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Review Article

Association of Cytochrome P450 with Cancer Induced by Betel Quid (BQ): A Review

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ABSTRACT

Betel quid (BQ) products have been classified by the International Agency for Research on Cancer (IARC) as group I human carcinogens that are associated with an elevated risk of oral potentially malignant disorders (OPMDs) and cancers of the oral cavity and pharynx and others. The human genome encodes fifty-seven cytochrome P45O (P45O, or CYP) proteins. The majority of these are involved in the metabolism of steroids, bile acids, fatty acids and xenobiotic compound which activate carcinogens. The present review focuses on the mechanism of CYP450 with betel quid which induces cancer.

Keywords: Betel quid, Cancer, Cytochrome P450.

INTRODUCTION

Cytochrome P450 in general

The term cytochrome P450 was coined in 1962 as a temporary name for a coloured substance in the cell[1]. At first, CYP450 was believed to represent a single enzyme. Today it seems likely that humans and other mammals have approximately 50 distinct CYP450 enzymes. The total number may be higher in plants. In the last 15 years of the 20th century, research was largely concerned with defining CYP450 multiplicity in humans and a diverse range of other organisms. This pigment, when reduced and bound with carbon monoxide, produced an unusual absorption peak at a wavelength of 450 nm. Cytochrome P450 (CYP450) is the generic name given to a large family of versatile enzymes that metabolise most drugs and chemicals of toxicological importance (termed xenobiotic metabolism). Along with xenobiotic metabolism, many CYP450 enzymes play pivotal roles in diverse physiological processes including steroid and cholesterol biosynthesis, fatty acid metabolism (prostacyclin, thromboxane) and the maintenance of calcium homoeostasis.

Cytochrome P450 enzyme (P450, or CYP) reactions were first recognized in the oxidation of drugs, carcinogens, and steroids, and generally show the mixed-function oxidase stoichiometry:
$NADPH+H^+ + R+O_2 \rightarrow NADP^+ + H_2O+RO$.
(R = substrate, RO = product).

In mammals, all P450s are membrane bound, most are found in the endoplasmic reticulum, but five are localized primarily in mitochondria[2]. The human genome encodes fifty-seven P450 proteins[3]. A recent survey classified fifteen P450s involved in the metabolism of xenobiotic chemicals (i.e., chemicals, such as drugs, not normally found in the body): fourteen primarily involved in the metabolism of sterols (including bile acids); four that oxidize fat-soluble vitamins; and nine involved in the metabolism of fatty acids and eicosanoids[4]. Substrates (either xenobiotic and endobiotic) are essentially unknown for the remaining fifteen of the fifty-seven. P450s are found throughout the phylogenetic spectrum: three have been identified in *Saccharomyces cerevisiae*, eighteen in *Streptomyces coelicolor*, eighty in *Caenorhabiditis elegans*, 257 in *Arabidopsis thaliana*, and perhaps surprisingly, none in *Escherichia coli* or *Salmonella typhimurium*.

CYP enzymes have been found in all domains of life such as animals, plants, fungi, bacteria, and even in viruses[5]. But the enzymes have not been found in *E. coli*[6,7]. More than 18,000 distinct CYP proteins are known[8]. Most CYPs require a protein partner to deliver one or more electrons to reduce the iron (and eventually molecular oxygen). Based on the nature of the electron transfer proteins CYPs can be classified into several groups[9]:-

