BETEL QUID AND ORAL CARCINOGENESIS

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SYNOPSIS

Betel chewing is a popular habit in Asia. Literature review revealed regional variations in the compositions and consumptions of the betel quids. Prolonged habit of betel chewing may predispose to adverse changes to the oral mucosa. Clinical reports from countries with high incidence of oral cancer demonstrated a close etiological association between the betel chewing habit and this disease. Numerous laboratory studies have been performed in parallel with clinical investigations to identify the carcinogenic agent in the betel quid. Various ingredients in the quid either alone or in different combinations were tested on the animal experimental models. These findings together with the pharmacological activities of the quid ingredients were extensively reviewed. Betel nut alkaloids and polyphenols were reported to be the important carcinogens, while tobacco and slaked lime were suggested to possess co-carcinogenic agents. Other factors such as oral sepsis, chronic irritations and malnutrition were believed to precondition the oral tissue and promote the latent tumour to frank carcinoma. Betel leaves, gambir and other ingredients in the betel quid were not known to possess carcinogenic activities. Emphasis were also made concerning the role of genetic and immunity in the genesis of oral carcinoma. The review suggests oral cancer is a process of syncarcinogenesis which involves both the intrinsic and extrinsic factors.

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INTRODUCTION

Betel chewing habits are commonly seen in elderly and lower income population. The habit occupies the same position that tobacco smoking does in western countries. Betel quid refers to a chewing mixture of betel nut (areca catechu nut) and various other ingredients. The combination is collectively known as 'pan' (1). The common ingredients of pan are betel nut, slaked lime, betel leaves (leaves of piper betel vine) and gambir. In many regions of Asia, tobacco is also included into the chew. In some remote villagers and hill tribes their quids also contain coconut, spices, nutmeg, roots and flavouring agents (2).

Oral tissue changes associated with the habit of betel chewing have been intensely studied (3-11). The changes that have received particular attention by dental researchers is oral carcinoma. In India the incidence of oral cancer is high and constitutes about 48% of all magligNancies (12). Clinical and laboratory findings revealed the significant relationship of the betel quid and oral cancer.

The aim of this article is to present an extensive review on the form and usage of the betel quid and also its role in oral carcinogenesis. It is also intended to identify the important aspects for future investigations so that the knowledge on the genesis of oral cancer can be well understood. Such discussions have never been presented in the earlier papers.

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THE COMPOSITIONS AND PHARMACOLOGY OF THE BETEL QUID:

The compositions of the betel quid often varies from place to place. In most parts of Asia, betel nut, betel leaf and slaked lime appear to be the constant ingredients in the quid. Betel nuts are chewed either as raw nuts or priorly processed by boiling, soaking or roasting. Slaked lime is prepared from seashell, however in certain communities it is derived from lime stone. Chewers in Indian, Pakistan, Bangladesh, Sri Lanka, Malaysia and Indonesia often incorporate tobacco and gambir (an extract of Uncaria Gambir leaf) into their quids. The ingredients are wrapped in the betel leaves and chewed as such or crushed prior to chewing. The chew is then swallowed or spat out especially when it contains tabacco at the end of the chewing period. The amounts of each ingredient in the quid varies with chewer's personal taste (1, 2, 13, 14). Other ingredients are infrequently included to improve the flavour of the betel quid. These agents also vary from place to place. For instance, the hill tribes of Thailand, Cambodia, Burma and Laos include cloves, cinnamon and certain roots of local plants into their betel quids (14). Chewers from Taiwan however only chew betel nut alone or sometimes in combination with slaked lime (15). Ready-made preparation of betel quids are easily available in the Indian markets and bazaars. This form of betel quid contains many different ingredients including the colouring agents and neatly wrapped in the alluminium foil (14), figure 1.

