



Sub-chronic toxicity study of arecae semen aqueous extract in Wistar rats

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Chemical compounds studied in this article:

Arecoline hydrobromide (PubChem CID: 9301)

Guvacoline hydrobromide (PubChem CID:

15560296)

Arecaidine hydrochloride (PubChem CID:

12305194)

Guavacine hydrochloride (PubChem CID:

11957555)

Arecoline (PubChem CID: 2230)

Arecaidine (PubChem CID: 10355)

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ABSTRACT

Ethnopharmacological relevance: Arecae semen, the ripe seed of *Areca catechu* L., has been used as vermifuge and digestant in traditional Chinese medicine (TCM). However, the potential toxicity effect of arecae semen has not been completely investigated.

The aim of the study: The present study was aimed at evaluating the sub-chronic toxicity of arecae semen by oral administration in Wistar rats.

Materials and methods: A total of 120 Wistar rats were randomly divided into 4 groups (15 males and 15 females per group). The treated groups were given arecae semen aqueous extract (ASAE) at the dose of 750, 1500 and 4500 mg/kg/day by oral administration respectively, and the control group was received distilled water only. The rats and their consumed feed were weighted every 3 days. The clinical changes and mortality were observed and recorded daily. Hematological parameters, biochemical parameters, organ weights, urinalysis and histopathological examination of all rats were tested at the end of the 30-day treatment period and another 10-day recovery period.

Results: Deaths, weight loss, diarrhea, sluggish action, tremors and body curl up were observed in the 1500 and 4500 mg/kg groups during the study. The relative organ weights of liver and testis in male rats of 4500 mg/kg group were significantly different compared with the control group at the end of the treatment period. As for laboratory parameters, there were no significant differences at the dose of 1500 and 4500 mg/kg groups compared with the control group in the study, except the white blood cell count (WBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), blood urea nitrogen (BUN), creatinine (Cr), glucose (GLU) and total cholesterol (CHOL). In addition, the results of histopathological examination and feed intake showed no significant difference compared with the control group.

Conclusions: The results showed that ASAE at the dose of 750 mg/kg/day was safe, but long-term oral administration of ASAE with high dosage was toxic. Moreover, the toxic ingredients of ASAE including arecoline, and also some other compounds should be researched.

1. Introduction

Herbal remedies are generally considered as safe and effective therapies treating various diseases in folk traditional medicine for thousands of years. However, in recent decades, numerous of studies have reported the adverse effects or toxicity of herbal medicine for a long term usage (Feuston et al., 1996; Baliga et al., 2004; Boudreau et al., 2013). Therefore, it is necessary to estimate the toxic properties of herbal medicine for security reasons.

Areca catechu L. (Palmeaceae) tree is a palm geographically grown in the tropical Pacific, Asia and parts of the East Africa (Garg et al., 2014). Betel quid and areca nut chewing, made of fruits, pericarps or seeds from *Areca catechu* L. with or without additives (shown in Fig. 1), are

widely prevalent used by 600 million people around the world. Betel quid and areca nut chewing are the fourth most common habit after consumption of tobacco, alcohol and caffeine-containing beverages (IARC, 2004), and they are chewed for many reasons, including for its psychostimulating effects, to induce euphoria, to satisfy hunger, to sweeten the breath and as a social and cultural practice in daily life (IARC, 2004). However, the chewing habit has been demonstrated that it is closely associated with the cancers of the oral cavity, pharynx, esophagus, liver, biliary tracts and uterus by many toxicological and epidemiological studies owing to the toxic effect of arecoline, the additional various additives and continually mechanical stimulation to the oral cavity (Tsai et al., 2013; Javed et al., 2010; Garg et al., 2014; Jeng et al., 2014; Wollina et al., 2015; Wu et al., 2009; Zhou et al.,

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Fig. 1. The different chewing products from *Areca catechu* L. (A) Typical ingredients of hand-made betel quid in India (Wollina et al., 2015). (B) Some commercial brands ready to use made in India (Wollina et al., 2015). (C) The unripe fresh fruits ready to use in Hainan province of China. (D) The commercial products of unripe pericarp with additives ready to use made in Hunan province of China.

2014). Arecoline, the main alkaloids in betel quid and areca nut chewing, has been verified as the predominant toxicant in the chewing products which is cytotoxic to human cells including hepatocytes, splenocytes, myoblasts, lymphocytes, endothelial cells, and epithelial cells (Liu et al., 2016).

Moreover, arecae semen, as herbal medicine called *Binglang* in TCM

(shown in Fig. 2), is the ripe seed of *Areca catechu* L., firstly listed in *Yaolu* about 1700 years ago. Arecae semen has been widely used for treatment of parasites, dyspepsia, abdominal distension, abdominal pain, diarrhea, edema and jaundice in TCM (Anonymous, 2015). Among ancient TCM monographs, such as *Mingyi Bielu*, *Xinxiu Bencao* and *Compendium of Materia Medica*, there was no record about the



Fig. 2. The ripe seeds of *Areca catechu* L. (A) Arecae semen, used as an herbal medicine in TCM. (B) The raw arecae semen, a clinically form processed by cutting arecae semen into very thin slice.

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