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Risk of hepatocellular carcinoma due to aflatoxin infested areca nut consumption-a review

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SUMMARY

Areca nut (AN) consumption is a practice of great antiquity in India and reported to be consumed by 20% to 30% of the Indian population in the last 2-3 decades. Various mechanisms have been reported with reference to its adverse effects on the liver, one of which could be ingestion of aflatoxin infected AN, as aflatoxin B1 is a known hepatotoxin. Reports are available stating that most of the ANs available in the market are substandard and contaminated with cancer-causing fungus and chewing of such poor quality, infested ANs would definitely pose severe health problems on human beings in a long time. But, to our knowledge, scanty literature is available reporting the role of aflatoxin infested AN on the risk of liver cancer. The evolution of such risk factors provides insight into the understanding of the future burden of the disease.

Key words: areca nut, aflatoxin, liver, hepatocarcinogen

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INTRODUCTION

Areca nut (AN) is a fruit of the areca catechu palm tree, which is native of South Asia and the Pacific Islands. It is chewed regularly by at least 10% of the world population of all the groups and is the fourth most widely used addictive substance [1, 2].

In regards to the Indian scenario, India is the largest producer of AN, producing nearly half of global AN production. It ranks first in both areas (58%) and production (53%) of AN. It is estimated that nearly ten million people depend on AN industry for their livelihood in India [3]. Similarly, AN consumption is a practice of great antiquity in India and reported to be consumed by 20 to 30% of the Indian population in the last 2-3 decades.

As per the previous evaluation (1895) by the International Agency for Research on Cancer, chewing BQ with tobacco was stated to be carcinogenic to humans. However, the new evaluation (2004) concluded that chewing AN alone is also carcinogenic to humans [4-6]. For that reason, to study the consequences of AN consumption on the human body, including the liver is an area of keen importance.

Effects of AN on the human body in general

The great untoward effects of AN consumption on oral mucosa such as oral submucous fibrosis and oral cancer are widely reported in the literature [7, 8]. Accordingly, it is stated that bringing AN products into the ambit of the tobacco products act is absolutely essential to decelerate the rapidly evolving epidemic of oral submucous fibrosis and oral cancer among youngsters of the country [9]. But, it is equally essential to be aware of the systemic effects of AN as a result of its break down and excretion products, such as on liver, one of the vital organs.

AN contains water 30%, protein 5%, fat 3%, carbohydrate 47%, and alkaloids with arecoline been the major alkaloid constitute 0.2%-0.7% [10]. Alkaloids, flavonoids, tannins are the proven carcinogenic contents of AN. Though AN contains many alkaloids, arecoline is blamed mostly as it is responsible for fibroblast proliferation. Under the influence of slaked lime, arecoline gets hydrolyzed to arecadine, which has pronounced effects on fibroblasts [11]. Areca flavonoids, tannins, and catechins can cause increased fibrosis by forming a more stable and non-soluble collagen structure by inhibiting collagenase enzyme activity [12, 13]. Similarly the trace element, copper present in AN is also responsible for fibrosis as it enhances the functioning

of lysyl oxidase, a copper-dependent enzyme. So, these are the few AN induced mechanisms responsible for liver fibrosis, an early stage of liver cancer.

Apart from this, one of the reasons for liver damage in AN habitual could be the ingestion of aflatoxin (AF) B1 infected AN, as AF B1 is a known hepatotoxin [14]. Reports are already available that most of the ANs available in the market were of substandard and contaminated with cancer-causing fungus [15, 16] and chewing of such poor quality, infested ANs would definitely pose severe health problems on human beings in a long time. But, to our knowledge, scanty literature is available reporting the role of AF infested AN on the risk of liver cancer. The evolution of such risk factors provides insight into the understanding of the future burden of liver disease.

AFs are the groups of structurally related mycotoxins produced as food-borne metabolites by toxigenic strains of *Aspergillus flavus* and *A. parasiticus* due to bad storage conditions [17-19]. Four types of AFs, B1, B2, G1, and G2 commonly infest food items though there are others too. Among this B1 is considered to be the most potent and accounts for nearly 70% of the total AF content in food [17].

Infestation of AF in AN

AN may be infested by AF during various stages of its production, storage, and transportation. The ANs are generally dried naturally after harvest for 30-40 days, later dehusked and stored in hessian bags. The inner soft endosperm of the nuts may be colonized by a range of fungi [20]. Various studies have been carried out to check the occurrence of AFs in the marketed AN or betel nut samples and the infestation was found in a number of samples [17, 21-23]. AN has high moisture content and if they are not processed and dried properly or are harvested prematurely or allowed to dry in heaps then they can become infected with fungi like AFs.

