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THE PHARMACOLOGICAL AND ADVERSE EFFECTS OF THE BETEL NUT ON EXPERIMENTAL ANIMALS- A REVIEW

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ABSTRACT

Betel nut is a well-known plant product consumed mostly by people in Asian countries. Betel nut chewing seems significantly associated with susceptibility to oral, oesophageal, stomach, liver and lung cancers. Moreover, betel nut extracts at different concentrations induce significant genetic damage and histological abnormalities in the testis in tumour-bearing mice. The genotoxic and carcinogenic potentiality of betel nut extracts has been studied in different animal models. Therefore, our present review will discuss the mutagenic, carcinogenic and angiogenic effects of betel nut on animal model.

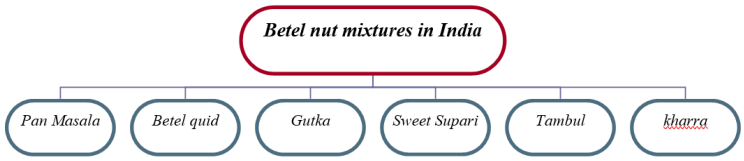
Keywords: Experimental Animals, Animal Models, Betel Nut, Genetic Damage

1. INTRODUCTION

Different smokeless chewing products are used extensively, mainly in developing countries like India, Pakistan, Bangladesh, Cambodia, Malaysia, Papua New Guinea and South African countries IARC. (2004). Betel quid / pan, pan masala, gutka, Kharra, etc., consumed by mixing betel nuts. Betel nut or Areca nut is the endosperm of the areca fruit from the tropical palm tree Areca catechu. It grows in most parts of South Asia, much of the tropical regions of the Pacific Basin, and parts of East Africa. The nut can be used fresh, dried, and roasting, or sun drying

Changrani et al. (2006), Petti & Warnakulasuriya (2018); Warnakulasuriya & Chen (2022). In mainland China, people consume the husk with the dried nut, while the people of Taiwan consume the whole unripe fruit Petti & Warnakulasuriya (2018).

Betel nut trees are mainly grown in tropical countries like India, Bangladesh, Thailand, Singapore, Malaysia, China, Taiwan, Thailand, and some African countries IARC. (2004). The average height of betel nut trees is 33 - 66 feet long, and they can reach 100 feet tall. The growing temperature of 15.5 ºC — 38ºC is suitable for growing a betel nut palm plant. The main product of this tree is the seed, which is consumed by people as chewing materials.



Different smokeless chewing betel nut products are available on the market Blank et al. (2008) Ahuja & Ahuja (2011). They are named as betel quid, gutka, pan parag, pan masala etc. Some smokeless chewing materials are described below –

Paan / Betelquid—The ingredients of betel quid are betel leaf, areca nut/betel nut, slaked lime, rose water, clove, cardamom, mint, etc. This product is popular in many Asian countries and all Indian states. Its uses are more common in rural areas than in urban areas Gupta & Warnakulasuriya (2002).

Khaini—Dried or fermented small-cut tobacco leaves with slaked lime are the main ingredients of Khaini. The product is consumed in most states of India, Bangladesh, and Nepal, and it is generally consumed by chewing for 10-15 minutes placed between the gums and cheeks in the mouth.

Gutka—The main components of gutka are betel nuts, dried or roasted tobacco finely chopped, slaked lime, and sweeteners and flavourings added. This material is used by the Indian people and Indian native people now living in different countries in Europe, America, etc.

Loose leaf / sada pata / chadha / tobacco leaf—Dried tobacco leaf is only used for chewing and smoking. It can also be used as an ingredient of betel quid. This process of tobacco consumption is widely used in the rural and urban areas of India, Bhutan, Bangladesh, and Myanmar.

Kharra: It is the combination of betel nut with tobacco, lime and other ingredients.

Figure 1

Figure 1 A: Betel nut tree, 1 B: Betel nut seeds are collected.

