Betel quid (BQ) chewing has been a popular oral habit in Taiwan, India, Sri Lanka, and many Southeast Asian countries for a long time [1,2]. BQ chewing habit has become the top five oral habits (including smoking, alcohol, tea, coffee, and betel chewing) in the world. There are about 200-600 million BQ chewers in the world [1,2]. BQ chewing has been linked to the risk of oral cancer and oral precancerous lesions [1,2]. Recently, this oral habit is thought to associate with hepatocarcinoma, diabetes mellitus (DM), cardiovascular diseases, and other systemic diseases.

For these reasons, the International Agency for Research on Cancer (WHO), Lyon, France (2003) organized a meeting to further remind populations about the critical health issues including its impact on oral cavity, gastrointestinal, cardiovascular, and endocrine systems, etc. [1]. BQ consumption is shown to be a risk factor in the initiation of hypertension [3], cardiovascular diseases [4], metabolic syndrome with hyperglycemia and hyper-triaclylglycerolemia, asthma, and other life threatening diseases [1,5]. The precise reasons why prolonged exposure to BQ components affects the cardiovascular system are still not fully clear. The increase of appetite in BQ chewers is a possible factor of obesity, which further contributes to later hypertension [6].

In 47 healthy chronic, occasional, and new BQ chewers, chewing BQ increases the heart rate lasting for an average of 16.8 minutes. Only new chewers show an elevation in systolic blood pressure [7]. An elevation of plasma noradrenaline and adrenaline in BQ chewers was also noted [8]. In addition, BQ chewing may elicit acute toxic symptoms including tachycardia/palpitation, tachypnea/dyspnea, hypotension/sweating, vomiting, dizziness, chest discomfort, acute myocardial infarction, ventricular fibrillation, and related manifestations as reported in 17 cases by the Taiwan Poison Control Center [9]. Chiang et al. [10] also reported two cases with cardiac dysrhythmias after chewing BQ. One case showed chest tightness, dyspnea, diaphoresis, palpitation, and finally death, even after cardiopulmonary resuscitation. The second case suffered from palpitation and paroxysmal supraventricular tachycardia, which was controlled after administration of verapamil. These events are possibly due to parasympthomimetic effects by areca alkaloids on vessels with abnormal endothelium in some people [9,11]. These reports raise
an important health issue of the acute detrimental effects of BQ chewing on the cardiovascular system. These cardiovascular effects by BQ chewing can be partially due to its contents of alkaloids such as arecoline, arecaidine, guvacine, etc.; however, more clinical studies are needed to further elucidate the mechanistic insight and other contributing factors.

Why BQ chewing may increase the risk of DM and cardiovascular diseases is still not clear. BQ is usually comprised of areca nut (AN) (Figure 1 and Figure 2), inflorescence *Piper betle* (IPB), and lime with or without betel leaf (*Piper betle* L., PBL) (Figure 3). DM and metabolic syndrome, which are independent risk factors leading to atherosclerosis and other cardiovascular diseases, show strong association with BQ chewing habit [5,12]. Patients with metabolic syndrome have greater risk of coronary heart disease and stroke, as well as 4-6 times greater risk of dying from atherosclerotic coronary heart disease than those of healthy subjects [13]. Additionally, triglyceride, a critical factor of atherosclerosis and other cardiovascular diseases [14], is also elevated in serum of BQ chewers relative to those who do not consume BQ (54% versus 29%) [15]. Dr Phatak also found that the saliva collected from BQ chewers with oral submucous fibrosis (OSF) has a thrombin-like enzyme activity, which promotes clot formation on citrated plasma, and a defective fibrinolytic activity [16,17]. In addition to local coagulopathy, presence of a chronic disseminated intravascular coagulation was also suspected in OSF patients [18].

Abnormal arachidonic acid (AA) metabolism and platelet aggregation has been linked to vascular thrombus formation and hypertension [19]. Interestingly, water extract of PBL inhibits platelet aggregation and induces vasorelaxation [2,20]. On the contrary, AN extract evidently stimulates platelet aggregation and thromboxane B2 production [21]. Arecoline, the major areca alkaloid, is shown to induce vasorelaxation as well as suppress endothelial cell growth [22]. Moreover, generation of higher amounts of inflammatory mediators (such as IL-1β, IL-6, IL-8, and TNF-α) by peripheral blood mononuclear cells isolated from BQ chewers relative to healthy persons was observed *in vitro* [23]. This is possibly due to stimulation the production of various inflammatory mediators such as prostaglandins, interleukin-6, and TNF-alpha by AN ingredients [24], because these inflammatory mediators are crucial for the pathogenesis of metabolic syndrome, DM, atherosclerosis, and other cardiovascular diseases [25,26].

In conclusion, BQ chewing as a major etiologic factor of oral cancer increases the risk of systemic diseases such as asthma, DM, metabolic syndrome, myocardiac infarction, hypertension, and other cardiovascular diseases. This highlights our attention to BQ chewing habit as a new and crucial health issue, because there are about 200-600 million chewers in the world. More *in vitro*, *in vivo*, and epidemiological studies are needed to further evaluate whether BQ chewing habit really has a health impact on the cardiovascular system and its mechanisms.

References

4. Tsai CC. The association between areca/betel quid chewing, cigarette smoking, alcohol drinking and asthma, heart disease and peptic ulcer in Taiwan. Master thesis. Kaoshiung Medical
Figure 1. *Areca Catechu* Palm trees were planted around the full area of some mountains in Taiwan.
Figure 2. Areca nut were collected from the *areca catechu* palm and transported by a truck to a local factory for further preparation.
Figure 3. Compositions of the betel quid (BQ) in Taiwan. Left: A BQ enrolled by a piece of betel leaf. Right: Lao-Hua BQ contains areca nut with red lime (brownish paste placed in areca nut) and a piece of *piper betle* inflorescence.