

Oral Cancer Induced by Betel Quid with Cytochrome P450 Gene Family: A Mini Review



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Abstract

Betel quid (BQ) products have been classified by the International Agency for Research on Cancer (IARC) as group 1 human carcinogens that are associated with an elevated risk of oral cancers. The human genome encodes fifty-seven cytochrome P450 (P450, or CYP) proteins. Reactive oxygen species (ROS) are generated during betel quid chewing in the oral cavity. The present mini review focuses on the mechanism of CYP450 with betel quid which induces oral cancer.

Keywords: Oral cancer; Cytochrome P450; Betel quid

Introduction

Head and neck squamous cell carcinomas (HNSCC) is the sixth leading cancer by incidence worldwide. The annual incidence of head and neck cancers worldwide is more than 5,50,000 cases with around 3,00,000 deaths each year [1]. Male to female ratio ranges from 2:1 to 4:1. About 90% of all head and neck cancers are squamous cell carcinomas (SCC). HNSCCs arise in larynx and hypo pharynx, the epithelial lining of the oral cavity and oropharynx [2,3]. In South Central Asia 80% of head and neck cancer are found in oral cavity and oropharynx [4].

There are estimated 600 million betel quid (BQ) users globally. BQ chewing is constitutes an important and popular cultural activity in many Asian and Oceanic countries, including Pakistan, The Maldives, India, Nepal, SriLanka, Bhutan, Bangladesh, Burma (Myanmar), China, Laos, Thailand, Malaysia, Indonesia, Cambodia, Vietnam, Taiwan, The Philippines, Palau, Yap, Guam, Papua New Guinea, The Solomon Islands, and Vanuatu [5]. In India, BQ chewing is popular traditional activity that is integrated into social and cultural practices and also ceremonies. It is the fourth most commonly used psychoactive substance in the world after caffeine, alcohol and nicotine. India has largest betel quid consuming population in the world. The habit of chewing betel quid is due to low cost, easily available and also as a mood elevator in the day to day busy scheduled life [6]. Archaeological evidence from Thailand, Indonesia and the

Philippines suggests they have been used in tandem for at least 4000 years [5].

Betel quid chewing and its association was recently classified as a Group 1 human carcinogen by the International Agency for Research on Cancer (IARC). The main ingredients used in betel quid are canut, catechu, betel leaf and slaked lime. The major areca nut alkaloids are arecoline, arecaidine, arecolidine, guvacine. Arecoline are the most abundant alkaloid. Calcium hydroxide content of slaked lime in the presence of areca nut is a major factor responsible for the formation of (Reactive oxygen species) ROS which cause oxidative damage in the DNA of buccal mucosa cells of BQ chewers. Secondary and tertiary amines which are present in the areca nut undergo nitrosation and give rise to N- nitrosamines. Betel quid specific nitrosamines (BQSN) which are produced by the nitrosation of arecoline, interact with DNA showed its carcinogenic activity. Early sign of damage to the oral mucosa with chewers of betel quid often develop clinically visible whitish (leukoplakia), reddish (erythroplakia), whitish-reddish (erythroleukoplakia) lesions and stiffening of the oral mucosa and oral submucous fibrosis (OSF).

Out of 14 gene families of the Cytochrome p450 (CYPS), the CYP1, CYP2 and CYP3 subfamily are primarily active in the metabolism of a broad range of chemicals. These CYPs families are implicated in the metabolic activation of BQ and areca nut-

specific nitrosamines [7]. The cytochrome P450 (CYP) enzyme system consists of a super family of hemo proteins that catalyses the oxidative metabolism of a wide variety of exogenous chemicals including drugs, carcinogens, toxins and endogenous compounds such as steroids, fatty acids and prostaglandins [8]. The CYP enzyme family plays an important role in phase-I metabolism of many drugs. CYP2A6 was found to be the most efficient activator of 3-methyl nitrosamino propionitrile (MNPN) which were detected in the saliva of chewers of BQ followed by CYP1A1, and N-nitrosoguvacoline (NGL), was activated by CYP2A6. Human CYP2A subfamily members play important roles in the metabolic activation of arecoline-related N-nitrosamines [9 -11].

CYPs are located on human chromosome 19. The CYP2A6 gene consist of 350 kilo bases located at 19q 12-19q 13.2 [12-14]. CYP2A6 gene may also effect susceptibility to pre carcinogen in the environment. People are classified as EM known as early metabolizers and PM known as poor metabolizers based on genetic variation [15]. Poor metabolizers are less prone to oral cancer than early metabolizers due to CYP2A6 gene polymorphism. The areca nut-specific nitrosamines (ASNA) and betel quid specific nitrosamines (BQSN) are forms due to the interaction of betel quid and CYPs family.

Conclusion

Betel quid chewing is an ancient custom in several parts of south-east Asia and India. ASNA and BQSN are forms due to the interaction of betel quid and CYPs. In our study we have screened 311 subjects from different areas of Eastern and North Eastern India and also from RKMS hospital, Kolkata, India. More than 60% (61.09%) had betel quid chewing habit. It has been found more than 50% of eastern region (except North 24 Pgs) were early metabolizers according to xenobiotics metabolizing property of CYPs family. Poor metabolizers are less prone to oral cancer than early metabolizer due to CYP2A6 gene polymorphism.

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