General uses of betel nut - The betel nut is the seed of *Areca catechu* L. It is widely used in India, Indonesia, Maldives, Malaysia, Sri Lanka, Thailand, and many Asian countries Strickland (2002). The betel nut is a popular chewing habit substance for nearly 600 million people in the whole world. It is believed that the

species of Areca nut plant is indigenous *to* Sri Lanka, West Malaysia and Melanesia IARC. (1985). In Hindi and Bengali its name famous as Supari. The nuts are used fresh, dried, baked or roasted, which is popular in betel nut-chewing countries. Consuming fermented betel nut is popular in some parts of Sri Lanka. In some parts, the most common way to consume betel nuts is as a vital ingredient in betel leaf (Pan), Gutka, and Pan masala Gupta & Warnakulasuriya (2002). School children even consume betel nuts in some countries like the Northern Mariana Islands (Micronesia) Oakley et al. (2005).

In India and its neighbouring countries, dry betel nuts are generally chewed alone or as a mixture of tobacco and slaked lime. The betel nut mixed with other products without tobacco is called 'pan masala'; the betel nut mixed with other products containing tobacco is called 'gutka' Nair et al. (2004). Unprocessed betel nut is processed by maltose and lime in southeastern China. Then, it is cut into small pieces and mixed with some drops of cassia oil consumed by chewing Tang et al. (1997).

Some studies reported that 30%- 40% of adults are using betel nuts as Gutka and Chaalia (just like Indian Pan masala) in urban places of Karachi in Pakistan Mazahir et al. (2006); Nisar et al. (2007); Tanwir et al. (2008). It is known that 40% of the adults in some particular areas of Bangladesh are consuming betel nuts with tobacco and slaked lime Eswar (2002).

The smoking and chewing study reports of Thailand were established by Mougne et al. 1982. They confirmed that the main components of betel quid are betel nut, slaked lime and betel vine.

In Cambodia, betel quid chewing is very popular Meng (1969). The betel quid comprises betel leaf, slaked lime and betel nut Ikeda et al. (1995). BN is chewed by the people of India and other local communities in Malaysia, Indonesia and Singapore Chin & Lee (1970), Cheong (1984), Kozlakidis et al. (2022).

Contents of betel nut: The most psychoactive agents in the world are caffeine, alcohol, and nicotine, and the fourth most commonly used psychoactive agent is betel nut. BN contains compounds like carbohydrates, crude fibre, fats, alkaloids, tannins, polyphenols (flavonoids and tannins), proteins, mineral matter and water, etc. Aziz, S. R. (2010), Anand et al. (2014), Banerjee et al. (1961); Mathew et al. (1964); Nagrajan & Seshadri (1961). Raghavan & Baruah (1958) found that alkaloids like arecoline, arecaidine, guvacoline and guvacin are present in betel nut. The carcinogenic property varies due to the amount of arecoline, which is the most important alkaloid present in large amounts in betel nut Awang (1986), IARC (2004), Lord et al. 2006). The contents of the betel nuts may vary in different geographical regions and climatic conditions Sharan (1996); Sharan et al. (2012); Sharan et al. (2020). The copper content of the areca nut is comparatively higher than that of other nuts consumed by humans. According to Trivedy et al. (1997), the nut's fibrogenic activity is due to the higher amount of copper in the betel nut. Chowdhury & Banerjee (2020) reported that betel nut extract contains high phenolic content. High phenolic components present in the nut may cause DNA breaks and chromosomal aberrations, as Stich (1991) demonstrated.

