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Betel nut chewing and human health: certain glaring lacunae in research

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Abstract: *Areca catechu L is a slender and tall palm grown mostly in tropical and subtropical climate. It's fruit or nut is called arecanut or betel nut or supari. This nut, in combination with several other ingredients, is considered to be the common masticatory being practiced since several centuries by human population all over the world as this nut is believed to have certain medicinal properties. However, several scientific reports say that chewing arecanut or betel nut is not good for human health and even causes cancer. On close examination of several such reports, it looks as if the conclusions were drawn hastily and the method of approach lacked clarity. In some reports the terminology itself was ambiguous. Several studies were conducted by unusual methods of application such as by injection or by applying directly on cultured cells. Correlating such results either with the chewing habits of arecanut or certain chewing products containing arecanut seems to be totally wrong as the processes themselves are different altogether from one another. Some researchers studied the effects of arecanut by using very high doses and claimed arecanut as harmful. Some even arrived at the conclusion with very small sample size. In several papers, the quality of arecanut or its chewing products used for the experiment were not at all ascertained. The synergistic effects of several other products used for chewing along with arecanut as betel quid, pan masala or gutka were not taken for consideration in several papers but simply blamed arecanut for all the consequences. Such pitfalls are discussed and highlighted in this paper.*

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I. Introduction

Botanically, arecanut or betel nut or supari is the fruit (nut / seed / endosperm) of the oriental palm Areca catechu L. (Family: Arecaceae or Palmae). This palm is mainly grown in tropical and subtropical climate[1]. Arecanut is the most common masticatory in the world especially in South and South East Asian countries[2]. The history of chewing arecanut is not a recent origin but goes back to several thousands of years. In India, the presence of areca has been mentioned as early as in 1300 BC as quoted by Sisu Mayana in 'Anjana Chaitra'[3]. In other countries such as Vietnam, the use of arecanut was even noticed during the brounze age of human civilization as identified by the stains of arecanut in the fossil remains of human teeth[4].

Arecanut has an important place in the ancient system of Indian medicine such as Ayurveda, Unani and Homeopathy[5-6]. In China and other South and Southeast Asian countries, arecanut is widely used in several clinical practices as well[7-9]. WHO has listed out as many as 25 different beneficial effects of A. catechu on mankind[10].. Arecanut is traditionally used to treat several ailments as it has properties such as laxative, digestive, antiulser, carminative, antidiarrhoeal, anthelmintic, antimalarial, antihypertension, diuretic, prohealing, antibacterial, hypoglycaemic, antiheartburn, etc.[11-14]. All the seven alkaloids (arecoline, arecaidine, guvacine, guvacoline, isoguvacine, arecolidine and homoarecoline) present in arecanut were reported to possess drug-like properties[15].

There are several research papers titled as 'arecanut or betel chewing is carcinogenic or harmful'. While going through such scientific reports it was seen that in most of the Research papers, the authors did the experiments either on betel quid chewers or chewers of some other masticatory products such as pan masala, gutka, etc which contained arecanut as one of the ingredients, but blindly blamed arecanut for all the ill effects caused by chewing such substances. The role of other ingredients or the combined effects of such combinations on human health were not considered at all while evaluating the results. Several such lacunae were identified and discussed in this paper.

II. Terminologies

Arecanut or betel nut is generally used for chewing. However, it is seldom chewed alone, but mostly masticated along with other substances like the leaf or inflorescence of a tropical vine (commonly called as betel vine), Piper betle of the family Piperaceae, calcium hydroxide (slaked lime), tobacco and several other flavouring agents or ingredients according to local preferences. Such mixture is collectively called as betel quid[2]. Hence, it is necessary to mention the ingredients and discuss their role on human health in the research papers before arriving at any solid conclusion.

Ironically, in most of the research articles which reported arecanut as harmful, data were either collected from betel quid chewing people or from people chewing other products such as pan masala, gutka, etc. in which arecanut is one of the ingredients, this nut was simply blamed for the overall adverse effects without discussing the role of other ingredients. One such example is that of a research paper where the prevalence of oesophageal cancer in betel quid chewing and smoking people in Taiwan was reported but in the title, instead of mentioning as betel quid only arecanut was highlighted[16]. Similarly, there was a paper entitled "Arecanut and its effects on the human body"[17]. The study was compiled mainly on betel quid chewers!. Strangely, there are so many publications with such vague terminologies[18-28]. It is strange to note that even certain review papers also did not notice such glaring mistakes while reviewing[29-31]. They all reviewed the results of chewing betel quid or other chewing products containing arecanut as one of the ingredients, but projected arecanut or betel nut as the sole culprit. In some other papers the betel quid is termed simply as betel[32-34]. To avoid ambiguity in scientific literature it is necessary to refer the nut of A. catechu as arecanut or betel nut.

