Review Article

Betel Nut and Arecoline: Past, Present, and Future Trends

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ABSTRACT

The areca nut, commonly known as betel nut, has been the subject of consistent scientific study over the past 5 decades. Betel nut is a natural compound chewed for its psychostimulating effects. Arecoline, the primary alkaloid of betel nut, is a muscarinic acetylcholine receptor agonist producing cholinergic effects on the parasympathetic nervous system and a psychoactive agent, contributing to the psycho-stimulating effects. Importantly the betel nut use is also associated with oral leucoplakia, submucous fibrosis, and squamous cell carcinoma. This narrative review explores the past, present, and future aspects of betel nut use, its historical applications, the development of biomarkers research, its health value concerns, and health economic impacts.

Keywords: betel nut, arecoline, carcinogenic, areca nut, south Asia

INTRODUCTION

The areca nut is the seed of the areca palm (*Areca catechu*), growing in the tropical Pacific, Southeast and South Asia, and parts of east Africa. It is commonly known as betel nut and has been the subject of consistent scientific study over the past 5 decades. Betel is a compound of natural substances chewed for its psycho-stimulating effects. Betel is composed of the nut of the areca palm, the leaf of the betel pepper (Piper betel), and lime (calcium hydroxide). Approximately 200 million persons chew betel regularly throughout the western Pacific basin Southeast and South Asia, and betel nut use altogether is estimated to involve as much as 10–20% of the global population.[1,2] Only three substances (nicotine, ethanol, and caffeine) are consumed more widely than betel or are considered more commonly addictive.[2] When betel is chewed, it produces mild psychoactive and cholinergic effects.

The major chemical components of betel nut are polyphenols, including tannins and alkaloids. Arecoline, the primary alkaloid, is a muscarinic acetylcholine receptor agonist linked to producing the cholinergic effects on the parasympathetic nervous system.[3] Chewing the betel nut results in copious production of a blood-red saliva that can stain oral structures. After years of chewing, the teeth may become red-brown to nearly black. Betel nut use is associated with oral leucoplakia, submucous fibrosis, and squamous cell carcinoma.[4] Use of betel is discouraged in high-income countries because of its reported carcinogenic and perceived dysesthetic properties; nevertheless, betel nut is widely available in the West.

This narrative review explores the past, present, and future aspects of betel nut use and arecoline in relation to ongoing research and development of biomarkers for preventing potential adverse effects of longer-term use, with a greater focus on current and future prospects. The review contains data that have been collected by reviewing the international scientific literature in English. As such, there might be further reports within other languages that might not be visible when applying international search engines (e.g., PubMed). Thus, this narrative review should be considered indicative of the current state-of-the-art, but not necessarily exhaustive.

Looking at the Past Work

Early Focus on Epidemiology

Most published studies so far have focused on the negative health impact(s) following regular consumption. Historically, the first report linking betel nut consumption and cancer appeared in the *British Medical Journal* in 1924[5] and the *Indian Medical Gazette* in 1926,[6] as India was under British rule at that time. These two reports were followed by sporadic reports on the same principle in subsequent decades. Most would be case reports of chronic users and the side effects of consistent use over a long period of time at the individual level, complemented by some very general epidemiologic reports on the geographic areas where betel nut use would be prevalent among the population.[7–9] These reports did not form a connected body of work, for example where one cohort of patients would be followed through for a number of years, yet they were useful snapshots of the observations in the field.

In the early 1950s, the US Pacific Medical services would publish the first attempt at a scientific description of the consequences of chronic betel nut use. These would be a short series of manuscripts where the main population under investigation were natives in the Pacific islands under US jurisdiction (e.g., in Guam),[9–12] driven by scientists and medical professionals who were stationed locally. In the 1960s, the use of betel nut was investigated from the perspective of psychiatric side effects, still in very isolated cases and populations in the Pacific islands (e.g., 1966 in Papua-New Guinea).[13] The first report relating to China in the international English scientific literature comes from Taiwan in 1964 and viewed in relation to oral cancer incidence, followed up by a second publication in 1966.[14,15]