The chemical constituents and their pharmacological activities of the principle ingredients in the betel quid have been studied by many workers (16-25). Betel leaves were reported to contain volatile oil such as betel phenol and chavicol (an isomeric with eugenol), tannins, sugar, vitamin C, starch and diastases (18). Betel phenols possess the property of reducing the central nervous stimulation, sialogogue and local anaesthesia.. Tobacco and betel nut contain nicotine and pyridine alkaloids respectively (17, 19). The betel alkaloids are arecoline, arecaidine, guva-

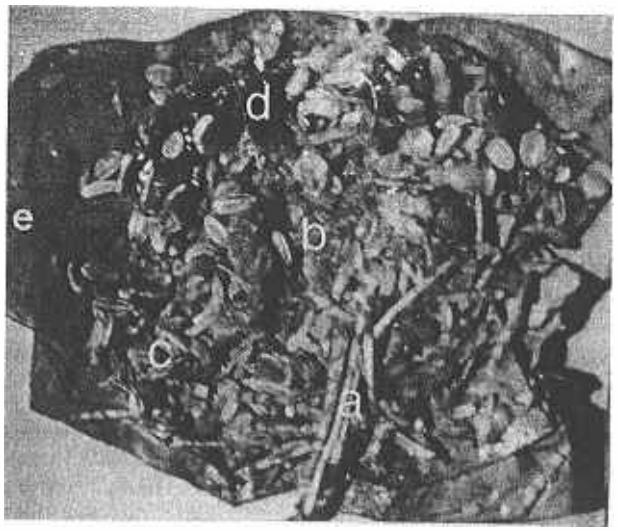

Figure 1: Commercial preparation of betel quid: a — Betel nuts, b — coconut, c — fennel seeds, d — colouring agent, e — betel leaf.

cine, guvacoline and arecolidine and they have stronger chemical reactivity than those of the nicotine alkaloids. The betel alkaloids only constitute about 0.2 — 0.4%. These alkaloids possess cholinergic, antihelmintic and inhibition of GABA (gamma amino butyric acid) activities (20). Inhibition of GABA activities in the central nervous system explains the addictive nature of the betel quid. Other important chemical constituents in the betel nut are polyphenols which form about 15% (21, 22, 26). Betel polyphenols can stabilize collagen, depress growth and possess antimicrobiol activities (24, 26). Slaked lime contains strong alkali — calcium hydroxide, which can release free alkaloidal bases from their esters and also results in the hydrolysis of arecoline to arecaidine (23-27). Thus incorporating slaked lime into the chew appear to potentiate action of alkaloids. Reports on the other quid ingredients are still lacking. This is probably due to the insignificance relationship of these agents in oral carcinogeneisis.

CLINICAL EVIDENCES OF BETEL QUID CARCINOGENESIS:

A close association of the habit of betel chewing and oral carcinoma were reported since early 19th-century. Orr in 1933 (28) concluded that this habit was the predorminant feature in the history of 100 cases of oral carcinoma. Various large scale epidemiologic studies conducted in countries with high incidence of oral cancer such as Indian (29-35), Pakistan (7, 36, 37), Papus New Guinea (38), Taiwan (5), Malaysia (39, 40) and other parts of Southeast Asia (41) also confirmed such findings.

Attempts were also made to estimate the relative risk of oral cancer with the betel chewing habit (8, 42). Chewers were observed to have the risk of developing oral carcinoma ten times more than those of non chewers. Jafarey et al (7) reported that inclusion of tobacco into the quid increased the risk of carcinoma formation from 4 to 29 times. Tobacco contains materials which although not themselves carcinogenic, can enhance the carcinogenic action of substances in the betel quid (43).

LABORATORY EVIDENCES OF BETEL QUID CARCINOGENESIS:

Extracts of betel quid have been shown to produce carcinoma, connective tissue sarcoma and hepatoma in harmsters and mice (23, 44-46). The induction of carcinoma were observed to correlate with the duration and frequency of tissue exposure to the extracts. These findings clearly suggest that betel quid contains the important carcinogenic agents that were responsible for carcinomatous changes. However these agents were believed to be present in trace quantities and possess weak carcinogenic actions. Optimal concentrations of these chemical carcinogens are only achieved when various ingredients are combined together (23, 47). Ranadive et al. (45) pointed out that induction of carcinomatous changes may be facilitated by the presence of other factors such as continous trauma, poor oral hygience and nutritional deficiencies which precondition the oral mucosa.