Some researchers did not evaluate the role of co-substances used in the betel quid in causing the problem. For example in the paper published by Wu et al, it was mentioned: "In this report we present another potential hazard of betel nuts, milk alkali syndrome" [35]. While going through that paper it was noticed that the patients were using high amount of calcium carbonate from oyster shell with arecanut for chewing. The role of calcium carbonate in causing milk alkali syndrome was not at all highlighted in this paper, instead, betel nut was blamed for that effect and projected in the title itself.

III. Types and developmental stages of arecanuts used

The chemical constituents of arecanut vary considerably during the development and storage of these nuts. At very tender stage of the nut, the arecoline content is nil which increases as the nut develops and reaches as high as 0.22 % in the ripe nut[36]. On the other hand, polyphenol (including tannin) content which is maximum (up to 48%) in tender nut decreases as the nut matures and reduces to 18% in ripe nuts. Further, all the major chemical constituents of arecanut, including arecoline decrease significantly while the nuts are dried and stored with husk and also while roasting, soaking and boiling[37]. In certain parts of the world such as Taiwan, Papua New Guinea, etc the betel quid is prepared not with mature arecanut but with tender arecanut along with its husk[38]. Accordingly, there is every possibility that depending on the type of arecanut used for chewing the results may also vary. Hence, it is not correct to blindly apply the results obtained on chewing betel quid in one region to all other regions where the substances used for preparing the betel quid are clearly different from one another.

IV. Types of solvents used for extraction

In most of the experiments conducted on lab animals, instead of arecanut its extract was used. It was noticed that the properties of the extract of a given plant part vary depending on the solvent used for extraction. This is also true for areca palm. In a study on the antibacterial action of arecanut it was reported that the butanol fraction of the nut was more potent than the methanol, ethyl acetate and water extracts against four strains of bacteria such as Staphylococcus aureus 96, S. aureus 2940, Streptococcus mutans and Mycobacterium smegmatis[39]. In another study on the antifungal effects of arecanut, three different solvent extracts (aqueous, ethyl acetate and hexane) of this nut was tested against Candida albicans and reported that the ethyl acetate extract was the most active one followed by aqueous and hexane extracts[40]. Similarly, on the anti-diabetic activities of three different solvent extracts (petroleum ether, ethanol and aqueous) of areca flowers it was noticed that there was significant reduction in blood glucose levels in ethanol and aqueous extract treated rats whereas such reduction was not significant in petroleum ether extract treated rats[41]. Among the petroleum ether, chloroform and methanol extracts of the leaves of areca palm, it was reported that the methanol extract was the most effective one followed by chloroform and petroleum ether extract in reducing the blood sugar level in Wister albino rats[42]. Hence, the selection of solvent is very important to study the full potency of the plant part used.

V. Effects of other habits

Cancers in general are multifactorial in origin involving several environmental factors and varied food habits. It was reported that oral hygiene, food habits, family history, etc play important role in oral, pharyngeal and oesophageal cancers[43-48]. It was also reported that certain dietary factors also play important role in inducing cancer. For example, it was reported that in pan - tobacco chewing people, the consumption of ragi (Eleusine coracana) as the staple food enhanced the risk of oral cancer by several folds (RR 29.3) than those eating rice (Oriza sativa) as staple food (RR 1.0)[49]. The effects of other habits and certain nutritional factors, etc., should also be worked out and discussed before arriving at any conclusion.

