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Systemic Health Effects of Areca Nuts with Particular Emphasis on Carcinogenesis – A Review

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Abstract

Areca (betel) nut (*Areca catechu*) is regarded as one of the most addictive masticatory substances in the world, with approximately 600 million users globally. Extensively grown and found in India, China and Indonesia; areca nut is also native to many other countries of the South and Southeast Asia. Its usage and beneficial effects have been reviewed since centuries. The systemic effects associated with areca nut usage have been in the limelight for many years. This review provides a narrative insight to assess and collate published data that reports the harmful effects of areca nut. An electronic search amassed literature from the NCBI and Google Scholar databases with the help of keywords. Various studies on the correlation of areca nut and its effect on the oral health, metabolism and the incidence of cancer were selected. Its usage is reported to be associated with cancers of the oral cavity, esophagus, pharynx, liver and has been declared a human group 1 carcinogen by the International Agency for Research on Cancer (IARC). It is also associated with the incidence of cardiovascular disease and chronic kidney disease. Hence, there is a dire need to identify the role of areca nut as a causative agent of cancer and several other health disorders. Clinical evidence has indicated and proved that the use of areca nut causes several types of head and neck cancers, as to effects on intracellular levels of GSH, and on tumor suppressing gene P53 are quite evident clinical evidence has indicated and proved that the use of areca nut causes several types of head and neck cancers, as to effects on intracellular levels of GSH, and on tumor suppressing gene P53 are quite evident.

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Introduction

Areca nut is the fruit of *Areca catechu* Linn, an oriental palm of the Palmaceae family. It is one of the perennial masticatory substances in the world partaken by human's worldwide (Arjungi 1976; Bhat *et al.*, 2017). With its use pertaining to several decades, its occurrence and consumption amalgamated with betel quid is now reported to have attained 600 million users all over the world (Gupta and Warnakulasuriya, 2002). It is extensively cultivated in countries of the South and Southeast Asia such as India, China, Indonesia, Thailand, Bangladesh, Vietnam, the Philippines and Myanmar (Lee *et al.*, 2016). Areca palm grows as a lone willowy and straight structure with a 50 cm perimeter and length up to 25-30 m, which is, at variegated phases of development, marked by 7-12 encircling leaves (Williams *et al.*, 2002; Bhat *et al.*, 2010). Over the years, the increment in users has meant that every individual or community ascertain their assortment of areca nut and other ingredients. It can be masticated in raw or processed forms (roasted, sundried, soaked, boiled and fermented), a practice rife in South Asia. Its second and frequently stereotyped use is traditional and home to India and its neighboring countries, where users typically roll areca nut and other condiments with slaked lime (locally called *chunna* or *chunan*) into Piper betel leaf (*Paan* leaf) (Krishnamurthy, 2008; Rahmatullah *et al.*, 2009) (Figure 1).

Areca nut is a botanical agent since ancient times as its medicinal properties have been a part of the antediluvian practices of Indian Ayurveda and Homeopathy. The seeds of areca nut have long been in extensive use in clinical practices in parts of the South and Southeast Asia as well as China (Peng *et al.*, 2015), as a potent astringent and are conventionally employed for its laxative, antioxidant, antimicrobial, anti-inflammatory, analgesic, anti-allergic, hypoglycemic and antiulcer, deworming properties (Jaiswal *et al.*, 2011). The extract of areca nut is reported to disclose antioxidant properties and an elevated phenolic content (Sazwi *et al.*, 2013), while its ability to inhibit the formation of bacterial biofilms was also reported in a recent study (Shamim and Khan, 2017). Areca nut mastication is reported to provoke parasympathetic effects of elation and ecstasy, stimulation of central nervous system, light-headedness, and salivation (IARC, 2004). On the basis of dry weight, the prime components of areca nut comprise of polysaccharides, polyphenols (including flavonoids and tannins), fiber, fat, proteins, and alkaloids (mainly arecoline) (Figure 2). Apart from arecoline, areca nut contains subordinate alkaloids such as arecaidine, guvacine, arecolidine and homoarecoline (Shivshankar *et al.*, 1969). All known alkaloids of areca nut are reported to exhibit drug-like features. Among these, arecoline is the principal alkaloid which is the most physiologically effective and causes a stimulating impact on the nervous system.