2. ANALYSIS OF BN BY GCMS STUDIES

Gas Chromatography-Mass Spectrometry (GCMS) analysis was performed to determine the phytochemicals present in betel nuts. Few carcinogens are present in it. It was noted that more than fifty different compounds were present in the ethanolic extract of BN, and more than thirty compounds are carcinogenic, toxic,

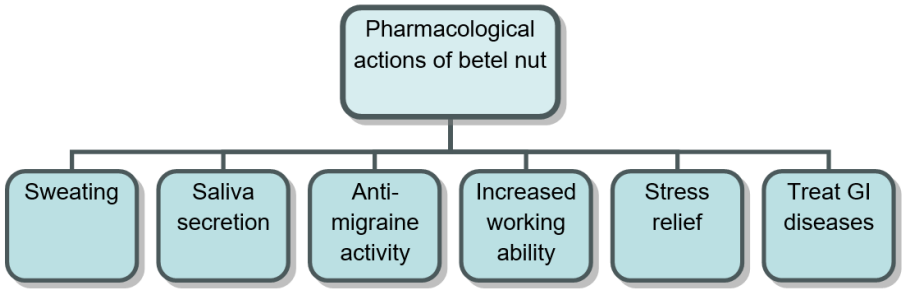
skin irritant, eye irritant, genotoxic and organ toxic to living systems. However, many compounds in the ethanolic extract have not yet been identified properly Chowdhury (2023)).

2.1. PHYSIOLOGICAL, PHARMACOLOGICAL AND ADDICTIVE PROPERTIES OF BETEL NUT

Betel nut has therapeutic effects such as increasing digestive function and treating diarrhoea, ulcers, constipation, and dyspepsia Salehi et al. (2020). Chewing betel nuts can cause warm feelings in the body, sweating, saliva secretion, increased working ability, anti-migraine, and other neurological effects, such as tolerance to hunger. These effects after consuming areca nuts are mainly caused by the effects on the central and autonomic nervous systems Chu (2002). Ethanolic and methanolic BN extracts also have antibacterial activity against some bacterial species, including E. coli, S. aureus, E. aerogenes Mubarokah et al. (2019), Liu & Chang (2023).

According to Garg et al. (2014), areca nut has adverse effects on the endocrine system. It can cause hyperthyroidism, hyperplasia of the prostate, and reproductive sterility. It also adversely affects the immune system, causing T–cell suppression and lower cytokine release.

Betel nuts affect the cardiovascular system, and they are a well-known herbal medicine because they lower the antihypertensive and diuretic effects. It can also increase heartbeat, body temperature, and cause heavy sweating. Some researchers suggest that betel nuts have a good hypotensive function (1986).



3. THE CARCINOGENIC PROPERTIES OF BETEL NUT ON THE HUMAN BODY

3.1. EFFECT OF BETEL NUT ON ORAL CAVITY

The colour of the teeth of those who have been chewing betel nuts for a long time has turned into a blood-like reddish colour. Oral leucoplakia and submucous fibrosis are the primary oral disorders caused by areca nut chewing that can initiate oral cancer and squamous cell carcinoma. Ex-chewers demonstrate lower risks than current chewers Mortazavi et al. (2014); Warnakulasuriya & Chen (2022). A British surgeon in India first noticed an association between betel quid (BQ) chewing and oral cancer Orr (1933). The areca nut is the primary ingredient in betel quid (BQ), consumed by people globally.

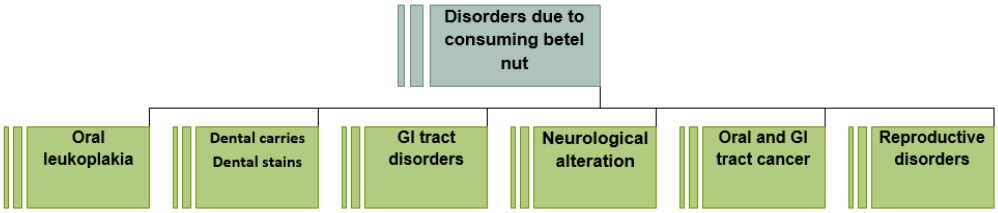
Experimental animals and human epidemiological studies reported the carcinogenic properties of betel nuts. According to the World Health Organization (WHO) and International Agency for Research on Cancer classification, betel nuts are a group 1 human carcinogen Jeng et al. (2001), Pankaj (2010).

