

BIOCHEMICAL ASPECTS OF BETEL NUT CARCINOGENESIS

Kishore Kumar Wary

Radiation & Molecular Biology Unit

Department of Biochemistry

School of Life Sciences

North-Eastern Hill University

Shillong - 793014 (INDIA)



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Phone :
Grams : NEHU

North - Eastern Hill University

Mayurbhanj Complex
Nongthymmai, Shillong - 793014 (Meghalaya)

Dr. R. N. Sharan
Department of Biochemistry

CERTIFIED that the thesis titled "BIOCHEMICAL ASPECTS OF BETEL NUT CARCINOGENESIS" submitted by Mr. Kishore Kumar Wary for the award of the degree of DOCTOR OF PHILOSOPHY in Biochemistry of the North-Eastern Hill University, Shillong embodies the record of original investigations carried out by him under my supervision. He has been duly registered and the thesis presented is worthy of being considered for the award of the Ph. D. degree. This work has not been submitted for any degree of any University.

Shillong
June 22, 1989

R.N. SHARAN, PH. D.
Radiat. & Mol. Biol. Unit
Department of Biochemistry
School of Life Sciences

*Forwarded
Examiners*
Department of Biochemistry
North-Eastern Hill University
Shillong

DEDICATED

TO

'Aai' and 'Aafa'.

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(Kishore Kumar Wary)

INTRODUCTION

With the advancement of knowledge and better understanding of physiology it seems certain that many diseases hitherto regarded spontaneous may be caused by environmental factors, nutritional habits and social customs. The impact of these burdens on human health has become an universal concern. With the advent of modern civilization, human beings are subjected to more toxic chemical in the environment and in food materials. Looking back, it is evident that ancient man lived on pure, wholesome and natural food procured from their surroundings. This, however, is now limited to very small groups of people viz., Hunza valley in Kashmir today. Modern man has come to deviate from these norms and burdens his body with a host of unhealthy foods. Due to variety of reasons, man has picked up unhealthy habits like areca nut chewing, tobacco chewing, alcohol drinking and smoking, which exert new and sometimes undesired biochemical reactions in the living system at cellular, subcellular and at the molecular levels. These interactions may bring about diseases which have no definite cure as yet. A dreadful disease, cancer, is one of them. These changes may not be visible at early stage of life. After substantial period of

incubation but at some points of our lives, some or many of us become engrossed by the terrible disease known as cancer.

In the last two decades there has been a sharp increase in the awareness that some naturally occurring compounds in food may cause or at least contribute to human diseases, notably, cancer. However, the chewing of areca nut (Areca catechu L.) stains the teeth and saliva red, which is a disgusting accompaniment, continues unabated in this region of North East India and elsewhere. "Kwai" (local name for raw areca nut) is consumed in large quantities in this region whereas "Pan", another form of consumption of betel nut, remains popular in many other parts of India. In Meghalaya, areca nut is grown profusely and the "Khasi" tribe employ this nut as masticatory. Some Khasis believe that chewing of betel nut is more of a form of courtesy rather than a habit and some people are of the opinion that chewing of betel nut is indeed a noble act. However, this chewing habit is considered as a part of social custom of Khasis and also other tribes. The raw areca nut is consumed along with betel leaf (Piper betle L.) and variable quantity of slaked lime. It shows an immediate thermogenic physiological response, lasting 2-3 minutes, with significant perspiration on forehead. This effect markedly differs from the effect of betel nut consumed

elsewhere in the world. Some preliminary work was carried out by Stich et al (1983a) in Meghalaya and was found to have tannic acid in the saliva of a population of betel nut chewers.

Areca nut contains a number of chemical components (Raghavan and Baruah, 1958) and much work has been done to catalogue the chemical, pharmacological and toxicological properties of areca nut and its chemical constituents (IARC, 1985). Similarly animal experimentation and in vitro tests have so far given a limited knowledge about biochemical events preceding/leading to carcinogenesis associated with areca nut chewing. Nonetheless, the knowledge gained so far clearly points to the fact that chewing of betel nut is supposedly a major factor in the etiology of oral and associated cancers. The betel nut chewing has been shown to induce oropharyngeal cancer in India which accounts for over 50% of total cancer incidence in India (Sanghvi, 1981).

Areca nut and its chemical constituents have been tested for mutagenicity, carcinogenicity and teratogenicity (Shirname et al, 1983; Sinha, 1984). Various extracts of betel nut have been tested for their ability to bring about changes in the genome. The saliva from areca nut chewers have been found to

be mutagenic (Stich et al, 1985). Elevated frequency of micronucleated cells in the buccal mucosa of individuals as a result of chewing betel nut and tobacco use have been reported (Stich et al, 1983b). So far these data have given a limited understanding of the mechanism of carcinogenesis associated with betel nut chewing (IARC, 1985). Our knowledge in connection with raw (unprocessed) betel nut, "Kwai", is further limited.

Formation of N-Nitrosocompounds from arecoline (a major alkaloid from areca nut) upon mild nitrosation condition have been reported (Wenke and Hoffmann, 1983). N-Nitroso-guvacoline has been found to occur in the saliva of betel nut chewers; tobacco specific nitrosamines have also been detected in the saliva sample of betel quid chewers (Wenke et al, 1984). From existing data it is apparent that betel nut can undergo N-Nitrosamine formation. The nitrosation condition may be offered by various food and drinks which contain significant amounts of nitrates which occurs freely in fruits and vegetables. Formation of nitrosamines and occurrence of nitrosamines in food and food-additives are mainly due to the metabolism of nitrites in in vivo which in turn are responsible for development of cancer (Scanlan, 1983). Therefore, in areca nut chewers the formation of nitrosamine(s) is not unexpected.

The human body is complex organization of biological macromolecules. These are adapted to this complex system since time immemorial. Various proteins, enzymes and metabolite are involved in the metabolic process. The metabolic processes include detoxification of harmful substances which may either be produced within the body or ingested from outside as foreign substance. One of such enzyme involved in detoxification is Cytochrome P-450, which are actively involved in activation and deactivation of xenobiotics (Guengerich, 1988). There has been no report on the possible detoxification or deactivation of areca nut alkaloids (IARC, 1985). This study, however, seem relevant due to the fact that all betel nut chewers or all betel quid chewers do not automatically suffer from cancer.