid, and have been found to have numerous health benefits (Figure 4). Traditionally, areca nuts have been thought to possess aphrodisiac properties [178,179], whilst betel leaves have been used as stimulant, antibacterial, and breath freshener. Despite the widespread use of BL in ancient times, there is no compelling evidence to suggest that oral cancer was prevalent during that era. In fact, Hydroxychavicol (HC), a phenolic compound present in Betel leaf in significant amounts, has been shown to exert anti proliferative activity in prostatic and other cancers. Studies have demonstrated that HC impedes cell-cycle progression in cultured oral KB carcinoma cells, while Paranjpe has recommended HC as a potential compound for management of prostate cancer [180,181].

The flavonoid compounds in areca nut have also been found to have strong cytotoxicity activity in human gastric cancer cell line (SGC-7901) and SMCC-7721, a human liver cancer cell line [182]. Further, the data strongly suggests that catechin-rich AC (*kattha*) has anticancer potential, which may be attributable to its ability to positively modulate tumour markers as well as the antioxidant system, which could decompose the peroxides and, thereby, offer a protection against lipid peroxidation. Also, methanolic extract of A. catechu (ACME) has shown significant cytotoxicity against human breast adenocarcinoma cell line (MCF-7) [183]. Ghate *et al*., found evidence that ACME is able to inhibit

the proliferation of MCF-7 cells by inducing apoptosis through intrinsic pathway [184].

Macromolecular polysaccharides, such as xyloglucans pectic polysaccharide and arabino-3,6-galactans, extracted from rose petals have been found to modulate the intestinal immune system activity through actions on Peyer's patch cells, and increase IL-6 production in murine macrophages. The carbohydrate fractions of the pectic polysaccharides mainly consist of galacturonic acid, arabinose and galactose, and the immunomodulating effect in mice intestine is presumably due to active carbohydrate structures such as the arabino-3,6- galactan present in rose petals [96]. Sunil *et al*., 2018, demonstrated that heartwood extracts of Acacia catechu produced an enhancement in the number of antibody producing cells in the spleen [55]. Their study also displayed an increased phagocytic response by peritoneal macrophages upon treatment with the AC extract, as evidenced by its effect on NBT (nitroblue tetrazolium) reduction and increased cellular lysosomal enzyme activity. The AC extracts also inhibited the release of the pro-inflammatory cytokine TNF-α and the production of NO, alongwith significantly increasing IL-10 production [63]. IL-10 plays a role in immunoregulation and inflammation, by enhancing the proliferation of B cells and mast cells, and by suppressing the secretion of proinflammatory cytokines from macrophages. It also has the ability to block the actions of NF-κB, a major transcription factor that modulates genes which participate in inflammation. The results of the studies by Sunil *et al*., clearly showcase the immunomodulatory effects of A. catechu extracts on humoral, cell mediated and non-specific immune functions [63].

Apart from this, other ingredients of the betel leaf quid possess good anti-oxidant activity. Areca nut contains polyphenols and flavonoids such as syringic acid, procyanidin, and epicatechin. The latter compound has stronger free radical scavenging activity than ascorbic acid [185]. The polyphenolic compounds in methanolic extracts of rose, including quercetin, kaempferol and their glycosides, hydrolysable tannins, flavonols and their glycosides show satisfactory DPPH scavenging activity [186]. Areca nut contains abundant procyanidins, which possess anti-inflammatory activity, as demonstrated by Huang *et al*., who found that procyanidins significantly down-regulated the expression of TPA-induced cyclooxygenase-2 (COX-2) by inhibiting ERK phosphorylation in oral cancer cell lines, known as SAS cells [187]. Further, the workers also found that treatment of rats with procyanidins suppressed the carrageenan-induced inflammatory oedema and PGE2 levels.

Betel quid constituents also have beneficial effects on the gut microbiome. While pulverized rose petals exhibit antibacterial and prebiotic activity, Zhao *et al*., in 2018 showed increase of beneficial gut flora by areca nut. In a study conducted on rodents, Zhao found that areca nut increased microbial abundance and diversity, regardless of the form of administration of areca nut [188]. The Chlorophyll in betel leaf has recently been found to exert antioxidant, antimutagen, and anticarcinogenic activities, alongwith ameliorating gut dysbiosis. Hence, betel leaf, rose jam and areca nuts are beneficial for gut health in general.

Several ingredients of the betel leaf quid are endowed with antibacterial effects. Essential oil of betel leaves has shown antibacterial activity against S. aureus, St. mutans, Lactobacillus acidophilus, St. epidermidis, K. pneumoniae [189]. In particular, the high concentration of phenolic contents in the extract of Piper betel leaves exhibits antibacterial and anthelmintic activities against Salmonella typhi and Shigella dysenteriae [190]. Piper betel extract has also shown potent antibacterial activities against five Gram positive cariogenic bacteria, Enterobacter faecalis, Lactobacillus fermentum, Lactobacillus salivarius, Streptococcus sobrinus and Streptococcus mutans, and two Gram negative periodontopathogenic bacteria, Aggregatibacter actinomycetemcomitans and Fusobacterium nucleatum . The major constituent of P. betel extract, which is responsible for the antibacterial and antibiofilm actions against oral pathogens, was found to be 4-chromanol [191]. Radunz *et al*., have shown that unencapsulated and encapsulated clove essential oil inhibits S. aureus, E. coli, L. monocytogenes, and S. Typhimurium bacteria [192]. Clove oil has also been reported to show antifungal activity against C. tropicalis, C. albicans, and C. guilliermondii [193]. Mentha extract (peppermint) has demonstrated good antibacterial potential against Pseudomonas aeruginosa, Klebsellia pneumoniae, Styphylococcus aureus, and Shigella flexineri [194]. A crude extract of rose petals (gulkand), showed antibacterial and disinfectant activities against Bacillus cereus, Staphylococcus epidermidis, S. aureus and Pseudomonas aeruginosa [195].

