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## **ACUTE AND CHRONIC EFFECTS OF BETEL NUT QUID CHEWING ON THE CARDIOVASCULAR SYSTEM AND ITS ROLE AS A CARDIOVASCULAR RISK FACTOR: A REVIEW**

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## ACUTE AND CHRONIC EFFECTS OF BETEL NUT QUID CHEWING ON THE CARDIOVASCULAR SYSTEM AND ITS ROLE AS A CARDIOVASCULAR RISK FACTOR: A REVIEW

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### ABSTRACT:

Betel nut quid chewing is a common cultural practice in the Asia-Pacific region. Much is known about betel quid and its association to pre-malignant and malignant lesions in the oral cavity but little is known about its link to other poor health comes. There is a growing body of evidence to suggest that betel nut quid chewing may play a role in the development of cardiovascular abnormalities in pre-disposed individuals. This review examines some of the current available literature suggesting betel nut quid chewing as cardiovascular risk factor.

**KEYWORDS:** *betel nut quid chewing, cardiovascular risk.*

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### INTRODUCTION:

Betel nut (areca catechu) quid chewing is a common habit in the Asia-Pacific Region, including Papua New Guinea (PNG) although the method of chewing varies between countries [1, 2, 3]. The habit can be addictive and its popularity is thought to be due to the mild euphoric effect and mental alertness it produces [4, 5, 6]. In PNG, betel nut (areca nut) is chewed with piper betle inflorescence dipped in lime powder without addition of tobacco or spices, as practiced in Asian countries [3, 7].

The betel quid that forms is kept in the mouth and chewed. Lime (calcium hydroxide) used for chewing betel nut is made from heated sea shells or white corals [3].

The link between betel nut chewing and oral pre-malignant and malignant lesions is well established [7] and betel quid chewing is regarded as carcinogenic by the World Health Organization [7, 8]. Betel quid chewing has also been linked to aggravation of asthma [9, 10, 11], reduced tendon reflexes [3], poor pregnancy outcome [12, 13], adverse effect on

Vitamin D metabolism [14], manganese toxicity [15] and abnormal psychological and EEG profile [16]. Betel quid chewing has even been proposed to be a possible treatment for schizophrenia [17, 18, 19] although the data to support this is scanty. Betel nut has been used as a traditional herbal medicine. However, a study from Cambodia has raised the possibility of transmission of infectious diseases through its use [20]. The possible role of betel quid chewing in the transmission of tuberculosis has been discussed in various forums in PNG but no study has been done to support this claim.

There is growing epidemiological evidence that betel nut chewing is associated with ischaemic heart disease [21, 22, 23, 24], hypertension [2, 25], metabolic syndrome [26, 27, 28] and poor glycaemic control in diabetes [29]. Earlier study done by Kevau et al [30] and anecdotal evidence from Port Moresby General Hospital suggests that betel quid chewing may have an effect on the cardiovascular system. Betel quid chewing is increasingly being recognized as cardiovascular risk factor in the Asia-Pacific region where this habit is commonly practiced [21, 22, 24, 30]. This paper reviews current literature on the acute and chronic effects of betel quid chewing on the cardiovascular system and its potential roles as a cardiovascular risk factor.

Pharmacological action of betel nut quid:

Betel nut contains numerous compounds but the four main active ingredients are alkaloids; arecoline, arecaidine, guvacoline and guvacine [16]. The main alkaloid producing pharmacological effects is thought to be arecoline, a naturally occurring acetylcholine agonist acting on muscarinic and nicotinic receptors [16, 31]. Acetylcholine is a neurotransmitter in the autonomic nervous system; acetylcholinesterase converts it to acetate and choline [16, 31, 32]. Apart from the autonomic nervous system this enzyme is also present on red blood cell membranes where it is used to monitor cholinesterase-inhibiting properties of pesticides and toxicity among agricultural workers [32, 33]. Laboratory experimental evidence suggests that arecoline may be broken down by acetylcholinesterase and carboxylesterase [34]. Pharmacological effects of betel nut chewing are thought to be due to parasympathetic stimulation which includes euphoria, central nervous system stimulation, vertigo, excessive salivation, miosis and tremor [16, 31].