3.2. DENTAL CARIES

Some researchers have reported that the areca nut may protect against dental carries. However, some researchers have suggested that there is no difference in the chances of dental carries between people who chew betel nuts and those who do not Schamschula et al. (1977), Nigam & Srivastava (1990). Betel nut stains in the teeth may provide a protective layer against dental carries Howden (1984).

3.3. THE CARCINOGENIC EXPRESSION OF BETEL NUT

Betel nut chewers are susceptible to affect oral and GI tract cancers. The result of betel nut chewing with tobacco is related to oesophagal cancer, and a clear dose response is found in Assam. The cancer risks are higher in males than females because males start their chewing habit at earlier ages and chew longer times throughout the day Jussawalla & Deshpande (1971). Pan Masala is the well-known betel nut containing chewing mixture which has also a carcinogenic activity Bhisey et al. (1999).



It was reported that betel nut chewers might not only cause a higher risk of cancer, but their prognosis is worse than that of non–chewers Yang et al. (2021). Some areca nut-derived nitrosamines may cause premalignant lesions in the oral cavity Shirzaiy & Neshat (2020). 3-methyl nitrosamine propionitrile (MNPN), a potent carcinogen Nair et al. (2004), has been identified in humans chewing betel nut. Almost half of oral cancers are caused by betel nut chewing. Cessation of betel nut chewing can reduce oral cancer cases. Travasso (2013). The betel nuts extract-induced rat caused ROS-induced oxidative stress in the male reproductive system Wu et al. (2010).

3.4. EFFECT OF BETEL NUT ON EXPERIMENTAL ANIMAL MODELS AND REPRODUCTIVE TOXICITY

Betel nut extracts can create toxicity in normal Swiss albino mice after injecting different doses of BNE on three alternative days. Different animal experiment results showed that betel nut extract in Swiss albino mice caused a deleterious effect on the reproductive system. Betel nut extract-treated experimental male mice showed a significant decline in sperm count and sperm motility, as well as abnormalities in sperm morphology Chowdhury & Banerjee (2020). It is known that BN extract may be unsafe to consume during the time of pregnancy, as shown in the rat experimental model Bernstein et al. (2021).

Figure 2

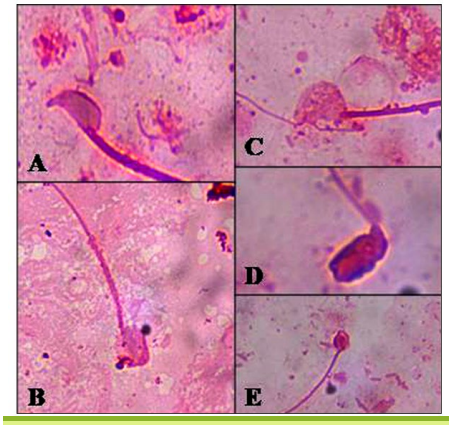


Figure 2 A- Normal Sperm Head without any Abnormalities. B, C, D- Amorphous Sperm Head of Mice in Betel Nut Extract Treated Series. E- Pin Headed of Sperm of the Mice in Treatment Series (H And E -Stained)

The cellular and biochemical seminal fluid analysis can diagnose male reproductive system disorders. Different components such as fructose, citric acid, glucose, potassium, zinc, flavins, etc. Owen & Katz (2005) are present in seminal fluid. These components are essential to provide nutrition, motility and viability of mature sperm or spermatozoa. Fructose is a vital component of seminal fluid, and it is produced by seminal vesicles for the nourishment and movement of spermatozoa Schoenfeld et al. (1979). So, fructose is an essential marker for knowing the secretive functions of the gland of the accessory reproductive system. Seminal fructose is also useful for diagnosing diseases related to the reproductive duct. According to Chowdhury et al. (2019), Chowdhury & Banerjee (2021)ethanolic betel nut extract can decrease seminal fructose concentration in normal and tumour-bearing mice.