- **Microsomal P450 systems** in which electrons are transferred from NADPH via cytochrome P450 reductase (variously CPR, POR, or CYPOR). Cytochrome b5 (CYB5) can also contribute reducing power to this system after being reduced by the cytochrome b5 reductase (CYB5R).
- **Mitochondrial P450 systems**, those employ adrenodoxin reductase and adrenodoxin to transfer electrons from NADPH to P450.
- **Bacterial P450 systems**, that employ a ferredoxin reductase and a ferredoxin to transfer electrons to P450.
- **CYB5R/cyb5/P450 systems** in which both electrons required by the CYP come from cytochrome b5.
- **FMN/Fd/P450 systems** are originally found in the *Rhodococcus* sp.
- A subset of cytochrome P450 enzymes play important roles in the synthesis of steroid hormones (steroidogenesis) by the adrenals, gonads, and peripheral tissue:
- CYP11A1 (also known as P450scc or P450c11a1) in adrenal mitochondria effects "the activity formerly known as 20, 22-desmolase" (steroid 20α-hydroxylase, steroid 22-hydroxylase, cholesterol side-chain scission).
- CYP11B1 (encoding the protein P450c11β) is found in the inner mitochondrial membrane of adrenal cortex has steroid 11β-hydroxylase, steroid 18-hydroxylase, and steroid 18-methyloxidase activities.
- CYP11B2 (encoding the protein P450c11AS) is found only in the mitochondria of the adrenal. It has steroid 11β-hydroxylase, steroid 18-hydroxylase, and steroid 18-methyloxidase activities.
- CYP17A1, in endoplasmic reticulum of adrenal cortex has steroid 17α-hydroxylase and 17, 20-lyase activities.
- CYP21A1 (P450c21) in adrenal cortex conducts 21-hydroxylase activity.
- CYP19A (P450arom, aromatase) in endo-plasmic reticulum of gonads, brain,

adipose tissue, and elsewhere catalyzes aromatization of androgens to estrogens.

CYP families in humans

Humans have 57 genes and more than 59 pseudogenes divided among 18 families of cytochrome P450 genes and 43 subfamilies[10]. This is a summary of the Cytochrome P450 family with their functions:- (See table 1.)

P450s in other species

Animals

Many animals have as many or more CYP genes than humans do. For example, mice have genes for 101 CYPs, and sea urchins have even more (perhaps as many as 120 genes)[11].

CYPs have been extensively examined in the mice, rats, dogs, and less so in zebrafish, in order to facilitate use of these model organisms in drug discovery and toxicology. Recently CYPs have also been discovered in avian species, in particular turkeys, that may turn out to be a great model for cancer research in humans [12]. CYP1A5 and CYP3A37 in turkeys were found to be very similar to the human CYP1A2 and CYP3A4 respectively, in terms of their kinetic properties as well as in the metabolism of aflatoxin B1[13].

CYPs have also been heavily studied in insects, often to understand pesticide resistance. For example, CYP6G1 is linked to insecticide resistance in DDT-resistant Drosophila melanogaster[14] and CYP6Z1 in the mosquito malaria vector Anopheles gambiae is capable of directly metabolizing DDT[15].

Microbial

Microbial cytochromes P450 are often soluble enzymes and are involved in critical metabolic processes. Three examples that have contributed significantly to structural and mechanistic studies are listed here, but many different families exist.

- Cytochrome P450cam (CYP101) originally from Pseudomonas *putida* has been used as a model for many cytochromes P450 and was the first cytochrome P450 three-dimensional protein structure solved by X-ray crystallography. This enzyme is part of a camphor-hydroxylating catalytic cycle consisting of two electron transfer steps from putidaredoxin, a 2Fe-2S cluster-containing protein cofactor.
- Cytochrome P450 eryF (CYP107A1) originally from the actinomycete bacterium Saccharopolyspora *erythraea* is responsible for the biosynthesis of the antibiotic erythromycin by C6-hydroxylation of the macrolide 6-deoxyerythronolide B.

Fungi

The commonly used azole class antifungal drugs work by inhibition of the fungal cytochrome P450 14α-demethylase. This interrupts the conversion of lano sterol to ergo sterol, a component of the fungal cell membrane. (This is useful only because humans' P450 have a different sensitivity; this is how this class of antifungals work)[16].