It is important to note that all the previously mentioned reports were isolated in nature. For example, they referred to specific patient cases (case studies, e.g., in 1970),[16] specific isolated communities (e.g., in Vietnam [1967],[17] Ceylon [1967],[18] India [1967],[19] New Guinea [1968],[20] Malaysia [1960][21]), or specific types of cancer that were relevant to the expertise of the investigator.[22, 23] In other words, for 3 decades there was sporadic reporting, and no consistent international monitoring or an international study using harmonized protocols until the 1980s. The study of betel nut was almost always as part of wider studies on cancer, i.e., all other aspects that would currently be included in population-wide studies (e.g., socioeconomic benefits) or biomarkers development for cancer detection were completely absent until a limited study in 1967[24] and two brief reports on potential benefits in 1969.[25,26]

Chemical and Biochemical Investigations

The first investigation on the active chemical compounds of betel nut use was published in *Nature* in 1971, focusing on the effects of dimethyl sulfoxide (DMSO) in the oral tissues of laboratory model animals, specifically in hamsters.[27] This was the starting point for experiments on the consequences of betel nut extracts on different laboratory animals, such as baboons (1972),[28] rats (1972),[29,30] and others.

Pharmacologic Investigations

The first review from a pharmacologic perspective was in 1976,[31] where it recognized that the betel nut might have pharmacologic properties, based on practices from the Indian and Chinese traditional medicine systems. However, no evidence was provided, comparable to other ongoing studies to be able to support those claims. The existence of arecoline hydrobromide, as an active ingredient in the oral cavity, was also highlighted as having potential pharmacologic properties; circumstantial evidence was provided to this end from experimentation in dogs as an animal model.[32]

It is important to note that in many of these studies, the authors did not differentiate among (1) the use of betel, (2) the use of tobacco and betel (not at the same time, by the same user), and (3) the use of tobacco and betel (at the same time and by the same user). This resulted in a number of publications where the impact of betel use could not be disassociated from the impact of chronic tobacco use in terms of health consequences.[33] It was also shown that skin application of DMSO extracts of tobacco and of betel nut separately did not result in skin lesions in C17 mice, but when a mixed DMSO extract of tobacco and betel nut was used, skin papilloma and epidermoid carcinoma developed in some animals, including mice, hamsters, rats,[34] and *Drosophila melanogaster*.[35]

Consolidated Scientific Investigations

This ongoing situation, in which different studies in different populations or laboratory animal models were executed but lacked scientific transparency and comparability, was highlighted by a critical paper in *The Lancet* in 1979 with the title "Is 'betel chewing' carcinogenic?"[36] The latter article called for international, harmonized studies for betel nut consumption and in particular on clear evidence relating to biochemical substances and their potential carcinogenic effect as a prelude to biomarkers development. As a result of this publication, a number of renewed efforts were made. Generally, from the 1980s to the 2000s efforts focused on (1) identifying the substances involved, (2) if these substances are biochemically active, (3) how they display this activity and under what conditions, (4) whether there is any direct correlation between betel nut use and cancer, and (5) if that is dose-dependent and for which substance (s).[37–40] The introduction of omics technologies in the 2000s brought a renewed attention on the betel nut use field, as molecular studies could now be produced, and increasingly in a high-throughput manner. Regarding the scientific literature output as recorded in the PubMed scientific repository for the betel nut use, 2020 was the highest year in terms of publications, with a total of 173 scientific peer-reviewed manuscripts published. Compared with other cancer fields (e.g., colorectal cancer, cervical cancer) in which annual scientific publications are in the thousands of articles per year, this is a very low number and shows that even currently the volume of registered scientific interest remains consistently marginal. Other recent reviews also report a similar low volume of scientific work relating to betel nut (e.g., 139 works identified on the epidemiology and use published from 1970 to 2019),[41] although most of the studies were focused on the oncogenic properties of using betel nut.

MATERIALS AND METHODS

A narrative review approach has been chosen to investigate the topic of betel nut and potential impact of its use, as the aim was to provide a broad perspective and explore the general debates and developments on the topic, rather than implementing a systematic review approach, as the latter focuses on unique and specific queries, using explicit methodology.[42] The search terms "areca nut" OR "betel nut" were used in the databases PubMed and Google Scholar since inception, to identify the published literature pool. More than 2000 items were identified, after filtering out conference proceedings, poster presentations, and non-English publications. Any articles that contained simple mention of betel nut, but not containing a dedicated investigation on the subject were also removed. The remaining abstracts were indexed by theme until thematic saturation was achieved, by the two authors (Z.K. and I.H.C.) and validated independently by the third one (H.W.). Primary references were used as much as possible over secondary references to previously published material.