Systemic effects of areca nut

Upon consumption, areca nut is believed to exert effects like elation and ecstasy. Arecoline, which is regarded as a cholinergic and anthelmintic agent, is widely used in veterinary treatment. In humans, arecoline is an expensive intermediate compound and is used in the manufacturing of drugs such as paroxetine and femoxetine (US6132286A). Paroxetine is a drug often employed in the treatment of acute and chronic mental disorders such as anxiety, mania and depression. Both of these compounds are reported to restore serotonin levels because of its very high affinity towards serotonin transporters (Nevels *et al.*, 2016). Several published studies highlight the role of areca nut in the manifestation of many cancers like oral submucous fibrosis, esophageal oral squamous cell carcinoma, malignant oral lesions, and head and neck cancers (Table 1). However, the incidence of oral cancer can be multifactorial, with both intrinsic and extrinsic factors in play, wherein the induction of carcinogenicity from areca nut is the result of nitrosation of arecoline that takes place when areca nut is masticated. To gain a better insight on the carcinogenic effects of areca nut, those published studies that shed light on the role of areca nut in carcinogenesis and its relevant effects on human metabolism, obesity, cardiovascular diseases and chronic inflammation were selected respectively.

Areca nut mastication and oral health

The manner of arrangement and mode of practice of areca nut all differ globally which also produces a much different semblance pertaining to every region. Precarious health effects of regular areca nut (betel nut) use are noted because of its reported carcinogenic nature to man. Its effects upon regular habitude of young adults were explored in a study where the predominance of the habit of chewing betel nut among secondary school going Micronesian children (n=309) was probed. A survey about the use of areca nut was subsequently led by an observation of the mucosa for any significant changes and afflictions. The results shed light on the habitual use by 63.4 % of all subjects. Serious oral ailments were also detected among many subjects. 12.9 % were diagnosed with oral leukoplakia, while oral submucous fibrosis was detected in 8.8 % of children (Oakley *et al.*, 2005). The study affirms that the habit takes off from a young age. Another study evaluated the chewing practices of areca nut in pre-adolescent children in India. Majority of the subjects were frequent areca users, and were oblivious to its deleterious effects. More than 25 % of the subjects were habitual chewers and a 2:1 ratio arose of male to female users (Khandelwal *et al.*, 2012). Two studies in Guam examined the social and cultural effects that coerce the people of Guam into chewing areca nut, as well as their chewing behavior. In the first study, the subjects were elected in order to study about the habits of areca nut chewers (Paulino *et al.*, 2011) where the vast distribution of disparate areca nut chewing practices among Micronesian populations in Guam, which were the outcome of peer pressure and social acceptance, were evaluated. Murphy and Herzog, (2015) supported these results with the conclusion in their study that the practice of areca (betel) nut chewing is socially accepted and considered as a rite of passage between cultures. The studies in Pakistan also investigated about the relative areca dependency issue. The subjects comprised of smokers (34.7 %), users of areca with tobacco (28.4 %) or singularly areca nut (36.8 %), which demonstrated that areca nut usage was consequently affiliated with its dependence. Comparatively, cigarette smoking subjects were at the risk of being addicted to tobacco use along with subjects using areca with tobacco (Mirza *et al.*, 2011). The areca nut users pertaining to public and private health-care among males and females are well identified (Liaquat *et al.*, 2016), which showed that a significantly higher percentage of private clinic subjects were comparatively more knowledgeable on the subject than were subjects in public hospitals. Nevertheless, the degree of dependency remained the same. Moreover, the effect of areca nut use upon the otolithic reflex system indicated the absence of such reflexes with intensity ranging from pronounced to interim in persistent and maiden users, respectively (Lin and Young, 2017).