Plants

Plant cytochromes P450 are involved in a wide range of biosynthetic reactions, leading to various fatty acid conjugates, plant hormones, defensive compounds, or medically important drugs.

CYP'S related with cancer

Experimental models have clearly demonstrated that the modulation of P450 expression can modify the susceptibility of animals to cancers produced by various chemicals[17,18]. The relevance of P450 modulation to cancer risk has not been easy to establish in humans, however. Nonetheless, *in vitro* studies have largely established that

human P450s can activate most major chemical carcinogens[19-21]. The main P450s involved in carcinogen activation appear to be CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2E1, and CYP3A4, with some contributions from CYP4B1[22] and CYP2A13 also possible[23,24]. Another set of studies on lung cancer investigated CYP2D6 and a possible reduced risk in smokers with the poor metabolizer phenotype[25]. CYP2E1, known to activate many carcinogens[26] with cancers[27,28] suspected association between CYP3A4 and prostate cancer[29] has not been reproducible[30-32]. Some of the best current candidates are CYP1A2 and CYP2A6. CYP1A2 activates many heterocyclic amines present in pyrrolyzed food, especially charred meat. Epidemiological studies have shown increased risk of colon cancer in individuals with high CYP1A2 activity. CYP2A6 activates some nitrosamines and is expressed in the head and neck; a cancer risk may thus be associated with higher expression of CYP2A6[24]. A study by Kamataki and colleagues associated a poor metabolizer genotype with decreased risk of lung cancer in Japan[33]. One factor in the analysis, however, may be a tendency for smokers deficient in CYP2A6 to smoke less because of its involvement in nicotine metabolism[34]. Two other candidates possibly connected with cancer include CYP1B1 and CYP2A13. CYP1B1 is expressed in several organs and tissues (e.g., breast, prostate, and ovary) and activates numerous carcinogens *in vitro*[35]. The estrogen 4-hydroxylation activity of CYP1B1 is of particular interest with regard to estrogen-responsive tumors[36,37]. CYP2A13, which is similar to CYP2A6, activates nitrosamines and is localized in tissues of the respiratory tract[23,24].

CYP1A1

The human enzyme CYP1A1 is the most active among the CYPs in metabolizing procarcinogens, particularly, the polycyclic aromatic hydrocarbons (PAHs), into highly reactive intermediates[38]. When these compounds bind to DNA and form adducts, they may contribute to carcinogenesis. The aromatic hydrocarbon receptor is a key activator of the CYP1A1 gene[39,40]. PAHs were classified among important toxicants as they induce CYP1A1 gene and act as pre carcinogenic substrates[41,42]. Asignificant association between metabolizing phase I genes (CYP1A1) and UADT cancers was found[43]. Nagaraj *et al*.[44] identified molecular factors which contribute to the increased risk of smokers for oral squamous cell carcinoma (OSCC). In fact, they evaluate gene expression profile change according to cigarette smoke condensate in normal epidermal keratinocytes, oral dysplasia cell lines Leuk1 and Leuk2, and a primary oral carcinoma cell line 101A. Their results have shown that treatment by cigarette smoke condensate acts on several cell types and usually leads to over expression of CYP1A1. Several studies have been since performed examining the potential association between the polymorphic CYP1A1. The CYP1A1 (426Val/Val) genotype was found three times more frequent than in controls in 3% of oral cancer patients. In spite of the absence of any statistical significance, these results strongly supported the previous ones showing that the mutant allele CYP1A1 426Val is related to an increased risk of oral cancer in Caucasians, in the United States[45], among Asian populations[46], and in Indians[47]. Cigarette smoke has been shown to upregulate CYP1A1 under *in vitro* conditions as well as in smokers[48,49]. In five earlier different studies investigating CYP1A1 genotype smoking interactions[50-54] CYP1B1. Human CYP1B1 is located on chromosome 2 at the 2p21-22 region[55,56]. CYP1B1 gene is activated by PAHs that constitute the major constituents of cigarette smoke and tobacco, hence making it responsive to smoked and smokeless (chewing) tobacco[55,57,58]. As CYP1B1 is

crucially involved in the bioactivation of chemically diverse tobacco-related procarcinogens to reactive metabolites, its expression is considered as a significant parameter of carcinogenesis[59]. CYP1B1 is over expressed in several human tumors in comparison with normal tissues[58,60,61].