A good number of sperm cells is necessary for successful fertilization. Different environmental carcinogenic factors, like consuming betel nuts, can cause sperm head abnormalities. Production of sperm head abnormalities and sperm DNA damage can be observed from isolated mouse spermatozoa by the toluidine blue staining method Talebi et al. (2012); Chowdhury & Banerjee (2020).

Figure 3

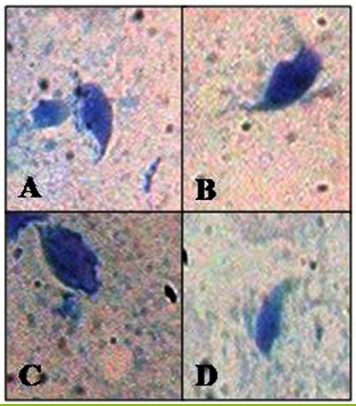


Figure 3 Toluidine Blue Stained Sperms. A & B: Normal Sperms with no DNA Damage. C & D: DNA Damaged Sperms

It was observed that the maximum percentage of sperm DNA damage was observed in 300mg/kg BNE treated tumour-bearing mice compared with control and other treated groups. Ethanolic betel nut extract also affects the histological structures of mice. The high concentration of ethanolic BNE affects the testicular cells of mouse. Chowdhury & Banerjee (2021).

Figure 4

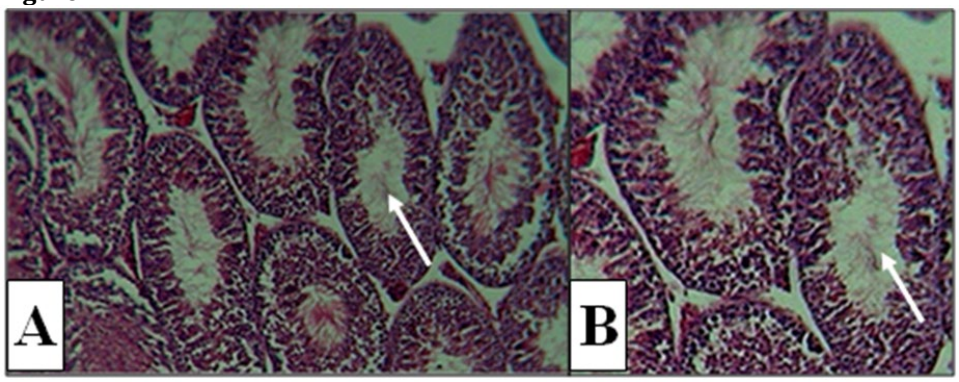


Figure 4 Histological Section of Testis Of 300mg/Kg BNE Treated Mice (Stained by Haematoxylin and Eosin). A. Section of Testis (10 X 10 Magnifications) Showing Abnormal Seminiferous Tubule (Arrowed) B. Section of Testis (10 X 40 Magnifications, Enlarged View) Showing Abnormal Seminiferous Tubules (Arrowed)

3.5. EFFECT OF BETEL NUT EXTRACT ON BLOOD CELLS

Ethanolic BNE may also induce different haematological abnormalities, such as a decrease in RBC count, an increase in the percentage of WBC, and an increase in the percentage of lymphocyte count in normal, ascitic, and solid tumour-bearing mice Chowdhury & Banerjee (2020).