VI. Effects of other ingredients

The action of other ingredients of the chewing products containing arecanut, such as the leaf or inflorescence of P. betle, calcium hydroxide, catechu, condiments, etc., should also be studied in detail. The synergistic actions of such products should also be noted before labeling any one individual product for all the adverse effects. It is a known fact that the action of a product varies considerably depending on the ingredients used. For example, Minakshi and Sunderesan studied the effects of betel quid components, individually as well as in combinations on the kinetics of salivary amylase[50]. They reported that arecanut alone when mixed with human saliva reduced the amylase activity by 800%, whereas the amylase activity was increased by 30% when arecanut was mixed with betel leaf and lime. When catechu (Acacia catechu) was mixed with such betel quid, the amylase activity was again found to decrease by 100%. On the other hand, the betel leaf (leaf of P. betle) alone increased the amylase activity by 14.3%, whereas the amylase activity was decreased by 300% when betel leaf was mixed with lime. This clearly shows that the activity or the property of arecanut changes drastically depending on the ingredients used. Hence, it is highly necessary to study the activities of arecanut, alone and in combination with other ingredients, before arriving at any solid conclusion.

In certain countries such as Taiwan, Papua New Guinea, etc., the betel quid generally does not contain the leaf of P. betle but it includes the inflorescence of this vine[38]. The chemical constituents of the leaf and inflorescence of P. betle are not the same, but different. The inflorescence of P. betle contain good amount of safrol, a chemical carcinogen but the leaf consists of hydroxichavicol, an anti carcinogen[21]. When that is the case, the results of chewing betel quid containing the leaf of P. betle should differ significantly from that containing its inflorescence. It was further confirmed that in Taiwan, the people who chewed arecanut with P. betle inflorescence were 24.4 times more likely to develop oesophageal cancer than those who chewed arecanut with the leaf of P. betle[21]. This also shows that the action of betel quid differs significantly depending on the ingredients used even though they are from the same plant. In India and several other countries of South and South East Asia people use the leaf of P. betle instead of its inflorescence to prepare the quid. Hence, the data collected in Taiwan and Papua New Guinea where they mostly use the inflorescence of P. betle in the betel quid cannot be applied in total to all other regions unless the properties of the chewing products used in these regions are studied in detail. The researchers should take care of such aspects also before publishing the result.

Calcium hydroxide (slaked lime) is another ingredient invariably used with arecanut and the leaf or inflorescence of P. betle in preparing betel quid. Dunham and Herrold could not induce any tumor in the cheek pouches of hamsters while treating with betel quid containing the mixture of arecanut, the leaf of P. betle and lime[51]. On the other hand, in another study conducted on such animals by Dunham et al, it was revealed that repeated application of lime alone severely injured the cheek pouches of hamsters[52]. Three of the inflammatory and hyperplastic lesions that developed in the pouches of 26 treated hamsters progressed to epithelial atypia. Such actions and irritations may predispose to cancer of the mouth. To substantiate this observation, it was reported that nearly 77% of 169 cases of oral cancer in Papua New Guinea was concentrated precisely in the site of application of lime[53]. Hence, it is necessary to discuss in detail the actions of other ingredients of betel quid before arriving at any conclusion.

VII. Contamination and adulteration in arecanut and its chewing forms

Aflatoxins are fungal toxins inducing acute toxicity, carcinogenicity and several other adverse effects on human health[54]. Sub standard or poor quality arecanuts usually found infested with such toxin producing fungi (Aspergillus flavous and A. parasiticus) much above the permissible limit of 15-30 ppm[55]. Continuous consumption of such fungal contaminated food, even if they are in small doses could lead to many human health problems[56]. Adulteration of arecanut products is another menace in India and in several other countries. It is mostly done by mixing with pesticides and heavy metals. Certain pan masala products were reported to contain Polycyclic aromatic hydrocarbons and insecticides (DDT and HCH) much above the tolerance limit[57]. Hence, the quality of arecanut and the chewing product containing this nut should be verified before arriving at any conclusion on the effects of arecanut or betel nut on human health.

VIII. Target animals

Most of the studies on arecanut carcinogenicity were carried out on laboratory animals such as mice, rats and hamsters. It is to be noted that the physiology and tolerance to chemicals differ widely from one species to another. It is true even in the same group of animals. For example, among rodents, the LD50 of arecoline to a mouse is 550mg/kg, whereas it is 2,500mg/kg for a rat[58]. This shows that the data obtained for one species of animal cannot be generalized for all other species unless separate studies are conducted on them. It applies to human beings also and detailed studies should be undertaken on human conditions using arecanut alone before making any solid statement on the carcinogenicity of arecanut or betel nut on them.