Areca nut and carcinogenesis

The oral cavity is the habitat of several microorganisms (Wade, 2013). The habit of areca nut consumption altering or driving a series of changes in the oral microbiome have been reported in emerging literatures, but whether these microbial changes are thereby involved directly in the development of oral carcinoma is exploratory. In a study conducted on present areca nut chewers, subjects who were prior chewers, and non-chewers, and the changes in their oral microbiome were investigated using pyrosequencing. The study revealed that areca nut chewers had mitigated levels of normal oral commensals, with the incidence of some species being found to be elevated (Hernandez *et al.*, 2017). Another study reported a shift in the prevalence of commensal bacteria, and also suggested that the mastication of areca nut is likely to cause physical damage to the oral cavity, disturb homeostasis due to the release of acidic products during mastication and lead to overall changes in the microbial diversity (Xiong *et al.*, 2018). Various published literatures present proof that areca nut consumption is related to oral cancers (when used with or without tobacco). The relationship between betel nut chewing and oral carcinogenesis and its underlying mechanisms is not well understood. The oral carcinogenesis owing to a long-term use of areca nut and its various forms is an intricate, multi-step process which includes commencement, advancement, and development resulting from the advancing amalgamation of genetic lesions followed by long term use of areca nut and its various forms (Shah *et al.*, 2012).

Table 1. A summary of areca nut and its associated systemic effects.

Sr. No	Effect	Health afflictions	Reference (s)
1.	Carcinogenesis	Oral leukoplakia and malignant oral lesions	Shah *et al.*, 2012 Hernandez *et al.*, 2017
		Oral submucous fibrosis	Trivedy *et al.*, 1997 Trivedy *et al.*, 1999 Trivedy et al., 2001 Rajalalitha and Vali, 2005 Tsai *et al.*, 2009 Khan *et al.*, 2012 Gupta *et al.*, 2014 Mathew *et al.*, 2014 Hosein *et al.*, 2015 Mathew *et al.*, 2015 Yongxiu *et al.*, 2016
		Esophageal squamous cell carcinoma	Jemal *et al.*, 2011 Chen *et al.*, 2017 Chung *et al.*, 2010 Lin *et al.*, 2011 Chen *et al.*, 2017
2.	Cardiovascular disease	Coronary artery disease	Tsai *et al.*, 2012 Khan *et al.*, 2013 Yamada *et al.*, 2013
		Carotid artery intima thickness	McClintock *et al.*, 2014
3.	DNA damage	Generation of reactive oxygen species	Illeperuma *et al.*, 2015
		Induction of fibroblasts to provoke DNA damage	Pero *et al.*, 1990 Hu *et al.*, 1995 Chang *et al.*, 2014 Rehman *et al.*, 2016
4.	Metabolic disorders	Systemic and chronic inflammation	Shafique *et al.*, 2012
		Liver cirrhosis	Lin *et al.*, 2008
		Chronic kidney disease	Wang *et al.*, 2018
5.	Erectile dysfunction (ED)	Elevated risk of ED	Huang and Jiann, 2017
6.	Obesity	Induction and progression of obesity	Esposito and Giugliano, 2011

Oral submucous fibrosis

The effect of long-term areca (betel) nut usage in Malaysian and Indian areca (betel) nut consumers led to severe alterations of oral mucosa in a significant number of Indian cases entailing fused tobacco with betel quid. Global correlational studies proposed higher degree of mucosal changes in betel quid comprising of tobacco when compared to mucosal alterations in betel quid *sans* tobacco (Chin and Lee, 1970). Over the years, several studies have highlighted the harmful and precarious nature of areca nut products and their abuse. One such study investigated and uncovered the effects of areca nut chewing that led to the diagnosis of various ailments such as oral leukoplakia, oral submucous fibrosis (OSF) and squamous cell carcinoma in India (Ray *et al.*, 2013). Areca nut use and its frequency has been linked to be proportional to the developments of various clinical stages of OSF, the risk of disease and its onset in patients in Karachi, Pakistan (Hosein *et al.*, 2015). The long-term use of areca nut and its multivariate forms can subsequently lead to chronic irritation and systemic inflammation that has deleterious effects on the epithelial cells and the oral cavity as a whole. It has been reported that the practice of consuming dried form of betel nut is relatively more precarious and carcinogenic to health than consuming fresh betel nut, highlighting the presence of such compounds that present dried betel nuts as carcinogenic, and the development of oral mucosal ailments (Yongxiu *et al.*, 2016). The predominance of areca nut use has also been said to increase the risk of OSF manifestation and development (Franke *et al.*, 2014). OSF is characterized as a persistent inflammatory disease which is marked by the overabundance of collagen. The consumption of areca nut has been suggested as a pivotal causative agent for disease exposition. In a study carried out by Khan *et al.* (2012), mastication of areca nut has been associated directly to OSF, where the aqueous extract of areca nut was capable to instigate TGF-β signaling and its downstream targets. The mechanism of areca nut in the elevation of plasma levels of FDPs, which may be termed as a premature marker of OSF was investigated in the study of Gupta *et al.*, (2014).