CYP1B1 in modulating the incidence of several types of cancers[62,63]. CYP1B1 with the increased risk of ovarian, endometrial, renal, and prostate cancers as well as smoking related lung cancer has been reported in the Caucasian and the Japanese populations[64]. CYP1B1 is upregulated in numerous cancers such as esophagus, lung, skin, breast, brain, testis, and colon cancers[65].

CYP2D6

The CYP2D6 gene is localized on chromosome 22q13.166.Cytochrome P450s consist of the major enzymes required for phase I metabolism of xenobiotics. Cytochrome P450 2D6 (CYP2D6) is one of the enzymes that catabolize about 20% of commonly prescribed drugs. Cytochrome P450 2D6 has also a variety of activities among human populations. In fact, the interindividual metabolism rates differ more than 10000 folds[66-69]. CYP2D6 gene is activated by some xenobiotic carcinogens such as nicotine which is the major constituent of tobacco[70].

CYP2E1

The CYP2E1 human gene is located on chromosome10 (10q24.3-qter), contains 9 exons, and encompasses several polymorphisms. Some of them have an effect on the protein expression[71]. The CYP2E1 enzyme is responsible for the metabolism of alcohol and some tobacco carcinogens such as low-molecular weight nitrosamines[72-74]. CYP2E1 enzyme activity is needed during the metabolic activation of many carcinogens such as nitrosamines. CYP2E1 is expressed in oral epithelial cell lines cultures, in human oral mucosa, and in tongues of rats[75,76]. Association of the CYP2E1 polymorphism with the risk of lung cancer[77], gastric cancer[78,79] and pancreatic cancer[80] . CYP2E1 metabolizes ethanol and generates reactive oxygen species, and it has been suggested that it is important for the development of alcoholic liver disease and cancer, including hepatoblastoma and HNC.

Cancer production due to betel quid

Betel quid chewing habit (betel leaf, areca nut and lime) in India are at least 2,000 years old. Tobacco was introduced around the sixteenth century. It is estimated that at least 200 million individuals consume areca nuts in one form or another worldwide. The habit is now widespread in Southeast Asia and the South Pacific islands and in people of Indian origin elsewhere in the world. The betel quid chewing habit is in fact found all over the world wherever Indians have settled. The BQ is a mixture of areca nut (Areca catechu), catechu (Acacia catechu) and slaked lime (calcium oxide and calcium hydroxide) wrapped in a betel leaf (Piper betle). Betel nut is composed of 11.4% – 26.0% tannins, 0.15 - 0.67% alkaloid, 1.3 -17% fat, 0.13 -2.35% phosphorus, 1.5 -11.6% iron[81]. The major areca nut alkaloids are arecoline, arecaidine, arecolidine, guvacoline and guacine[82]. Arecoline (1, 2, 4, 5-tetrahydro-1-methylpyridinecarboxylic acid; molecular weight 155.19) is the most abundant alkaloid of areca. These alkaloids undergo nitrosation and give rise to N-nitrosamines[83]. Chewers of BQ with or without tobacco often develop clinically visible whitish (leukoplakia) or reddish (erythroplakia) lesions and/or stiffening of the oral mucosa and oral submucous fibrosis (OSF). Leukoplakia is one of the commonest lesions in betel quid chewers. The WHO has classified these into two groups, homogeneous and non-homogeneous. Among no homogeneous leukoplakias, nodular leukoplakia tends to