IX. Methods Of Application And The Quantity Involved

The method of application and its dose are very important for the success of any drug. The actions may vary depending on the method of application. In an experiment conducted on Swiss mice and C17 mice by feeding the extracts of arecanut as well as betel leaf separately by intubation (gavage) it was reported that the arecanut extract induced tumors in both these mice but not in the betel leaf treated mice[59]. On the other hand, when arecanut and betel leaf powder mixed foods (both at 20% concentration) were given separately to rats for direct feeding through mouth for more than 300 days no tumor was developed in arecanut fed rats, whereas a fore stomach papilloma was observed in betel leaf treated mice[60]. This clearly shows that the method of application is very important in deciding the effects. As human beings masticate these products and not consume them by gavage, the results of the latter may be more apt in such conditions. In another experiment, the LD50 of arecoline to a mouse was calculated by three different methods. By intravenous (iv) injection the LD50 of arecoline was reported to be 36mg/kg, whereas by intraperitonial (ip) injection it was 190mg/kg, and by oral feeding it was calculated to be 500mg/kg for the same animal[58]. This shows that the method of application is also very important in determining the action of any drug. Hence it is suggested to look into the effects of the actual chewing of arecanut, in the normal dose by chewing mode and not by any other mode or by using higher doses.

X. Time of application

Sometimes, the time of application also plays an important role on the result. While studying the anti-ulcerogenic activity of arecanut in Wistar albino rat, it was noticed that the ethanol induced gastric mucosal injury was significantly reduced when these animals were pretreated with arecanut extract 30 min before ethanol administration [61]. Similar results were also observed on Sprague Dawley rats. Pretreatment with the aqueous extract of arecanut at 2g/kg body weight 30 min before the induction of gastric ulceration by absolute alcohol showed potential anti-ulcerogenic effect almost comparable to that observed with Ranitidin, the standard gastric anti-secretory drug at a concentration of 50mg/kg body weight[62]. Strangely, the results were quite opposite when such rats were pre-treated with arecanut extract 60 min before ethanol administration. In such case the gastric mucosal injury was reported to increase[63]. This does not mean that arecanut is not effective against ulcers, but the time of its application is very important as any other drug.

XI. Sample Size

It is known in science that the larger the sample size, the more authentic are the results. When the sample size is very small compared to the population, the results varied from one study to another and in most they are fully biased. This is clear in several studies. In one report where the sample size of Oral Submucous Fibrosis (OSMF) patients with betel quid chewing habit was 40 and control individuals 31, the serum levels of copper in the OSMF patients and control subjects were 75.6µg/100ml and 80.5 µg/100ml, respectively[64]. In another report where the sample size was 35 OSMF patients and 35 control subjects, the serum level of copper in them were 133.3µg/100ml and 113.9µg/100ml, respectively[65]. It is interesting to note that in the former study, the serum in OSMF patients with BQ chewing habits contained less copper than the control subjects whereas in the latter study it was quite reverse!

In two largest cohort studies conducted till today to find out the effects of betel quid (without tobacco) chewing on pregnancy and child birth involving 7,685 pregnant women in Thai-Myanmar border[66] and 2,700 pregnant women in Madang Province of Papua New Guinea[67] no significant adverse effects were reported.

Whereas, in certain studies using smaller sample size, some adverse effects were noted. In studies conducted in Taiwan on 1,264 pregnant women in which only 40% consumed betel quid[68], in Papua New Guinea on 310 pregnant women [69], in Eastern Taiwan on 229 pregnant women[70] and in Southern Taiwan on 186 pregnant women[71] adverse birth outcomes were reported. This clearly shows the importance of sample size in scientific research.

XII. Conclusion

The present review clearly shows that there are several pitfalls or lacunae in most of the research works and review papers which highlighted arecanut or betel nut chewing as dangerous. Such papers seldom revealed the actual constituents of chewing products, the quality (contaminants and adulterations) of such materials, the synergistic effects of arecanut with other chewing substances incorporated in the betel quid, the role of different food habits, etc. but simply blamed arecanut for all the ill effects. Several studies were also made by unusual methods of application of arecanut such as by injection or putting directly on cultured cells. The results obtained by such studies cannot be applied in total to human beings who use arecanut for chewing and not for injection. Such methodology are totally incorrect as far as the normal chewing process of arecanut in human beings. Some other researchers studied the effects of arecanut by giving very high doses and claimed arecanut as harmful. Some others even arrived at the conclusion using very small sample size for their study.

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