Fig. 1. Areca nut, as available in its commercially available form called "Supari" in local languages of Asian countries.

The study incorporated more than 90 subjects, with more than half of the subjects habitual of areca nut mastication with and without diagnosed OSF. The experimentation concluded that elevated fibrin deposition is proportional to the increment of plasma FDPs. The advancement and onset of OSF was investigated in laboratory rats administered with areca nut extracts. Rt-PCR was used as an effective method to quantify the gene expression of TGF-β1. The results showed that areca nut and pan masala extracts positively induced OSF.

The mastication of areca nut has been associated with the pathogenesis of OSF, due to the presence of the elevated copper agglomerate in areca nut. It can be implied that copper is discharged into the oral cavity upon chewing of areca nut, where it is engulfed in saliva and absorbed into the oral mucosa (Trivedy *et* *al*., 1997; Mathew *et al*., 2014). Lysyl oxidase is the main enzyme in the pathway of collagen metabolism. Copper found in areca nut is thought to regulate this activity, thereby augmenting its generation with the aid of fibroblasts, exacerbating its cross linking and eventually restricting its degradation (Trivedy *et al*., 1999; Rajalalitha and Vali, 2005) (Figure 3). Over the years, few studies have highlighted the part of copper in the simulation of OSF. Mathew *et al*., (2014) shed light upon the elevated levels of copper present in the commercially available forms of areca nut, which are subsequently consumed at a larger scale than the raw form of areca nut. Furthermore, the upraised level of copper at serum and tissue levels in patients afflicted with OSF was also discovered in a study (Trivedy *et al*., 2001). To evaluate the amount of copper found in areca nut among plantations in South India, the effect of a locally administered copper-infused fungicide (BM) was compared with the effect of fungicide *sans* copper infusion. The results demonstrated that elevated standards of copper were indeed present in the samples of areca nut which had previously been treated with copper-based fungicide (Mathew *et al*., 2015). The consequence of areca nut on fibroblasts and keratinocytes was also evaluated in a study, and it was demonstrated that areca nut had a cytotoxic effect on epithelial cells whereas the fibroblasts encountered a pro-proliferative effect. Treating keratinocytes with arecoline and copper had resulted in a spike in the cytotoxicity too (Khan *et al*., 2015).

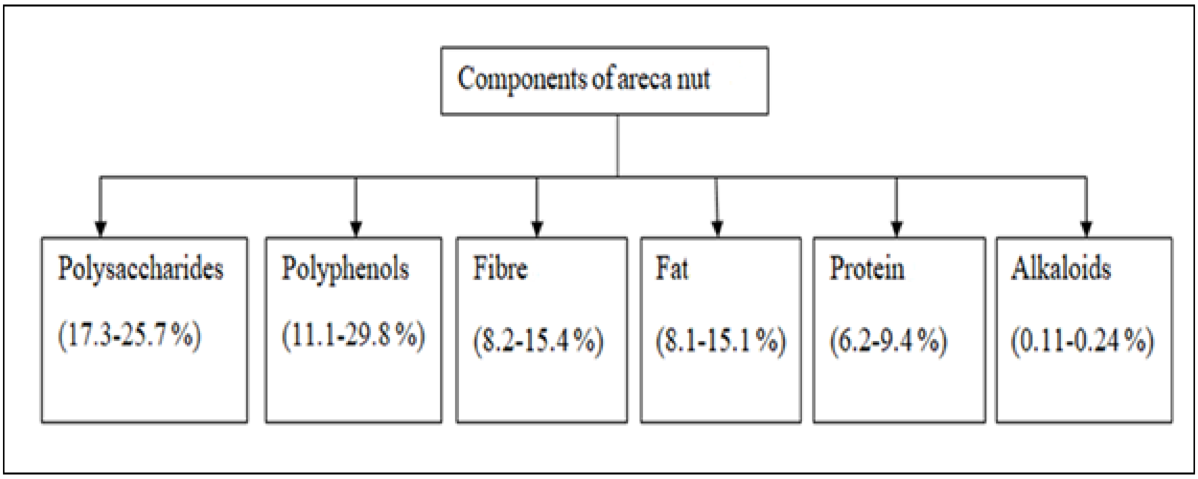

Fig. 2. The basic components of areca nut (based on dry weight).