It is important to note that there exist records and documentation in a number of local Asian languages relating to the application and use of betel nut. However, these have not been investigated, despite regular indications in the published English scientific literature that they do indeed exist. For example, the applications in traditional Chinese medicine (TCM) contain detailed records about betel nut application as part of prescribed herbal interventions. Modern records can be traced back within the *Chinese Medicine Pharmacology Handbook* since 1953,[43] in which there are 60 betel nut–related formulations. Most of these formulations are used to treat digestive and endocrine diseases. Such applications require professional training before being prescribed and compliance to relevant regulations, and as per many other traditional medicine herbal-based formulations, they do rely on an evidence base, though the latter might not be directly comparable to the western medicine clinical research model. Some basic research stemming from those applications shows that the muscarinic cholinergic agonist arecoline stimulates the rat hypothalamic-pituitary-adrenal axis through a centrally mediated corticotropin-releasing hormone-dependent mechanism.[44] Thus, there exist non-English sources that are potentially insightful and requiring further systematic research.

CONSIDERING THE PRESENT STATUS

Physiology

In terms of biochemical composition, recent reviews provide a summary view of the biochemical substances involved in betel nut consumption and the formation of oral cancer (oral submucous fibrosis [OSMF]). Although occasionally preceded by and/or associated with vesicle formation, OSMF is always associated with a juxta-epithelial inflammatory reaction followed by a fibro-elastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and progressively causing trismus and inability to eat.[45] Recent studies have also investigated the relationship between betel nut and cancers at sites other than in the oral cavity, such as colon cancer.[46] As the most likely effects of betel nut use are of inflammatory nature, and therefore systemic, it is likely that betel nut use will be correlated with other cancers too, in particular where a sustained low-level inflammatory response can act as an oncogenic trigger mechanism. For example, chronic kidney disease, directly linked to kidney cancer and kidney failure, has been linked to sustained betel nut use in Chinese nationals.[47] However, such associations are challenging, as they involve a systemic response (and hence multiple confounders), and this inherent challenge, despite the evidence that inflammation is an inherent component of cancer, seems to be ignored in most biomarker studies.[48]

Oxidative stress and the generation of reactive oxygen species can drive affected cells to proliferation, senescence, or cell death. Chronic occurrence of events creating oxidative stress can lead to lesions in the oral cavity and could drive some of these lesions to malignancy. Thus, multiple features of the carcinogenic process have been observed in vitro and in situ in the oral cavity of betel quid chewers, as well as in model animals treated with the betel quid ingredients areca nut, arecoline, catechu, and slaked lime.[49]

Biochemistry

Regarding the active substance of the betel nut, arecoline, it was demonstrated as causing the inhibition of both humoral and cell-mediated immune responses in mice. In addition, it was established that the betel nut contains approximately 11–26% tannins and 0.15–0.67% alkaloids, known to be both cytotoxic and genotoxic. Areca nut extract produced adverse effects on the proliferation of phytohemagglutinin-stimulated human lymphocytes in vitro, suggesting that there may be impaired immune surveillance in areca nut chewers. Arecoline modulates matrix metalloproteinases and their tissue inhibitors, as well as the activity of lysyl oxidase, which leads to the accumulation of collagen in oral mucosal fibroblasts.[50] Furthermore, areca nut polyphenols inhibit collagenases and increase the cross-linkage of collagen, reducing its degradation. These biologic processes may underly the generation of oral submucous fibrosis, which could be further enhanced by the presence of copper ions.[51] Thus, a tentative pathway of the effects has been created; however, the authors of these studies note that in almost all cases, betel quid chewing was combined with smoking.[52]