show the highest rate of malignant transformation. The relative risk compared with individuals with tobacco habits but without any precancerous oral lesion was also found to be the highest for nodular leukoplakia[84]. Oral sub mucous fibrosis (OSMF) is a chronic condition characterized by mucosal rigidity of varying intensity due to fibro elastic transformation of the juxta epitheliallayer[85]. Areca nut chewing could be one of the most important etiologic factors in OSMF[86]. The areca nut, the major constituent of pan masala is responsible for mutagenic, clastogenic and carcinogenic properties[87]. Chewing of tobacco with BQ results in high exposure to carcinogenic tobacco-specific nitrosamines (TSNAs), to ~1000 mg/day[88], compared with ~20 mg/day in smokers[89], as well as leading to exposure to nitrosamines derived from areca nut alkaloids. The carcinogenic TSNAs N'- nitrosonornicotine (NNN), 4-(N-methyl-N-nitrosamino)-1- (3-pyridyl)-1-butanone (NNK) and N-nitrosoanabasine (NAB), as well as the volatile nitrosamines N-nitrosodimethylamine and N-nitrosodiethylamine, have been detected in the saliva of chewers of BQ with tobacco[90-93]. The areca nut-specific nitrosamines (ASNAs) N-nitrosoguvacoline (NG)[90-92,94] and the carcinogenic 3-(methyl-N-nitrosamino) propionitrile (MNPN)[95] were also detected in the saliva of chewers of BQ without tobacco(Table II). ASNAs were not detected in BQ containing areca nut. Nitrosation of BQ with nitrate and thiocyanate *in vitro* at neutral pH resulted in the formation of NG[91]. Presence of ASNAs in the saliva of BQ chewers could arise from their formation during chewing of BQ. The highest levels of an ASNA (NG) were found in the sediment of saliva collected from Taiwanese BQ chewers[94], whereas the highest levels of TSNAs have been found in saliva samples collected in India 93. Secondary and tertiary amines present in areca nut and tobacco can be nitrosated during BQ chewing when they react with available nitrite in the presence of catalysts such as thiocyanate[91,92]. Using a modified N-nitrosoproline (NPRO) test[96], it was clearly shown that NPRO, a marker of endogenous nitrosation, is formed during chewing of BQ[92]. Elevated levels of nitrite and nitrate reductase activity have been reported in the saliva of Indian chewers of BQ with tobacco[97]. There is increased nitric oxide and nitrite formation in subjects during deposition of dental plaque[98].

Many chewers swallow the quid that contains precursors of nitrosamines. The acidic pH of the stomach would favour the nitrosation of secondary and tertiary amines in the quid. Detection of NG and its metabolite Nnitrosonipecotic acid in the urine of Syrian hamsters fed areca nut and nitrite[99,100] also supports the notion that exposure to carcinogenic nitrosamines formed by endogenous nitrosation is likely to be higher in BQ chewers who swallow the quid.

Relation with betel quid and CYPs

Cytochrome P450s regulate the expression of enzymes that convert procarcinogens to their ultimate carcinogenic forms[101,102]. The nitrosation of arecoline, which contains a 3- ethylenic bond at the 3-4 position on the pyridinium ring, may produce a variety of betel-nut-specific nitrosoamines (BSNA). Although cytochrome p450 CYP2D6, CYP1A1 and CYP2E1 loci have been examined for oral cancer patients and control individuals, there are no differences between them in the frequencies of presumed risk genotypes[103].