Furthermore, many *in vitro* studies show that there is considerable amount of work being done on determining the mechanism of action of arecoline and its direct and indirect effects, wherein the onset of OSF can be an indirect result of a series of arecoline mediated pathway, such as the augmented expression of heme oxygenase-1 (HO-1) in OSF that is induced by areca nut consumption (Tsai *et al*., 2009) (Figure 4). In another *in vitro* study, it was demonstrated that higher concentration of arecoline (100, 300, 500 μmol/L) in breast cancer cell line MCF-7 had anti-proliferative and apoptotic effect in a dose-dependent manner with elevated levels of p53 and Bax, whereas reduced levels of Bcl-2 were demonstrated (Feng *et al*., 2016). Arecoline was also shown to affect STAT3 and IL-6 levels in hepatocytes in a study, where it induced anoikis in hepatoma cells (Cheng *et al*., 2010) (Figure 4).

Esophageal squamous cell carcinoma

The consumption of areca nut has long been connected as a risk factor for squamous cell carcinoma in females and males alike, with it causing varying degree of oral and submucous ailments, which had been affirmed (Muttagi *et al*., 2012). Esophageal cancer is one of the most frequently occurring cancers globally (Jemal *et al*., 2011; Chen *et al*., 2017) with squamous cell carcinoma and adenocarcinoma being its most recurrent types. The esophageal squamous cell carcinoma (ESCC) is generally reported as the prevalent type of cancer form in Asia (Chung *et al*., 2010). Many studies affiliated the use of areca nut consumption with the manifestation and onset of ESCC in habitual users (Lin *et al.*, 2011; Wu *et al.*, 2013; Chen *et al.*, 2017), which shed light on the role of areca nut mastication and its alkaloids play in the early onset of tumorigenesis and their results demonstrated the correlation of profound substance abuse to the diagnosis of ESCC in patients. While numerous studies have exposed the role of areca nut in the onset of OSF, not much light is shed on the agents that cause the progression of disease.

Areca nut and cardiovascular diseases

Areca nut consumption has been linked with cardiovascular disease (CVD), though the mechanism of action through which areca nut mastication induces the manifestation of CVD is not precisely reported.

