

CHEMOPREVENTIVE PROPERTIES OF *Piper betle* LINN.

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Key words : *Piper betle*, Chemopreventive properties, anti-cancer activity, antimutagenic agent.

Piper betle Linn. (betel vine) possesses several bioactive compounds that comprise various health promoting attributes. Some of its constituents provide protection against cancer of various types. This paper reviews chemopreventive properties of betel leaf as reported over recent years.

INTRODUCTION

Piper betle Linn. (betel vine) is well-known plant grown and extensively used in most southeast Asian countries including India and Pakistan. Called *paan* in India, betel leaves are used as masticatory quid with or without catechu powder or paste, areca nut, lime and tobacco product referred as *zarda*. Apart from India and Pakistan, this evergreen perennial delicate climber is grown in Sri Lanka, Malaysia, Thailand, Myanmar, Taiwan and some other parts of the world (Guha, 2006, Pradhan *et al.*, 2013). In *Ayurveda*, known by the Sanskrit name *Tambool* and frequently also referred by its 'Vedic' name *Saptasira*, the plant is highly reputed due to its diverse medicinal properties and religiosity (Kumar *et al.*, 2010). It has been reported that chewing of betel leaf quid with the known carcinogenic tobacco elements, high pH lime, catechu and areca nut does not normally result in oral cancer as believed while the *Paan masala* and *Gutkha* products very frequently induce the deadly disease (Nair *et al.*, 2004). Despite the common belief that regular chewing of betel quid causes oral cancer, while it has been found that both tobacco and areca nut are carcinogenic and slaked lime helps to promote the process, the betel leaves are chemopreventive (Rai *et al.*, 2011) and probably nullify the effect of the other carcinogenic ingredients. In fact, Trivedi *et al.* (1994) reported that aqueous betel leaf extract provided protection against the genotoxic effects of *pan masala* in Chinese hamster ovary CHO cells.

Phytochemical Constituents - A variety of chemicals have been reported from the betel leaf. Apart from having about as much as 80-90% water, carbohydrates, proteins, fats, essential oil, fibre, minerals, tannin, vitamin C, Vitamin A, thiamine, riboflavin, nicotinic acid, phenol, chlorogenic acid and terpenoids such 1, 8-cineole, cadinene, camphene, caryophyllin, limonene, pinene, chavicol, safrol, eugenol, carvacrol and chavibetol have been purified from the leaves (Chopra and Chopra, 1958; Guha, 2006; Kumar *et al.*, 2010; Rai *et al.*, 2011; Periyanyagam *et al.*, 2012; Pradhan *et al.*, 2013).

Proliferative Inhibition and Chemopreventive Property

- Rao (1984) studied the effect of betel quid ingredients on B(a)P-induced carcinogenesis in the buccal pouch of hamster and reported that tropical application of betel leaf extract inhibited oral tumor formation. Rao *et al.* (1985) reported inhibitory effect of betel leaf extract on the initiation of mammary carcinogenesis in rats induced by 7,12-dimethyl

benz [a]anthracene. Amonkar *et al.* (1986) first reported that hydroxychavicol present in betel leaf is antimutagenic. Amonkar *et al.* (1989) and Padma *et al.* (1989) found that hydroxychavicol suppressed the mutagenic effects of tobacco-specific *N*-nitrosomonicotine and 4- (nitrosomethylamino)-1-(3-pyridyl)-1-butanone.

Azuine *et al.* (1991) investigated chemopreventive efficacy of betel leaf crude extract and its constituents on mouse skin and carcinogenesis reported positive results. Azuine and Bhide (1992) used betel leaf extract singly and in combination with turmeric to study the protective effects on methyl (acetoxymethyl) nitrosamine induced oral carcinogenesis in hamster and found that the crude extract and its constituents, β -carotene and α -tocopherol were highly effective as anti-tumor agents inhibiting tumor growth and enhancing tumor latency period. Even the expressed tumor was regressed. The combined betel leaf and turmeric extract was also significantly effective as chemopreventive agent. Chang *et al.* (2002) induced the cell cycle arrest and apoptosis of oral KB carcinoma cells by hydroxychavicol. They reported that KB cell apoptosis was accompanied with cellular redox changes. Tobacco induced mutagenesis in mice has been found to be inhibited by eugenol, a common constituent of betel leaf (Sukumaran *et al.*, 1994; Sukumaran and Kuttan, 1995). DMBA croton oil induced skin carcinogenesis was found to be restricted and regressed in mice by the application of eugenol due to downregulation of c-Myc and H-ras and activation of P53 dependent apoptotic pathway (Pal *et al.*, 2010).

Cell viability assay with MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2H-tetrazolium) of betel leaf ethanolic extract treated human -2-(4-breast cancer T47D cell line showed cytotoxic activity with IC_{50} (median inhibition concentration) at 55.2 μ g/ml (Widowati *et al.*, 2011). Using the tumor promoting 12-O-tetradecanoylphorbol-13-acetate induced Epstein-Barr virus activation in cells, Murakami *et al.* (2000) showed that betel leaf extract effectively acted as an anti-tumor agent and suppressed tumors. Wagh *et al.* (2011) reported that the standardized betel leaf extract inhibited the growth of human chronic myelogenous leukemia in xenograft models and proved to be highly effective oral active inhibitor of Bcr-Abl tyrosine kinase.

In addition to hydroxychavicol and eugenol, ursolic acid and chlorogenic acid components of betel leaf have been

reported to be anti-carcinogenic. Kassi *et al.* (2007), Yamai *et al.* (2009), Yu *et al.* (2010) and Shao *et al.* (2011) have shown that derivatives of ursolic acid are potentially active against human prostate cancer cells, human esophageal carcinoma cells, human hepatoma cell line SMMC-7721 and other forms of cancer. Rakshit *et al.* (2010) reported chlorogenic acid induced apoptosis of Bcr⁻ Abl⁺ CML cells.

A number of investigations since 1980s have proved that the betel leaves do not possess any mutagenic activity but instead possess anticlastogenic property (Umezawa *et al.*, 1981; Yokota *et al.*, 1986; Shirname *et al.*, 1983; Bhattacharya *et al.*, 2005). Yokota *et al.* (1986) had reported that the eugenol of betel leaf inhibited the activation of cytochrome P-450 which metabolizes benzo (a) pyrene to a mutagenic state.

In recent years, a number of patents have been filed and awarded relating to commercially exploitable medicinal attributes of betel leaf including chemopreventive properties (Kumar *et al.*, 2010).

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