Effect of betel quid chewing on heart rate:

Betel quid chewing causes tachycardia [35]. This effect is transient and lasts for 17 minutes regardless of the whether the chewer is a novice, occasional chewer or a habitual chewer [35]. It has also been suggested that the rise in heart rate is dose dependent [36]. Consumption of small amount of betel quid

results in an increase in heart rate, suggesting sympathetic stimulation while chewing large amounts reduces the RR interval variation suggesting parasympathetic stimulation [36]. Nicotinic receptors are present on adrenal medulla [31] and stimulation of nicotinic receptors by arecoline may release catecholamines into the circulation thus causing tachycardia [2,19]. Betel quid chewing has been shown to increase basal secretions of catecholamine [2] and it is possible that the tachycardia observed is due to this mechanism. In the presence of lime, arecoline is hydrolyzed to arecaidine which has sympathetic effects via inhibition of gamma-aminobutyric acid (GABA) uptake [4]. Piper betle inflorescence also has been shown to release catecholamines in-vitro [4, 19] which may also explain the transient rise in heart rate.

Acute transient rise in heart rate induced by chewing betel quid may be a risk factor for cardiac arrhythmias in predisposed patients [37, 38]. Epidemiological data from Taiwan also suggest this possibility [37]. Betel nut chewing has also been implicated in acute myocardial ischaemia [30, 39]. These earlier observations are now supported by epidemiological data showing association between betel nut chewing and cardiovascular death [21, 22, 23, 24, 40].

Effect betel quid chewing on blood pressure:

Blood pressure response is variable after chewing betel quid. Chu observed that only the systolic pressure increases in first time chewers [35]. In another study hypertension was observed in chronic betel quid chewers [2]. More studies are needed to explain these differences in the actions of betel nut chewing.

Betel quid chewing and ischaemic heart disease:

One of the first reported cases of sudden death from myocardial infarction linked to betel quid chewing was by Hung and Deng in 1998 [39]. It has been proposed that arecoline may play a role in coronary artery spasm due to parasympathetic effects on abnormal endothelium [39]. It has also been proposed that coronary artery ischemia may be induced by arecoline similar to the action of acetylcholine [41]. More recently it has been shown that long term betel nut chewing increases coronary artery disease in Taiwanese men as an independent risk factor [22]. Acetylcholine has been shown to cause vasodilation in coronary arteries with normal endothelium but vasoconstriction in atherosclerosed coronary arteries [41, 42, 43]. It appears therefore that the vasodilator effect of acetylcholine on coronary arteries is dependent on an intact normal endothelium. Arecoline from betel nut may be acting via a similar mechanism in normal coronary arteries but paradoxically induce vasoconstriction in

arterosclerosed coronary arteries [30]. This may be the underlying pathological mechanism explaining sudden death after chewing betel nut in high risk individuals [39]. Detailed laboratory based studies are needed to test this hypothesis.

Piper betle inflorescence has been shown in experiments to increase catecholamines [4, 19] but it is not clear if the sympathetic effect of betel quid chewing has a direct cause-effect relationship to clinical or sub-clinical ischaemic heart disease. Betel quid chewing has been associated with clinical and subclinical ischaemic heart disease in Taiwan [24] but proposed mechanisms has not been elucidated.

Betel quid chewing and its association with metabolic syndrome and diabetes:

Betel quid chewing has been strongly associated with central obesity [37] and the habit also has a negative effect on blood glucose control in diabetics [29]. It is unclear whether betel nut quid accelerates the development of ischaemic heart disease in diabetics. Using computational modeling arecoline was shown to inhibit endocytosis of low density lipoprotein (LDL) cholesterol by blocking LDL receptor function and also so prevent LDL cholesterol uptake by liver by interfering with high density lipoprotein (HDL) receptor [44]. The aforementioned mechanisms may possibly contribute to arteriosclerosis

[44]. Further, in-vitro studies have also provided evidence that arecoline induced fat cell dysfunction, which may contribute to Hyperlipidemia, hyperglycemia and insulin resistance; hence contributing towards development of metabolic syndrome [28].

Experimental models to study betel quid effect on cardiovascular system:

Most of the data currently available showing association between betel quid chewing and cardiovascular disease has been through population based cohort studies [40]. There is a need for laboratory based studies to determine the mechanism involved. One way is to use a rat model to observe dose dependent responses [40]. Using tissue perfusion systems to see effects on isolated arteries to compare responses from normal and abnormal endothelium is another way. Frog models can also be used to see dose dependant heart rate responses. Observation of blood pressure responses in-vitro will be technically challenging. Although there is mounting epidemiological data linking betel quid chewing and negative cardiovascular effects, the underlying mechanisms are yet to be elucidated.

#### **CONCLUSIONS:**

Betel quid chewing is a possible cardiovascular risk factor in susceptible individuals. Although there is mounting data from population based

cohort studies to support this link, there is lack of in-vitro studies to determine the underlying mechanisms.

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