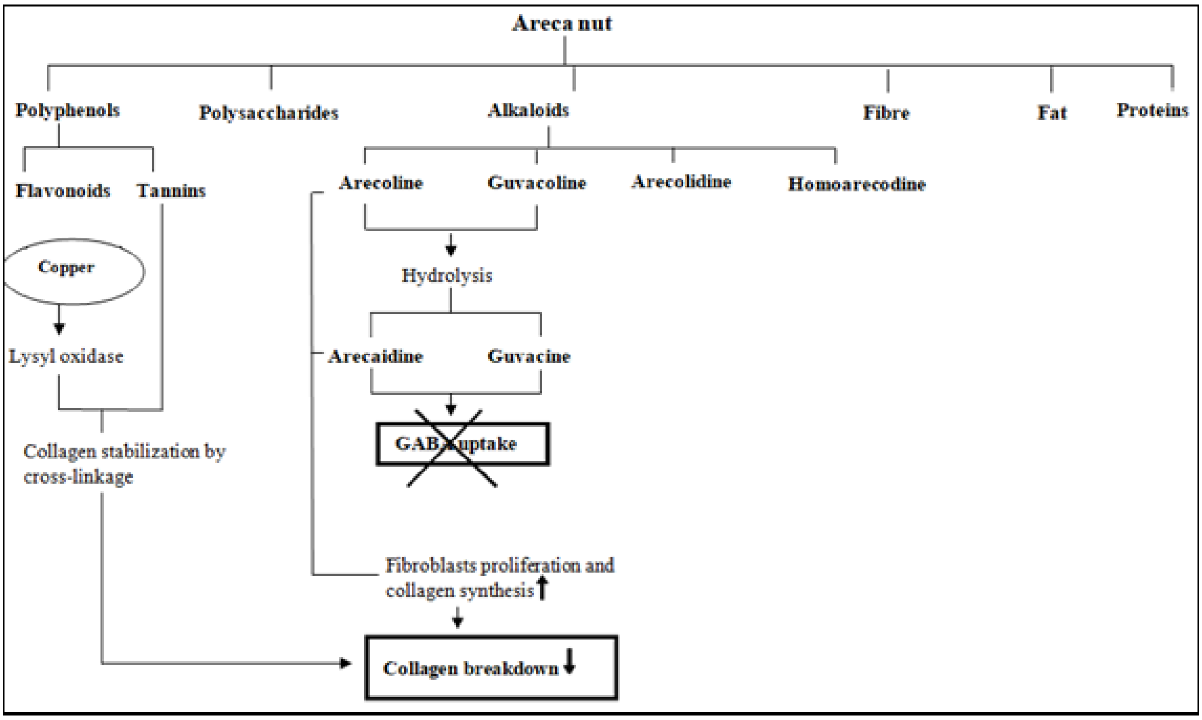

Fig. 3. Schematic representation of signaling pathways stimulated by areca nut.

In this review, published studies which shed light on the association of areca nut consumption with the risk factors of CVD were selected. Khan *et al.*, (2013) and Tsai *et al.*, (2012) probed the association of areca nut use with coronary artery disease (CAD). The case control studies consisted of healthy controls and case subjects afflicted with CAD. In conclusion, the results affirmed areca nut consumption as an autonomous risk factor said to be affiliated with CAD. The risk factors associated with areca nut usage and occurrence of metabolic and cardiovascular afflictions was investigated in a study analysis (Yamada *et al.*, 2013) which included (n=580) correlated studies which subsequently concluded that areca nut consumption directly elevates the risk associated with several lethal diseases. In 2014, McClintock *et al.*, (2014) sought out to investigate the link between areca nut consumption and carotid artery intima media thickness, with the latter being the intermediate in the progression of subclinical atherosclerosis. The results uncovered the manifestation of atherosclerosis at subclinical level, when exposed to long term areca nut usage, with the risk being most prevalent in cigarette smokers and males. There are several reported pathways that connect the mechanism of arecoline and its effect on atherosclerosis. Furthermore, in a contrasting study, arecoline found in areca nut reportedly improved vascular endothelial function in rats via increasing cystathionine-γ-lyase expression and activating K_{ATP} channels (Ling *et al.*, 2012). According to a study; the up-regulation of plasma levels of NO, eNOS protein, and mRNA expression, and the down regulation of ICAM-1, MCP-1 and CXCR-2 genes and IL-8 expression (Figure 3) are all regulated by it (Shan *et al.*, 2004). The studies have unveiled mastication of areca nut to be linked with many ailments, but not much is reported about fatality and re-hospitalization secondary to acute coronary syndrome (ACS) among areca nut users and non-users. A study (n= <300) was carried out and results showed that the rate of re-hospitalization of patients who were also areca nut chewers was substantially elevated than non-users (Karim *et al.*, 2018). The use of areca nut in the form of betel quid is also reported to be directly related to the increased risk and high incidence of premature ventricular contractions in patients demonstrating cardiac and pulmonary symptoms, with the most vulnerable being those who have previously suffered heart failures (Huang *et al.*, 2020).