In vitro studies suggest that superoxide anions are generated because of auto-oxidation of polyphenols found in areca nut and catechu, and can be further enhanced by the alkaline pH of lime.[53,54] The superoxide anion is then converted to H_2O_2, which reacts in the presence of transition metals, such as copper and iron, to generate hydroxy radicals. Copper and iron are present in microgram per gram amounts in the areca nut, pan masala, catechu, and slaked lime. This generation of radicals may be the critical step in carcinogenesis. In vitro studies demonstrated that areca nut and catechu in the presence of lime can induce oxidation of deoxyguanosine in DNA, a critical biomarker of oxidative stress and carcinogenesis,[55] which could induce DNA strand breaks.[56,57]

The International Agency for Research on Cancer considers betel nut use with and without tobacco to be carcinogenic to humans. One future option would be to set use limits and better inform risks to users, as per the models of public health information campaigns for tobacco use; however, such an approach would require further scientific evidence. In addition, some betel nut producers have developed plant varieties with a reduced amount of arecoline, yet there is uncertainty if such an approach would reduce the carcinogenic risks at all.

Biomarkers

Given the preceding biochemical characteristics and scientific developments, there has been a consistent effort in the past few years in the development of biomarkers that are appropriate for the betel nut use type (e.g., with or without tobacco), as well as bodily fluid (saliva). In addition, biomarkers might be used as key target indicators for public health cessation programs. Having said that, the biomarker discovery attempts remain at an early investigative stage and any future implementation within the public health set of routine operations remains a future probability. In such studies in Guam, in chewing saliva of users, the following substances were identified as potential biomarkers: guvacine, arecoline, guvacoline, arecaidine, nicotine, and chavibetol.[58] The same potential biomarkers were confirmed in an independent pilot study; they could be detected in saliva and urine for short periods of time postexposure,[59] and perhaps in buccal cells.[60]

Although the preceding biomarkers might relate to measuring the level of consumption and effectiveness of individual and/or public health cessation programs,[61] there is a second category of biomarkers specific to the development of cancer. Such studies are even fewer in number, and include hypermethylation[62] or general inflammatory response biomarkers.[63] The inherent difficulty in the latter approach is the multitude of different betel nut preparations that are available for consumption, as well as the tendency of user populations to use such formulations interchangeably, and as such might be difficult to tease apart when trying to correlate to specific biomarker profiles.

PLANNING FOR THE FUTURE

Although the use of betel nut has been characterized as a risk factor for many oral and esophageal cancers, to date, the exact role and mechanisms in oral carcinogenesis remain poorly understood in comparison with other popular addictive substances, such as tobacco and caffeine. As such, existing gaps and opportunities are summarized in the following paragraphs.

Systematic Use and Negative Side Effects

Although betel nut is increasingly available globally through international trade, their use remains highly prevalent in the Asia-Pacific region. However, to date there do not exist highly detailed studies in terms of the regional levels of use, including the admixtures with other products (such as tobacco), as there is wide regional variation.[64,65] There are many studies that report the levels of use for communities and populations, and for specific time periods, as mentioned previously. For example, epidemiologic studies showed that the prevalence of use varied widely between 0.2% and 60.8% in Cambodian population groups in 1995, whereas a prevalence of 21.9% was reported in a Malaysian population in 1995.[66] However, a more consistent approach is lacking in terms of a population cohort that will be followed over a longer period and be validated against comparable protocols or cohorts. Doing so at the population level would provide granularity on the dose-dependent correlation between use levels and different impacts and will provide some indication on potential other confounders.

Furthermore, at the personal level, betel quid and areca nut are associated with negative health side effects on the cardiovascular, nervous, gastrointestinal, metabolic, respiratory, and reproductive systems.[67–70] The creation of population cohorts that are representative of different national or regional populations and socioeconomic strata would be critical in establishing the exact level of association between betel nut use and these potential side effects in a dose-dependent manner at the individual level,[66] as well as the most appropriate biomarkers that would need to be monitored. The existing wealth of scientific literature that allowed for the International Agency for Research on Cancer classifications will be further supported by the current active research activities on the subject in Southeast Asia. Finally, one should also consider the psychological effects of regular use, as long-term use has been associated with effects in specific populations.[71–73] For example, in Taiwan, betel nut use is empirically considered to lead to sustained attention and inhibitory controls that have been impaired after one night of deprived sleep. Following sleep deprivation, chewing betel nut can immediately improve habitual chewers' selective attention.[74] As such, betel nut use might be habitual for particular types of employment or lifestyle. For instance, there are reports in Taiwan concerning the habit of taxi drivers chewing betel nut to stay awake during long shifts.[72]

