INTRODUCTION

Oral cancer is one of the most common cancers in South and Southeast Asian countries, in contrast to accounting for only 1 to 4% of the total malignant tumors in Western societies (Field and Spandidos, 1987). The term areca nut is used to denote the unhusked whole fruit of the areca nut tree and term betel nut is used exclusively to refer to the inner kernel or seed which is obtained after removing husk. It is widely used in betel quid (BQ) which is a prevalent habit in southeast Asian countries1-3. Approximately 600 million betel quid chewers are believed to be living in different regions of the world4,5. It is closely associated with premalignant lesions and conditions 1-3. The incidence of oral cancer for individuals who smoke, drink alcohol and chew betel quid has been reported to be 123 fold higher than for abstainers3. Research related to BQ in pathogenesis of premalignancy and malignancy are recently being attracting considerable attention6-9. The carcinogenicity, mutagenecity and genotoxicity of BQ ingredients is reviewed by many researchers. The present review attempts to update the recent advances in this field.

BQ preparations

BQ preparations differ for different regions in the world. The preparation of BQ varies for different countries of world. In India, the betel quid generally contains admixture of arecanut, lime, tobacco with or without piper betel leaf (PBL)(1,4,5). In Taiwan and papua new guinea (2,3,10), instead of tobacco, piper betel inflorescence is used. Due to complex range of BQ preperations and ingredients, it is difficult to accurately assess the carcinogenic potential. It is generally having psychotropic effect owing to the presence of areca alkaloids. Four alkaloids have been conclusively identified in biochemical studies i.e. arecoline, arecadine, guacine and guacoline. Arecoline is considered to be predominant agent.

Nitrosation of arecoline leads to the formation of areca nut specific nitrosamine namely nitrosooguvacoline, nitrosogucvace and 3-methyl nitrosomino pripionitrile, which they alkylate DNA. Metabolism of these areca nut specific nitrosamine will lead to formation of cyanooethyl, which adducts with o’methyl guanine in DNA. Prolonged exposure to this irritant leads to malignant transformation. (flowchart 1,2).

Carcinogenicity, mutagenecity and genotoxicity of AN

A number of studies have been designed study the carcinogenicity of BQ ingredients in experimental animals (11-12). A direct painting of dimethy-sulfoxide ( DMSO) extract of AN in hamster cheek pouch induces early malignant changes (13). A further elevation of tumor incidence in the hamster cheek pouch is found when the concomitant application of benzopyrene and AN extract is conducted (14). In vitro studies have shown that
AN extract promotes the bovine papilloma virus DNA induced malignant transformation of cultured cells. Keratinocyte inflammation

Carcinogenicity, mutagenicity and genotoxicity of areca alkaloids

Inflammatory mediators released by the affected keratinocytes has been shown to be a critical step in tumor promotion. (15-16) AN extracts upregulates cyclo oxygenase-2 (cox-2) mRNA and protein production, indicating the roles of Cox-2 in BQ- chewing related oral mucosal diseases. This may explain why Cox-2 mRNA expression and protein production for head and neck tumor tissues are higher than healthy tissues. 

The tannin and polyphenol derivatives of areca are believed to be the potential active carcinogens involved in the BQ-induced tumors. The nitrosamines are namely 3-(methyl-nitrosoamino)propionitrile (MNPN), 3-(methyl-nitrosamino)-propionaldehyde (MPNA), N-nitrosoguvacoline (NG) and N-nitrosoguvacine (NGC). DNA methylation is caused by MNPN.

ROS and areca alkaloids

Reactive oxygen species (ROS) are free radicals that contain the oxygen atom. ROS form as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling. However, during times of environmental stress (e.g. UV or heat exposure) or due to carcinogen exposure, ROS levels can increase dramatically, which can result in significant damage to cell structures. This cumulates into a situation known as oxidative stress. ROS are said to be generated due to the polyphenols and tannins in areca alkaloids. Harmful effects of reactive oxygen species on the cell are most often:
1. damage of DNA
2. oxidations of polydesaturated fatty acids in lipids (lipid peroxidation)
3. oxidations of amino acids in proteins
4. oxidatively inactivate specific enzymes by oxidation of co-factors

The polyphenols have been suggested to show metabolic activation of the activation to form reactive intermediates that bind to DNA, that supposedly lead to cancer formation.

Moreover it is also suggested that An suppress the mutagenicity of 2-amino-3-methylimidazole (4,5).

AN extract also induces cytogenetic effects as shown by the chromosomal aberrations in cultured Chinese hamster ovary cells. Oral keratinocyte and fibroblasts are the major target cells of BQ attack by its ingredients. It induces cytotoxicity, DNA strand breakage, DNA protein cross-linkage and unscheduled DNA synthesis (UDS) of...
oral keratinocytes and fibroblasts. AN extract also inhibits the DNA repair process and it also induces the terminal differentiation of buccal keratinocytes. This further leads to GSH depletion and no concomitant increase in glutathione levels, (GSSG). The alteration of these metabolic levels modulate the host susceptibility to other carcinogens as well.

ROS produced during betel chewing have been demonstrated to elicit multiple detrimental upon oral mucosa. Firstly, ROS can be directly involved in the tumor initiation process by inducing genotoxicity and gene mutation. Secondly ROS are able to attack salivary proteins and the oral mucosa, leading to a structural change in the oral mucosa such a change facilitating the penetration by other BQ ingredients and environmental toxicants. Thirdly, inflammatory cell infiltration has been regularly observed. Activated inflammatory cells have been shown to release ROS, such a release leading to the mutation of the adjacent cells and tumor promotion.

An extract has been shown to induce PGE₂ production, a compound that can mediate oral mucosal inflammatory responses. Chewers usually powdered lime to the chewed An with piper betel inflorescence in the corner of the mouth leading to an elevation of the salivary pH value to around 9.9. Due to the presence of lime, Ca(OH)₂, as a major component in BQ preparation, BQ-chewers’ saliva typically changes from an approximately neutral to an alkaline conditions and induce the mitotic conversion of cells. The ROS are also capable of inducing nucleotide modification and the formation of 8-hydroxydeoxyguanosine. This compound formation has been stated as the biomarker of chemical carcinogenesis.

CONCLUSION

The most important and decisive event of chemical carcinogenesis is the interaction between resumed carcinogens and cellular macromolecules such as DNA, proteins and lipids. The oral mucosal epithelial cells are subjected to continuous attack of genotoxic agents present in BQ, tobacco, alcohol or nitrates and ROS. Antioxidants such as GSH and superoxide dismutase form conjugates with ROS and degrades reactive toxic species and interacting with the critical cellular macromolecules. Thus repeated and continuous exposure of oral mucosal cells to BQ ingredients lead to impairment of cellular defense system. The DNA damage cells are subsequently induced by proliferative agents to replicate, DNA damage will remain permanently in the cells, leading to the formation of mutated “initiated” cells.

Further promotion and progression of such mutated cells lead to the occurrence of oral precancer and cancerous lesions.

REFERENCES