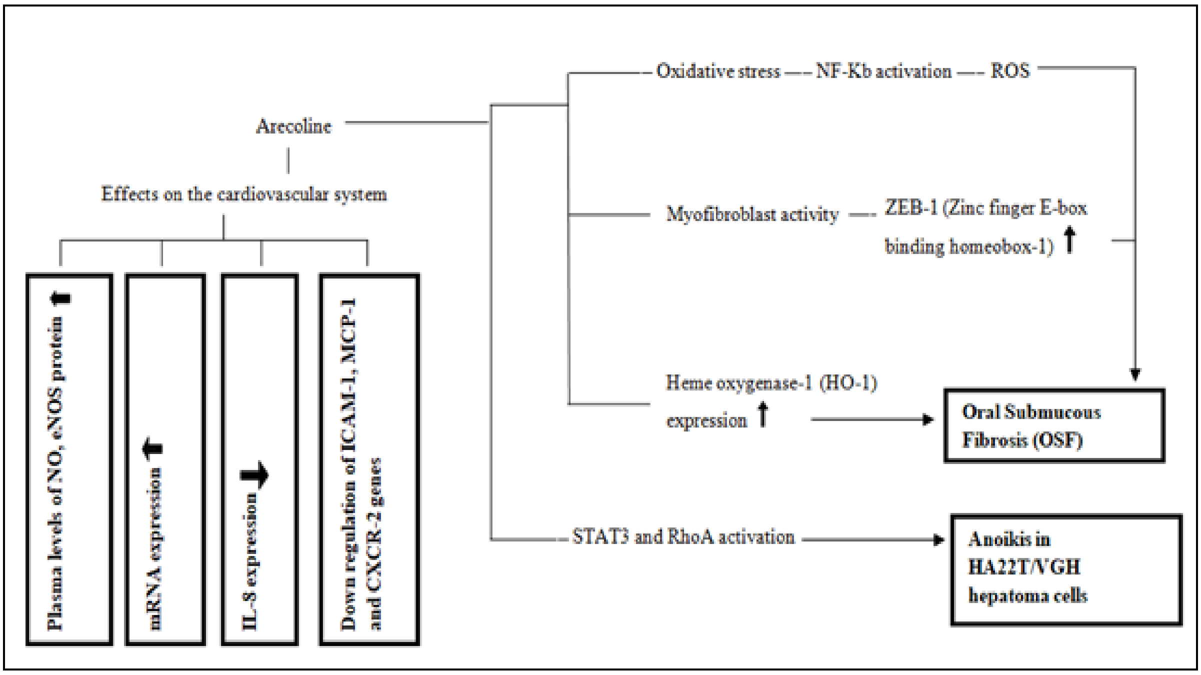

Fig. 4. Schematic representation of the signaling pathways stimulated by arecoline.

Areca nut and metabolic disorders

Chronic inflammation is characterized as an affliction in which overabundances of immune cells generate cytokines and ROS which consequently lead to the manifestation of cancer cells. Areca nut consumption is monotonous in many regions where its usage is affiliated with many systemic and intrinsic ailments.

The link between areca nut chewing and systemic inflammation was examined in a study (Shafique *et al.*, 2012) which included addicted areca users and non-addicted, healthy subjects from Pakistan. After a series of multiple analyses, it was concluded that areca nut consumption has a substantial link to systemic ailments and inflammation. To study the plausible factors and the individualistic role of areca nut in the progression of liver cirrhosis, subjects were included to evaluate the predominant risks associated with liver cirrhosis in a study (Lin *et al.*, 2008). The general predominance rate was evaluated for HBsAg, HCV, ALT, AST and GGT respectively. Of all subjects consented to abdominal scan for the detection of liver cirrhosis, n= 2 % were found to contain risk factors pertinent to the disease.

The correlation of areca nut chewing and metabolic disorders was investigated (Ling *et al.*, 2012), where the results demonstrated the harmful effects of chewing areca nut, with effects getting stronger when it is consumed with tobacco. Its consumption is also reported to increase the incidence of chronic kidney disease, thereby existing as a significant risk factor in betel nut chewers as compared to non-chewers (Wang *et al.*, 2018).