Potential Positive Side Effects

Betel nut is used as a compound in traditional medicine in India and throughout Southeast Asia to treat multiple disorders, such as inflammation (e.g., gingivitis, conjunctivitis, edema), flatulence, diarrhea and dysentery, hyperemesis in pregnancy, dysuria, and high blood pressure.[75–77] It also reportedly possesses astringent, analgesic, and aphrodisiac properties.[78,79] Furthermore, *Areca catechu* powder has been applied topically as an anti-inflammatory remedy or the nut is made into ash for local application. It is also used as collyrium, in a more refined form, to provide relief in conjunctivitis and epiphoria.[80] There exist also a number of compound preparations containing *Areca catechu*, such as Ma'jun Supari and Ma'jun Mochrus, which are applied topically in wound healing.[81,82]

Traditional Indian medicine uses betel nut as one of the treatments for glaucoma, as a mild stimulant, and as a digestive aid.[83] Furthermore, in veterinary medicine, an extract of areca is used as herbal method for expelling tapeworms in cattle, dogs, and horses; to empty animals' bowels; and for treating intestinal colic in horses.[84,85] However, none of the treatments have experienced any systematic research attempts, neither at a population nor at an individual level. Therefore, the systematic, long-term view for a potential positive side effect is currently absent.

Socioeconomic Aspects

The socioeconomic aspects of betel nut consumption have been largely overlooked. There exist very few narrative reviews, focusing mostly on the Indian market, and conducted to establish some of these features of areca nut consumption.[24,86,87] There are also studies that provide snapshots for individual locations across Southeast Asia.[88–90] Although these studies form useful indications, this is not sufficient information nor evidence to consider the socioeconomic aspects in depth, such that an effective public health policy can be informed and targeted to the most vulnerable groups. For example, there are no socioeconomic studies in the international, scientific, peer-reviewed literature regarding China. Although studies on isolated communities in Papua-New Guinea provide a useful context in terms of changing rural cultivation practices,[90,91] they cannot be generalized to the wider Southeast Asian context. Some of the challenges in trying to acquire a full overview of the socioeconomic aspects of betel nut, are that South Asian economies are at different stages of development and have varying and very different areca nut cultivation practices. In addition, they have very different cultural beliefs, employment opportunities, and marketing strategies, coupled with a lack of detailed data for a number of countries. Thus, there are few studies of narrow financial impacts, but not on a potential wider contribution.[92,93] Interestingly, this variation is reflected in secondary markets too. For example, the retail practice among the South Asian communities of the United Kingdom was found to reflect the diverse consumer practices and price structures that are current in their countries of origin.[94]

It is believed that India is the largest producer of areca nuts in the world accounting for more than 50% of global production (Food and Agriculture Organization, average annual production data from 1994–2020). India is followed by Myanmar, Indonesia, Bangladesh, China, and Taiwan, by approximately 6–9% for each location, and much smaller volumes (less than 2.5% each) are grown in Sri Lanka, Thailand, Nepal, and Bhutan. However, the lack of consistent published evidence makes those relative amounts and their year-on-year fluctuation difficult to validate.[95]

Traditional Medicinal Aspects

In China, the first report of the TCM properties of betel nut and betel leaf use was reported by the Portuguese ambassador to China, indeed during the very first ambassador mission, in a letter to King Manuel I in 1516.[96] As such, betel nut constitutes a mainstay component of TCM. Currently, the southern part of China, especially Hainan, is the main production and consumption area for betel nut.[97] Betel nut is part of the gamut of TCM compounds used to treat parasitic diseases, various gastrointestinal disorders (abdominal distension, abdominal pain, dyspepsia, and diarrhea), and jaundice.[98] Ongoing studies in China, driven by such TCM observations are continuing to identify active ingredients (e.g., alkaloids) with potential therapeutic properties.[99–101] As one of the main TCM uses is for gastrointestinal conditions, an area of study has developed relating to the effects of betel nut use on the microbiome. It has been shown that there are distinct changes to the microbiome of regular betel nut users, as anticipated; however, the microbiome alterations have not been definitively correlated with either a negative or positive side effect for the users themselves.[97] Last, betel nut is one of the ingredients used to prescribe treatment for respiratory-related infections, according to most recent published guidelines in Chinese medicine.[102]