Betel leaf quid also has beneficial effects cognition and memory. These nootropic effects are partly due to the fragrance compounds that are inhaled, and then reach the frontal cortex and limbic system of the brain directly along the olfactory nerve fibrils piercing the cribriform plate at the roof of the nasal cavity [140]. Sun *et al*., in 2019 explored the impact of peppermint essential oil aromatherapy on the learning and memory function of the APP/PS1 mouse model by conducting behavioural experiments [196]. Peppermint essential oil therapy was seen to decrease Aβ precipitation (implicated in Alzheimer's disease), and reverse the morphology of neurons to the normal state. Moreover, the content of MDA in the brain tissue was reduced and the activities of GSH-PX and SOD increased significantly. These results suggest that peppermint oil possesses neuronal cell-protecting capabilities and ameliorates peroxidation damage in the brain. Peppermint essential oil can also affect key metabolic

pathways including inositol phosphate metabolism, arginine and proline metabolism, and methionine and cysteine metabolism, thus helping to prevent the onset and progression of Alzheimer's disease. Further, sniffing mint essential oil can reduce the content of serum AchE and facilitate cognitive function in patients with mild cognitive impairment [196]. Moreover, Awale *et al*., 2011, found that a very long polyunsaturated fatty acid C(37)H (64)O(2) from Rosa damascena containing extract, exhibited significant neurite outgrowth activity and suppression of the Amyloid β fraction-induced atrophy and cell death [99]. The researchers demonstrated the beneficial effect of the rose extract against dementia and postulated that the isolated compound stated above may act as a nerve growth factor [99].

Paan Ingredients also display hepatoprotective and metabolic actions. A study conducted by Ray showed that ethyl acetate extract of Acacia catechu (katha) has significant antipyretic, antidiarrheal, hypoglycaemic and hepatoprotective properties [64]. Ding *et al*., 2017, showed that Clove extract reduces the development of high fat diet-induced obesity, whole body and abdominal adipose tissue weight, regulates total triglyceride and low-density lipoprotein cholesterol, and lowers lipid accumulation in the liver and epididymal adipose tissues [91]. Arecanut contains abundant tannins, and shows potent antihypertensive activity in spontaneously hypertensive rats via inhibition of the activity of angiotensin-converting enzyme (ACE) [197]. Cardamom has a blood thinning action, due to its high concentration of linoleic acid [198]. A reduction in systemic blood pressure along with blood thinning effects can prove protective against vascular thrombosis in general, and coronary thrombosis in particular.

## 8. CONCLUSION

The south-east Asian tradition of chewing paan quid is rooted in the culture of these regions. Chewing the *paan* quid after meals and after taking a bath, as proposed in Ayurvedic texts, can be a health promoting regime. It is amply clear from the research studies mentioned above, that betel leaf, areca nut, acacia heartwood extract and slaked lime have no harmful effects if taken in moderation. Rather, the use of *Paan* after meals can provide several beneficial effects on the body metabolism and on the mental state too. In general, the spices used as ingredients in preparing the *Paan* quid, contain phytochemicals that help to tone up the various organ systems, improve the metabolism, and relax the mind. Also, the chlorophyll of betel leaf, and phytoconstituents of areca nut, are beneficial for the gut microbiome, which can further lead to improved immunity and diminished inflammation [172-199].

The anti-oxidant and anti-inflammatory actions of the condiments added to the betel quid can help protect the brain, liver, and heart from age-related degenerative effects. Sleep quality may improve, and cognitive ability can be enhanced. The immuno-boosting and anti-microbial actions can help prevent minor infections. The anti-parasitic activity of some phytochemicals is useful in the Indian context, where the hot tropical climate engenders parasitic diseases, caused by organisms such as roundworms, shigella and Entamoeba histolytica. The anti-peroxidation and DNA-protective actions of several phytoconstituents are promotive for anti-mitotic activity and are protective against cancers. Enjoying a betel leaf quid after meals can thus, prove highly beneficial for both mental and physical health.

**Abbreviations**

BL -Betel leaf, PBLE- Piper betel leaf extract, AChE- acetylcholinesterase, ChA - Chlorogenic acid, MDA- malondialdehyde, DMBA -7,12-dimethylbenz[a]anthracene, VCAM-1- Vascular cell adhesion molecule-1, PON- postoperative nausea, ANP - Areca nut polyphenols,

EO-Essential Oil, APC- 4-allylpyrocatechol, AC- Acacia catechu, CHV-Chavibetol, ROS – Reactive oxygen species, DPPH - diphenylpicrylhydrazyl, GABA-Gamma-aminobutyric acid,

TG- Triglycerides, VLDL- very low density lipoproteins, LDL- low density lipoproteins, DMBA – dimethylbenz[*a*]anthracene (a potent carcinogen), TPA – 12-O-tetradecanoylphorbol-13-acetate (a potent skin tumor promoter), AQCE - aqueous extract of Acacia catechu heartwood, HFD- High Fat Diet, ERK – Extracellular-signal-regulated kinases,

NBT- Nitroblue tetrazolium test (measures ROS generated by leukocyte), TXB- thromboxane, COX-Cyclooxygenase, AC – Acacia catechu, IP-10 - Interferon γ-induced protein 10, I-TAC- Interferon-inducible T-cell α chemoattractant, MIG- monokine induced by γ interferon,

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