Areca nut and DNA damage

Fibroblasts are generally regarded as the agents that are associated with the early onset of cancer, by exuding cytokines and eventually inducing DNA damage in cells. The consumption of areca nut has been reported to provoke such fibroblasts, which lead to the early and precipitous progression of carcinogenesis. The gingival fibroblasts exposed to areca nut are reported to induce cytokines that consequently result in DNA damage by the generation of ROS in keratinocytokines (Illeperuma *et al.*, 2015). The mutagenic property of arecoline in both prokaryotic and eukaryotic cells has been established since long, as it plays a major role in increasing the prevalence of micronuclei and chromosomal aberrations in mouse bone marrow cells *in vivo* and in Chinese hamster ovary cells *in vitro* (Panigrahi and Rao, 1982; Shirname *et al.*, 1984). Arecoline is a depurinating agent and its binding with the DNA strand leads to the breakage of phosphodiester bond between adjacent nucleotides. Thus, the increased concentration of arecoline induces different types of genome damage e.g. chromosomal breaks, and nicks and gaps in the DNA strand. An increased frequency of chromosomal segmental exchanges in blood lymphocytes and in cells of buccal mucosa in areca nut users was seen in a study (Dave *et al.*, 1992). On the contrary, certain studies demonstrate no influence of arecoline content either upon DNA strand breaks or un-regulated synthesis of DNA in keratinocytes (Sundqvist *et al.*, 1989; Jeng *et al.*, 1999). The damage to DNA is induced by endogenous concentration of GSH and ROS which are produced in abundance when cells are treated with superoxide dismutase and arecoline in anoxic conditions (Deb and Chatterjee, 1998). Therefore, the extent of DNA damage by raw betel nut extract is reportedly enhanced due to synergistic effect of buthioninesulfoximine (BSO) which increases the concentration of endogenous GSH (Bagchi *et al.*, 2002; Kumpawat *et al.*, 2003). Similarly, in comparison with intraperitoneal injection, an oral administration of areca nut leads to higher frequency of DNA damage (Chatterjee and Deb, 1999). Furthermore, the presence of metal ions such as iron in the areca nut and alkaline conditions in the cells favor the production of ROS such as H_2O_2, superoxide and hydroxyl free radicals (Chen *et al.*, 2002). Such free radicals not only hinder the repair mechanism of DNA but also cause DNA damage in human peripheral mononuclear leukocytes (Pero *et al.*, 1990; Hu *et al.*, 1995). Moreover, the role of areca nut alkaloids was investigated for inducing senescence in fibroblasts in the oral cavity (Rehman *et al.*, 2016). The oral fibroblasts were subjected to arecoline and arecaidine and TGF-β and MMP-2 levels were quantified by the aid of ELISA and statistical analysis. The conclusions affirmed the hypothesis that the alkaloids affirmatively induced senescence in fibroblasts and encourage the secretion of TGF-β that eventually leads to malignant OSMF. Arecoline also induced myofibroblast differentiation from human buccal fibroblasts which was in turn mediated by Zinc finger E-box binding homeobox-1 (ZEB-1), whose expression is increased in the presence of arecoline (Chang *et al.*, 2014).

Areca nut and obesity

Consumption of areca nut has demonstrated to elevate the overall risk of heart disease and fatality. The affiliation between areca nut consumption and obesity was previously unknown. The interrelation between areca (betel) nut consumption and obesity was analyzed in one study conducted in Taiwan (Lin *et al.*, 2009). The results demonstrated that men who were formerly or currently in the habit of consuming areca nut had a higher correlation to obesity to those who did not. Conclusively, its chewing was found to be strongly associated with obesity in Taiwanese men (Esposito and Giugliano, 2011).

Areca nut and erectile dysfunction

Areca nut was deemed an aphrodisiac since the time it was first used, centuries ago. In current times, erectile dysfunction (ED) is currently is one of the main driving factors of infertility and affects males of all class, race and gender all over the world. It is hence a prevalent issue in men, with its risk factors such as obesity, hypertension, and cardiovascular disease common in areca nut users as compared to non-chewers (Feldman *et al.*, 1994). A single study published was selected for assessing the linkage between areca nut and erectile dysfunction. A cross-sectional study investigated the effect of betel nut chewing was affiliated with an elevated risk of ED (Huang and Jiann, 2017). The results of the data were not sufficient in proving positive correlation; hence its usage is not evidential in being considered as a direct etiological factor in causing ED in men.

Conclusion

Areca nut has been in use since centuries; with its adverse effects and active role in various ailments having being come into the light until recently. This raises the question as to why its practice has been perennial since many eras. Areca nut usage is reported to be associated with cancers of the oral cavity, esophagus, pharynx, liver, biliary tracts and uterus as well as causing various disorders in almost all organs of the human body. Many studies are now being published that study the mechanism behind its pathogenesis, yet deep, insightful studies are very crucial to gauge its detrimental effects as well as advantageous facets.

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