CYP2A6 was found to be the most efficient activator of 3-methylnitrosamino propionitrile (MNPN) followed by CYP1A1, and N-nitrosoguvacoline (NGL), was activated by CYP2A6. The genotoxicity of NGL was observed to be substantially lower than that of MNPN or 3-methylnitrosamino propionaldehyde (MNPA)[104]. CYP1A1 Exon7 polymorphism G/G genotypes are

susceptible to BQ-related oral cancer and OPMDs[105]. Human CYP2A and CYP2E subfamily members play important roles in the metabolic activation of arecoline-related N-nitrosamines[106-108]. Located on human chromosome 19, CYP2A express at least 13 different isoenzymes, among which CYP2A6 metabolically activates the N-alkylnitrosamines, N-nitrosonornicotine, and 4- (methylnitrosamino) - 1 - (3-pyridyl) - 1 - butanone, which have relatively long alkyl chains[109,110]. Miyazaki *et al*. first reported that CYP2A subfamilies play important roles in the mutagenic activation of AN-derived N-nitrosamines[104].

CONCLUSION

Betel chewing is popular habit in Asia. Prolonged habit of betel quid and its ingredients chewing may predispose to adverse changes to the oral mucosa. The cytochrome P450s are a super family of enzymes involved in the metabolism of numerous exogenous and endogenous substances including drugs, environmental chemicals, steroid hormones and also pre carcinogenic substances to active carcinogenic substances. ASNA and BSNA are forms due to the interaction of betel quid and CYPs. We have screened 311 subjects from different areas of Eastern and North eastern India and also from RKMSP hospital, Kolkata. Out of which 61.09% had betel quid chewing habit. It has been found that more than 50% cases from North eastern region were poor metabolizers whereas more than 50% of eastern region (except North 24 Pgs) were early metabolizers according to xenobiotics metabolizing property of CYPs family.

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Table 1. CYP their families, name and their functions

Family	Function	Members	Names
CYP1	Drug and steroid (especially estrogen) metabolism, benzo (a) pyrene toxification	3 subfamilies, 3 genes, 1 pseudogene	CYP1A1, CYP1A2, CYP1B1
CYP2	Drug and steroid metabolism	13 subfamilies, 16 genes, 16 pseudogenes	CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9,CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, CYP2W1
CYP3	Drug and steroid (including testosterone) metabolism	1 subfamily, 4 genes, 2 pseudogenes	CYP3A4, CYP3A5, CYP3A7, CYP3A43
CYP4	Arachidonic acid or fatty acid metabolism	6 subfamilies, 12 genes, 10pseudogenes	CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4 F3, CYP4F8,CYP4F11, CYP4F12, CYP4F22, C YP4V2, CYP4X1, CYP4Z1
CYP5	thromboxane A_2 synthase	1 subfamily, 1 gene	CYP5A1
CYP7	Bile acid bio synthesis 7-alpha hydroxylase of steroid nucleus	2 subfamilies, 2 genes	CYP7A1, CYP7B1
CYP8	Varied	2 subfamilies, 2 genes	CYP8A1 (prostacyclin synthase), CYP8B1 (bile acid biosynthesis)
CYP11	Steroid bio synthesis	2 subfamilies, 3 genes	CYP11A1, CYP11B1, CYP11B2
CYP17	Steroid bio synthesis, 17-alpha hydroxylase	1 subfamily, 1 gene	CYP17A1
CYP19	Steroid biosynthesis:aromatase synthesizes estrogen	1 subfamily, 1 gene	CYP19A1
CYP20	Unknown function	1 subfamily, 1 gene	CYP20A1
CYP21	Steroid bio synthesis	2 subfamilies, 1 gene, 1 pseudogene	CYP21A2
CYP24	Vitamin D degradation	1 subfamily, 1 gene	CYP24A1
CYP26	Retinoic acid hydroxylase	3 subfamilies, 3 genes	CYP26A1, CYP26B1, CYP26C1
CYP27	Varied	3 subfamilies, 3 genes	CYP27A1 (bile acid biosynthesis), CYP27B1 (vitamin D_3 1-alpha hydroxylase, activates vitamin D_3), CYP27C1 (unknown function)
CYP39	7-alpha hydroxylation of 24-hydroxycholesterol	1 subfamily, 1 gene	CYP39A1
CYP46	Cholesterol 24-hydroxylase	1 subfamily, 1 gene	CYP46A1