Various attempts were made to isolate the chemical carcinogens in the betel quid. Local painting of oral mucosa with extracts of betel leaves alone have failed to produce tumour in animal (48); while Abraham et al (47) found no evidence of genetic disturbance inspite of high concentration of the extract used. Interesting observations by Ranadive et al (45) were that the incidence of the carcinoma were reduced from 53 to 22% with the quid extracts containing betel leaves. These findings demonstrate that betel leaf is not only free from active carcinogenic agents but may contain tumour inhibitory substances. The important role of natural anticancer substances in prevention of tumourigenicity of various carcinogens have been highlighted by Wattenberg in 1978 (49). Further work would be required to confirm the presence of such anticancer substances in the betel leaf.

The carcinogenic activities of the tobacco extracts were argued in view of the inability of the extracts to produce tumour in animal studies (10, 50-53). Suri et al (43) argued that the failure to demonstrate the carcinogenic activities of the tobacco extracts could be due to the extracts were prepared with solvents in which the active substances were not soluble. Having improved the extraction technique of tobacco extract these workers found an increased in the tumour formation in harmsters mucosa from 38% to 76%. They concluded that tobacco by themselves are not carcinogenic but can enhance the carcinogenic actions of substances present in the betel quid. They did not rule out the carcinogenic activity of tobacco extract if the extract has been applied to the mucosa for a very long time or the extract was derived from more potent tobacco variety.

The importance of slaked lime in oral carcinogenesis have been emphasized by several workers (5, 38, 54-56). Studies on oral cancer in Pappua New Guinea have shown that the patients include slaked lime rather than tobacco into their betel quids (38). Epithelial cells of animals readily undergone atypical changes following their exposure to slaked lime (54, 56). These changes often becomes reversible with the removal of the irritant. Interestingly, similar reverible changes were also observed in large scale follow-up epidemiologic studies (57, 58). Slaked lime prepared from shell appear to be more potent than the one derived from limestone. The former contains a purer calcium hydroxide (28). Slaked lime causes severe caustic damage to both epithelium and the underlying tissues. Thus allowing a weak carcinogen to exert its effect. Hammer (54) concluded that slaked lime serves as the preconditioning factor to oral mucosa and rendering it susceptible to the action of the weak carcinogen. Bhatt (55) believed that slaked lime is a tumour-initiating factor. He observed marked increased in salivary pH in patient who chew betel quids containing slaked lime. Increased alkalinity results in the escape of intracellular mucus and leads to inflammatory and proliferative changes in the tissue. A neoplastic change may be easily elicited in this disturbed tissue by oral microorganisms which act as a promoting factor. Certain bacterial enzymes can widen the intercellular space and breach the

basement membrane. Thus converting the latent tumour to frank malignancy. Oral hygience among chewers and cancer patients are poor. This provide a favourable source of the responsible microorganisms to elicit such reaction.