Figure 5

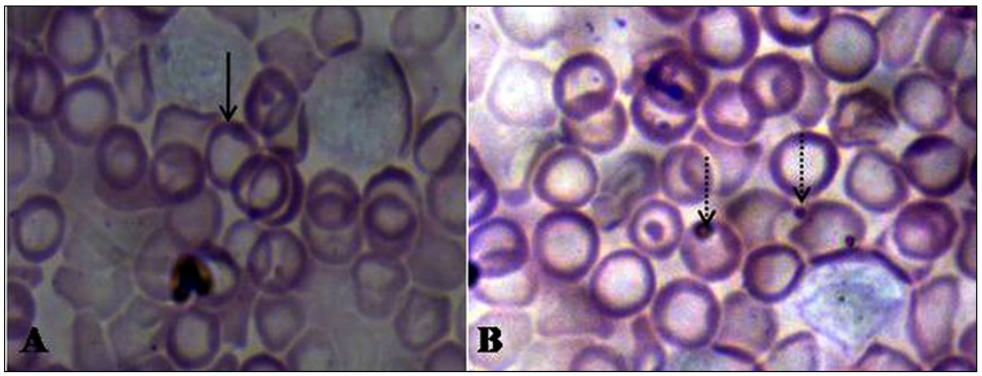


Figure 5 A: Blood Film Was Prepared (Without Treatment), A Straight Arrow Indicates Normal RBC. B- Blood Film Prepared From BNE-Treated Mouse; Dotted Arrows Indicate Micronucleated RBC

4. EFFECT OF BETEL NUT EXTRACT ON VIABLE AND NON-VIABLE CELL FREQUENCY

It was reported that ethanolic betel nut extract can increase ascitic tumour volume after treatments with different doses of ethanolic BNE on intraperitoneal ascitic tumour-bearing mice Chowdhury & Banerjee (2020).

Figure 6

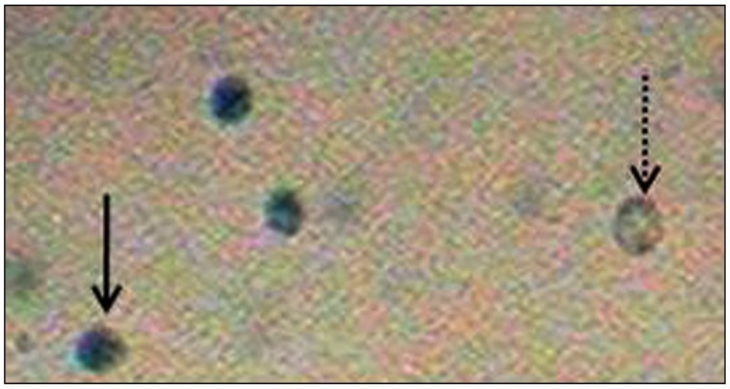


Figure 6 Viable and Non-Viable S-180 Ascitic Tumour Cells Were Evaluated by Trypan Blue Exclusion Method. The Dotted Arrow Indicates Viable or Living Cells and the Straight Arrow Indicates Non–Viable or Dead Cells

The trypan blue exclusion test is generally used to determine the viable and non-viable cells of the ascitic tumour. The percentage of ascitic viable cells was significantly higher in 300mg/KG BNE-treated groups than in control and other lower-concentrated groups Chowdhury & Banerjee (2020). Betel nut treatment can also reduce their life spans compared to normal healthy mice. After three alternative days of different BNE-treated mice, life spans can significantly reduce in both normal and tumour-bearing Swiss albino mice.

5. ANGIOGENIC POTENTIALITY OF BETEL NUT

Angiogenesis is the formation of new blood vessels. In malignant tumours, new blood vessels are formed to supply nutrients to the tumour cells and tissues. The betel nut can promote angiogenesis by activating some angiogenic factors like vascular endothelial growth factor (VEGF) and tumour necrosis factor-alpha. Betel contains a high amount of copper, which may stimulate different angiogenic factors Gao et al. (1997).

It was found that BNE induces angiogenesis in solid tumour mice and also significantly increases abnormal hepatocyte cells of Liver tissue. Solid tumour volume growth in different BNE-treated mice is higher than in control groups Chowdhury & Banerjee (2021).