The infestation of *A. flavus* was commonly reported in Indian AN. For example, the concentration of AF B1 was found to be 51.09 µg/kg in AN samples of Lucknow which was much higher than the tolerance limit fixed by WHO. Similarly, *A. flavus* and *A. niger* were also isolated from the AN samples from the Gulbarga cities of India [20, 21]. In another study conducted on the infestation of AFs in AN in India, an average AF B1 content was found to be as high as 94 µg/kg and average total AF (B1+B2+G1+G2) content of 37 µg/kg. So, the studies revealed that the concentration of AF largely exceeding the commonly accepted food limit of 5 µg/kg.

Another surprising issue is, even though India is one of the largest producers of AN, thousands of tons of dehusked ANs are imported from neighboring countries every year, which are also infested by AFs [21-24,25]. A rapid cross-sectional study conducted at Bangladesh on the extent of AF contamination in several human food items and poultry feed revealed the presence of AF at 30.6 ng/g level in the samples of their ANs [26]. In Nepal, it was reported that as many as 25% of AN samples were found to be contaminated with AF B1 or B2 [27]. In South Africa it was noticed that nearly 40 to 60% of dried AN samples (sliced or whole) imported were found to be contaminated with *A. flavus*, and the concentration of AFs B1 in such ANs was found to be in excess of the commonly accepted food limit [28, 29]. Based on the AN consumption data it was also calculated that chewers of un-boiled dried ANs in South Africa may consume a total AF (B1+B2+G1+G2) content of 3.6-1080 ng per day [28]. Similar observations are also reported in a study from Pakistan [30]. So, it can be presumed that in countries like India and Taiwan where the people mostly chew similar types of AN, it can be susceptible to AF induced liver disease [31].

AF and risk of liver disease

Amongst the number of ill effects of AF on the human body, liver toxicity is the one [32]. Rather the most severe effect of AF in the human body is seen in the liver [33]. AF is considered as the agent naturally causing hepatocarcinogens and the impact of AF on public health is detected in both acute and chronic exposure [34, 35]. Early symptoms of hepatotoxicity of the liver caused by AFs comprise fever, malaise, and anorexia followed with abdominal pain, vomiting, and hepatitis. Acute exposure of AF can result in fulminant liver failure [36, 37]. However, cases of acute poisoning are exceptional [38]. Chronic toxicity by AFs comprises immunosuppressive and carcinogenic effects that have been linked to the development of HCC [35, 39-41].

The hepatocarcinogenicity of AF is mainly due to the lipid peroxidation and oxidative damage to DNA [42]. Several studies have shown the detrimental effects of AFs exposure on the liver [43, 44]. AFs toxicity is regulated by factors such as age, sex, species, and status of nutrition of infected animals [45]. A recent study proposed that myofibroblasts may be involved in the fibrosis-associated liver damage induced by AFB1 exposure [46]. Molecular mechanisms involved in AF induced carcinogenesis include the formation of DNA and protein adducts, and also lipid peroxidation [47].

Gong YY et al. [48] reported that AF exposure can occur at any stage of life and is a major risk factor for hepatocellular carcinoma, especially when hepatitis B infection is present. They stated that AFs may lower cell-mediated immunity, thereby increasing disease susceptibility.

Prevention of AF infestation of AN

Multiple public health interventions exist to control the burden of AF in the body and to prevent HCC. These interventions can be grouped into three categories: agricultural, dietary, and clinical [49]. Agricultural interventions can be applied either in the field (pre-harvest) or in storage and transportation (post-harvest) to reduce AF levels in key crops. They can thus be considered primary interventions. Dietary and clinical interventions can be considered as secondary interventions. They cannot reduce actual AF levels in food, but they can reduce AF related illness, either by reducing AF's bioavailability in the body or by ameliorating AF induced damage. One highly effective clinical intervention to reduce AF related HCC is vaccination against HBV.

With reference to the prevention of AF infestation of AN, various methods like Ultra Hermetic storage, AF binders, physical, chemical, natural methods, etc which are mentioned for the protection of various food products including other nuts

may be recommended for AN also [50, 51]. But, in spite of recommending protection of AN from AFs, stoppage of the habit of AN consumption should be recommended; as irrespective of AF, many other components of AN are equally responsible for its adverse effects.

CONCLUSION

Two concerns are apparent from this review; i) AN are often infested by AF, ii) AF is known to cause liver damage. Based on this, it may be concluded that chronic consumption of AF contaminated AN can induce liver damage leading to hepatocellular carcinoma. Thus, scheming the areca nut consumption habit will definitely contribute to reducing the overall burden of liver cancer, which might be to a small extent. Due to the scarcity of literature pertaining to the consumption of AF infested AN and the risk of liver cancer; there is a dire need for more studies to better understand the overall scenario.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest among authors.

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