Betel nut, a constant ingredient in the quid was also being incriminated in the etiology of oral cancer. Earlier works failed to demonstrate carcinogenic activity of the betel nut (59). This could be possibly due to the extract were prepared with solvent in which the carcinogenic agents in the nut were not soluble. The use of an excellent solvent such as $DMSO_4$ in the later experiments produced promising results (53, 60, 61). Tumour formation were increased following the application of extracts of betel nut to the experimental animals (53). Shivapurkar et al (48) observed 16% increased while Kapadia et al (61) found 100% tumours in rats following subcutaneous injections of aqeous extracts of betel nut alone. Recent studies suggest carcinogenic activity of the betel nut extracts are attributed to the alkaloids and polyphenolic constituents in the nut. Nitrosamine was reported to be an important carcinogen. It can be formed from the reaction of betel arecoline, nitrite and thiocyanate in vivo (62). Saliva of betel chewers offer a favourable condition for nitrosamine formation in view of the presence of high levels of nitrites and thiocyanates. Furthermore, poor oral hygience may amplify the levels of nitrites in the saliva following the activity of oral microorganisms (60, 63). Betel alkaloids are biological thiol reagents analogous to other alkylating agents (17, 64). This is a feature of many chemical carcinogens and it has been shown that chemical interactions with thiol groups can lead to uncontrolled cell proliferation and cancer (65). Further work is required to confirm this finding with betel alkaloids. Betel alkaloids are present in the form of tannic esters. Chewing the quid containing slaked lime promotes the release of the free alkaloids. Recent clinical observations revealed an increased in the mucosal changes from 35% to 65% with quid containing nut and nut with slaked lime respectively (3). Other interesting observations were that processing the nut by boiling or soaking in water as commonly practise by some chewers reduced the alkaloid contents. Chewers consuming these nut varieties were observed to have lower mucosal changes compared to those who chewed unprocessed nuts (3). Salivary amylase activity in oral cancer patients have also been studied (66). Whether these findings could provide an early parameters preceeding to malignant changes require further investigations. The role of immune response in the pathogenesis of oral cancer have been reviewed by several authors (67-70). Turk (67) concluded that failure of the immune surveillance of the abnormal cells would result in tumour formation and growth. However the exact factor which produces such immune disturbance is still under criticisms. Studies on mice have provided with an important evidence indicating the significant role of the betel alkaloid in the immune disturbance phenomena. The arecoline were observed to inhibit both the humoral and cell mediated immune response (71). Such disturbance may be the result of direct action of the arecoline on the lymphocyte as it was observed that the arecoline and arecaidine are able to induce cellular transformation (72). Alternatively, this disturbance may be due to the indirect activity of the betel alkaloid on the immune chemical mediator — the interleukin 1. At present this interleukin 1 is believed to mediate an anti-tumour effect (73). The activity of this important immune mediator could become inhibited by the interaction with the betel alkaloid. This possible mechanism is worth considered for future investigations

Genetic control of a disease formation in human is a well established fact. This control is mediated by a specific locus in the HLA system. Immune response were believed to be under the control of the D locus or antigen in the HLA (67). The significance of this locus in the disease susceptibility were observed in oral submucous fibrosis, a precancerous lesion which is believed to associate with betel chewing habits (70). This finding explains the higher predilection of this disease in certain community of the population. The possibility of similar genetic control in the pathogenesis of oral carcinoma would merit further investigations.

Another chemical constituent in the betel nut that have received equal attentions is the polyphenols. Polyphenolic fraction of the betel nut extracts were observed to produce tumour in experimental animals (48, 59). Others observed maximum lesions in animals receiving the polyphenolic extracts (45). These findings suggest that polyphenols is a potent chemical carcinogen in the nut. Polyphenols bind to protein readily. Thus the possibility of betel nut polyphenols binding to the cellular nuclear materials and leading to the changes in cellular behaviour should be further investigated.

Evidence for carcinogenic activity of other common ingredients in the betel quid is still lacking. Earlier studies suggest that these agents play an insignificant role in the pathogenesis of oral cancer and merely serve to improve the flavour of the betel quid (4, 23, 28).

CONCLUSION

Prolonged habit of betel quid chewing highly predispose to oral cancer. Betel alkaloids and polyphenals appear to be the important carcinogens in the betel quid while slaked lime and tobacco serve as principle co-carcinogenic agents. The evidence are discussed. Overt malignant changes may be easily induced in tissue which has become preconditioned. Various factors which may act as the preconditioning agents are reviewed. The role of intrinsic factors in the pathogenesis of oral cancer is discussed. Useful areas for future investigations are also highlighted.

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