Figure 7

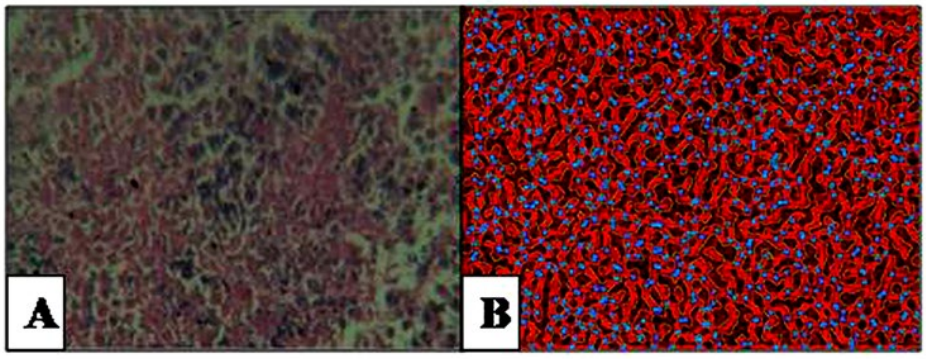


Figure 7 Histological Sections of Tumour Tissue of Solid Tumour-Bearing Mice. A: Histological Section of a Tumour Tissue (Haematoxylin & Eosin Stained). B: Output Image of Fig. 'A' Was Created by Angiotool 64_0.6A Software to Identify the Blood Vessels of a Tissue or Tumour Section

Gene mutations and chromosome breaks can rearrange the genome in cancer cells Kasparek & Humphrey (2011). Chromosomal aberrations, damage, and breaks may induce carcinogenesis and micronuclei formation Bonassi et al. (2004).

6. CYTOLOGICAL AND CYTOGENETICAL PROPERTIES OF BETEL NUT

The genotoxic potentiality of arecoline, the main alkaloid present in betel nut in a large amount, can be reported by chromosomal aberrations and sister chromatid exchanges to the ovary cells of Chinese hamsters. These experiments also showed that some water-extractable components are present in betel, but they are more genotoxic than arecoline. The damage to chromosomes is more significant and more severe after low concentrations of betel nut exposure for a long time. Dave et al. (1992).

It is known that betel nut consumption can cause cytological and cytogenetic alteration due to the presence of different types of alkaloids. Various experimental studies show that arecoline exhibits key carcinogen characteristics Gupta & Warnakulasuriya (2002), Tanwir et al. (2008), Gupta et al. (2020). Areca nut–induced oral carcinogenesis is attributed to arecoline and nitrosamine. Interestingly, arecoline can induce DNA damage in human epithelial cells Wary & Sharan (1988). Arecoline plays critical role in DNA strand breaks, micronucleus formation, chromosomal aberrations, and sister-chromatid exchanges in different cell lines Gupta et al. (2020). Arecoline plays a significant role in the tumorigenesis of betel nut–associated malignancies Tsai et al. (2008). Lin et al. (2011) proposed that the mutagenic effects of arecoline may be due to one of its primary metabolites: arecoline N-oxide.

Different types of simple and complex chromosomal aberrations are induced by treatments of different doses of BN extracts (i.e. 100mg/kg, 200mg/kg and 300mg/kg) on tumour-bearing mice. Different types of chromosomal aberrations are seen, such as chromosome breaks, fragmentation, multiple aberrations and deletions (simple chromosomal aberrations: SCA), other categories like centric fusion and translocations (i.e. complex chromosomal aberrations: CCA) Chowdhury, & Banerjee (2020).