Modern Chinese pharmacology shows that betel nut use can entail potential and varying pharmacologic properties, including antifatigue, antioxidant, antibacterial, antifungal, antihypertensive, antidepressant, anti-inflammatory, analgesic, and antiallergic properties; betel nut also promotes digestive function, inhibits platelet aggregation, and regulates blood glucose and blood lipids.[79] Therefore, there exist strong arguments for the further socioeconomic study of betel nut for potential identification of novel pharmaceutical products. For example, preliminary studies have shown a consistent positive effect for intestinal nematodes, such that TCM provides an alternative opportunity for using locally grown produce to support pharmaceutical production in resource-restricted settings.[103] Last, it is important to include the psychoactive substances in this review of potential therapeutic agents, as indications exist that betel nut components might be useful in the case of developing novel antidepressive and anti-epileptic active compounds.[104,105]

Future Biomarker Research

The pursuit of biomarkers identification in relation to betel nut remains at early stages, as compared with carcinogenesis biomarkers in other tissues (e.g., breast cancer). The recency of scientific discoveries is one of the reasons for this, as is the tissue type in which the detection is most likely to take place, that is, the saliva, which presents challenges in terms of biological variation (e.g., viscosity) and, thus, standardization of sampling.[58,59] Furthermore, there are different types of biomarkers pursued, reflecting the different needs. These can be biomarkers indicative of level of use, and biomarkers relating directly to carcinogenicity or both. The challenge posed is that many of the biomarkers proposed so far (e.g., nicotine) might be highly sensitive, but they are not specific enough.[106,107] Thus, further concerted efforts are required in this direction before a potential breakthrough can be achieved.

Setting Standards

Considering the risks associated with betel nut use, the attempts to regulate consumption would need to follow a more structured framework rather than rely on individual local or national initiatives. Betel leaf is perishable, and the preparation of betel quid is somewhat complex. Hence, over the past few decades, new formulations have emerged as commercial betel quid substitutes, such as a flavored and sweetened dry mixture of betel nut, catechu, and slaked lime either with tobacco (gutkha or khaini) or without tobacco (paan masala). These more standardized products with longer shelf life have become increasingly popular in India, where the largest regular use population exists.[108] Further variations exist, depending on the type of preparation of the actual plant product, and the different combinations of adjoint materials (e.g., tobacco, lime). All these make standardization particularly difficult, both with respect to the scientific studies, as well as for informing financial and socioeconomic policies.[109] Thus, the need for standardization remains acute internationally. This has been reflected in recent studies in China, where the wider public, including regular users, expressed the need for wider regulation in view of the identified risks relating to betel nut use.[110]

CONCLUSION

Betel nut and products derived from it are widely used as a masticatory among various communities, and in several countries across the world, as a socially endorsed habit, despite its addictive properties. Over a long period, several additives have been added to a simple betel nut preparation, thus creating the betel quid and encompassing chewing tobacco and other agents in the preparation, in variable amounts and combinations. The popularity of betel nut has subsequently led to the industrial preparations of convenient substitutes of the betel nut or betel quid in the form of paan masala, gutkha, and similar industrial concoctions in several countries across Southeast Asia and globally.

The wide variation of products available in the global markets, as well as the lack of standardization, have impeded the scientific progress toward understanding in detail the physiology, biochemistry, and even potential positive effects of betel nut use. There are sufficient data to link long-term betel nut use to carcinogenicity; however, there are many aspects still suboptimally investigated, such as biomarker development, and psychological, socioeconomic, and financial aspects. Furthermore, aspects relating to chemical makeup and traditional pharmacology remain to be studied in depth, as well as different formulations of the final product, which might contain reduced or chemically extracted arecoline options. Furthermore, despite attempts to increase public awareness with mass campaigns, particularly in India, there has been little reduction in the betel nut habit. This suggests a need for better targeted public health measures and communication strategies; however, those can only materialize once the current research gaps and challenges have been addressed.

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