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ORIGINAL ARTICLE

α-Mangostin from *Cratoxylum arborescens*: An *in vitro* and *in vivo* toxicological evaluation

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Abstract α-Mangostin (AM) is believed to be beneficial for health due to its versatile biological activities such as antioxidant, antiviral and anticancer properties. In this study, the air-dried stem bark of *Cratoxylum arborescens* was extracted consecutively with hexane, chloroform and methanol. The hexane extract was chromatographed, fractionated and purified to yield AM. The toxic effects of AM have not been completely investigated; therefore, the current study investigates its *in vitro* cytotoxicity on WRL-68 normal cells and *in vivo* effects on renal and hepatic histobiochemical parameters, relative organ weight, lipid profile, peroxidation and reduced glutathione of ICR female and male mice. AM was fed orally at single doses of 0 (as normal group), 100, 500 and 1000 mg/kg body

Abbreviations: AM, alpha mangostin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; OECD, Organization for Economic Cooperation and Development; MDA, malondialdehyde; GSH, glutathione; H&E, hematoxylin and eosin; ANOVA, analysis of variance; SD, standard deviation.

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weight. The results showed that AM did not show adverse effects on body weight, organ weight, serum biochemistry, histopathology and oxidative stress biomarkers. On the other hand, this natural compound showed low cytotoxic activities against normal liver cells (WRL-68) with IC_{50} = 65 μg/ml. To our knowledge, this paper is the first to report the toxicity effects of AM in rodents.

1. Introduction

Plants have been harnessed as medicines since the early centuries. Remedies were initially taken in the form of crude drugs such as tinctures, elixirs, compresses, powders and other herbal formulations (Alsarhan et al., 2012). Statistics about the origin of drugs that were launched in the last twenty five years revealed that both natural products and semi-synthetic compounds, derived from natural origin, comprised 34% of all new chemical entities, while 18% of them were synthetic mimics of natural compounds (Gurib-Fakim, 2006). However, many of these herbs and natural supplements have not been thoroughly evaluated, and their safety as well as effectiveness may not yet have been proven (Dunnick and Nyska, 2013). Pharmacological interest in the efficacy and safety of the herbal medicines has grown during the past decade because of the realization that many people are self-medicated using these agents (Calixto, 2005; Firenzuoli and Gori, 2007). However, the use of herbal products should be based on scientific origin; otherwise, they would be useless and unsafe (Mir et al., 2013). Furthermore, the irrational use of these herbal products may cause serious toxicity in humans (Parthasarathi and Olsson, 2004). Unfortunately, many people underestimate the toxicity of natural products and do not realize that these agents could be as toxic as, if not more than, synthetic drugs. A typical example for a toxic herbal product is the leaves of *Atropa belladonna* and *Digitalis purpurea*, which show severe systemic toxicity if taken orally (Mir et al., 2013).

In this regard, *Cratoxylum arborescens* Blume Guttiferae family (Fig. 1) is a traditional medicine and its natural range of distribution includes Malaysia, South Burma, Sumatra and Borneo. Due to its geographically wide-ranging natural habitat, it is often referred to by several Malay colloquial names depending on the region or locality where it is found. In Sabah, Serangan is synonymous with Geronggang. In Sarawak, it is locally called by different names depending on the community (Jensen and Zwieniecki, 2013). This plant is used traditionally as a cure for fever, cough, diarrhea and other ailments (Srithi et al., 2009). Phytochemicals which have been reported to be found in *Cratoxylum* are xanthones (Iinuma et al., 1996a; José et al., 1998), and some of these xanthones have been shown to exhibit significant pharmacological activities (Jiang et al., 2004). α-Mangostin (AM) (Fig. 2) is one of the major xanthones isolated from the stem bark of the plant (El-Seedi et al., 2009). AM has been reported to possess a wide spectrum of biological activities such as anti-inflammatory (Chairungsrilerd et al., 1996; Shankaranarayan et al., 1979; Tewtrakul et al., 2009), cardioprotective (Devi Sampath and Vijayaraghavan, 2007), anti-tumor (Akao et al., 2008; Chitchumroonchokchai et al., 2013), antidiabetic (Ryu et al., 2011), antibacterial (Iinuma et al., 1996b; Negi et al., 2008; Sundaram et al., 1983), antifungal (Kaomongkolgit et al., 2009), antioxidant (Jung et al., 2006; Márquez-Valadez et al., 2009), antiparasitic (Obolskiy et al., 2009) and can also act as well as anti-obesity (Jiang et al., 2010; Quan et al., 2012) agents. Therefore, the purpose of this study is to investigate the safety of the pure compound of AM and to evaluate its effect on the extent of tissue damages in mouse liver and kidney.

2. Materials and methods

2.1. Extraction and isolation of AM from C. arborescens

The stem bark of *C. arborescens* was collected from wild trees growing in Sarawak, Malaysia in June 2009. A voucher

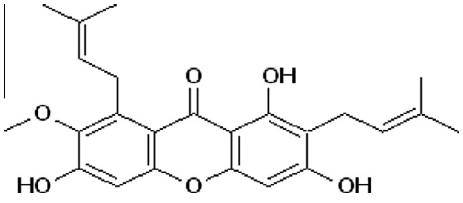

Figure 2 Chemical structure of AM. *Source:* www.chemfaces.com/natural/alpha-Mangostin-CFN97050.html.

Figure 1 *Cratoxylum arborescens* (Guttiferae); (A) the appearance of overall tree. (B) The flowers and leaves. *Source:* www.asian-plant.net/Hypericaceae/Cratoxylum_arborescens.htm.