Figure 8

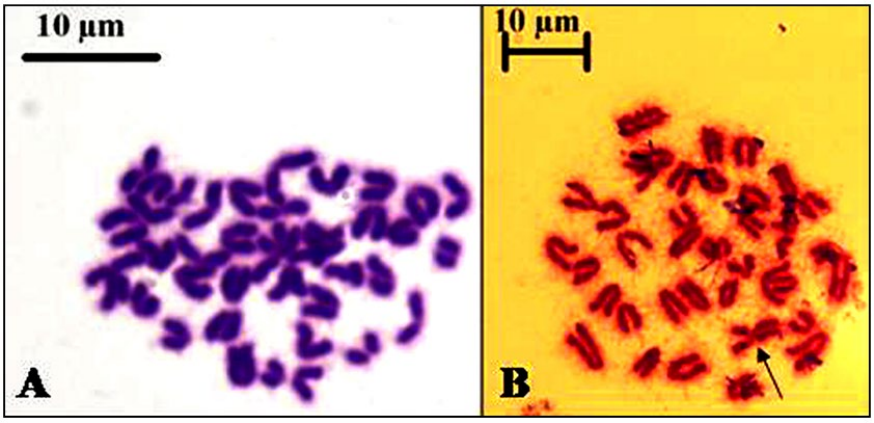


Figure 8 A: Chromosomes Prepared from the Bone Marrow of Mice. A: Normal Metaphase Chromosome is Showing no Aberrations. B: Chromosome Prepared from Betel Nut-Treated Mouse Bone Marrow Shows Chromosomal Aberrations; Arrow Indicates Metacentric Formation, a Type of Complex Chromosomal Aberration

7. DISCUSSION

Betel nut is the fruit of the plant *catechu*, which the people of India, Bangladesh, China, Cambodia, Malaysia and other Asian countries consume. It was reported that almost 600 million people are consuming betel nuts worldwide. It was also reported that 10-20% of the population worldwide consumes betel nuts alone and in different forms Warnakulasuriya & Chen (2022). Betel leaf can also be used as an ingredient in betel quid, pan masala, gutka, etc Gupta & Warnakulasuriya (2002). Its pharmacological actions include treatment as a drug against GI tract diseases, including constipation, diarrhoea, ulcers, and dyspepsia Salehi et al. (2020). Betel nut chewing can stimulate the nervous system, resulting in anti-migraine activity, warm feeling, saliva secretion, sweating, and increased working ability Chu (2001).

Some migrating to American and European countries consumes betel nuts IARC. (2012). Traditionally, betel nuts have been used since ancient times as an addictive agent, as they can alter the psychological situation to relieve physical and psychological stress IARC. (2004). Betel nuts also have pharmacological value, so they are a traditional herbal drug. Generally, ripe betel nuts are consumed after boiling and then cut into small pieces for chewing.

Lin et al. (2009) reported that betel nut chewing and obesity are strongly related. In China, it was reported that chewing betel nuts is related to kidney failure Chou et al. (2009). It can act as a stimulating agent as well as a carcinogenic agent. Chen (2009) The carcinogenic effect of betel nut may vary depending on the variety and growing region of the plant. Arecoline is the primary alkaloid that can cause addiction, and it is also liable to create cancer among people who chew betel nuts. Cancer cases in areas where a significant number of people chew betel nuts have been reported by many researchers.

GCMS analysis results proved that betel nuts contain many compounds, including toxic and carcinogenic compounds. Due to the high phenolic components, betel nuts' carcinogenicity may be higher Chowdhury & Banerjee (2020).

Previous research also reported that betel nuts can increase the rate of genotoxicity in the standard and S- 180 tumour-bearing experimental mice. Ethanolic BNE can also affect the male reproductive system as it results in a higher percentage of abnormal sperms, creates histological abnormalities on the testes, and increases the percentage of DNA-damaged sperms. Research on mice animals showed that ethanolic BNE could cause an increasing percentage of angiogenic activity Chowdhury et al. (2019), Chowdhury & Banerjee (2020),Chowdhury & Banerjee (2021),Chowdhury (2023).

8. CONCLUSION

The genotoxic activity of different plant extracts has been demonstrated in different animal bioassay systems. Betel nut chewing seems significantly associated with susceptibility to oral, oesophageal, stomach, liver and lung cancers. Addition of tobacco to betel nut mastication habit has also been found to increase the cancer risk. Despite the excessive usage of betel nut and its link with susceptibility to different types of cancer, no serious precaution seems to be taken to control this bad habit. The government should take serious, preventive measures to control the excessive usage of betel nuts. The carcinogenic potentiality of betel nut on normal and tumour-bearing mice in the present study will make humans aware of betel nut and betel-containing products like gutka, pan masala, etc. Moreover, this work will

be very helpful for future researchers who are focusing new light on plant product-related carcinogenesis.

CONFLICT OF INTERESTS

None.

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