



Antitumor effect of blister beetles: An ethno-medicinal practice in Karbi community and its experimental evaluation against a murine malignant tumor model



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ARTICLE INFO

Article history:

Received 13 October 2012

Received in revised form

9 April 2013

Accepted 6 May 2013

Available online 23 May 2013

Keywords:

Apoptosis

Cantharidin

Epicauta hirticornis

Mylabris cichorii

Zootherapy

ABSTRACT

Ethnopharmacological importance: The blister beetles *Epicauta hirticornis* and *Mylabris cichorii* are used as a folk medicine by the Karbi tribe in Karbi Anglong district of Assam, India for the treatment of different human ailments, including cancer cases.

Aim of the study: It includes field survey related to zoo-therapeutic aspects of two blister beetles in Karbi community, isolation of bio-active compound and evaluation of its antitumor potential with possible mode of action against murine Ehrlich ascites carcinoma (EAC).

Materials and methods: The main bio-active compound of blister beetles was isolated from ethyl acetate extract and the structure was confirmed as cantharidin using NMR, IR, Mass and X-ray diffractometer. The effect of cantharidin on apoptosis, necrosis, autophagy and the apoptosis related signaling pathways were determined using different bioassays, including cell cycle analysis, mitochondrial membrane potential, western blot analysis of cytochrome c, caspases 9, 3/7 assays, and lactate dehydrogenase (LDH) assay.

Results: Cantharidin induced apoptosis, necrosis and autophagy cell death in EAC cells. The decrease in mitochondrial membrane potential was observed, which may help to release cytochrome c from mitochondria to cytosol. Cantharidin treatment caused up-regulation of caspases 9 and -3/7 and a decrease in LDH activity in EAC cells.

Conclusion: The major bioactive compound of these blister beetles is cantharidin which induces severe apoptosis in EAC cells involving mitochondrial intrinsic pathway. Cantharidin-mediated inhibition of LDH activity may lead to short supply of NAD⁺ and cut off energy and anabolic supply to cancer cells.

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1. Introduction

Cancer and its treatment are among the most critical health issues. According to world cancer report released by the World Health Organization (WHO) in 2003, cancer rates could further increase by 50% to 15 million new cases during the year 2020 (Stewart and Kleihues, 2003).

Ehrlich ascites carcinoma (EAC) referred to as an undifferentiated carcinoma, has high transplantable capability, rapid proliferation with malignancy and does not have the tumor specific transplantation antigen (TSTA). Carcinoma in human is a malignant neoplasm of epithelial origin and arises in the body's organs like nose, colon, penis, breast, prostate, urinary bladder and ureter. About 80–90% of all cancer cases are carcinomas (Pazdur et al.,

2008). Cancers are mainly treated by surgery, chemotherapy and radiation therapy. In chemotherapy, hundreds of drugs have been approved for their clinical uses. However, the therapeutic efficacy of most of these drugs is limited owing to the development of a variety of side effects in the hosts (Florea and Busselberg, 2011).

Therefore, the research on the medicinal plants and animals is showing great promise to develop lead molecule(s) against cancer as it may have no or less toxicity to the host. Although plants and plant-derived materials constitute the principal source of ingredients for traditional medicine, identification of animal resources for medical cures is also gaining importance in human health care (Alves and Rosa, 2005; Bhanot et al., 2011). Insect toxins have been used in the treatment of various diseases all over the world before the advent of modern clinical drugs and are known to contain substances that can be used for therapeutic purposes or as precursors for the synthesis of useful anticancer drugs (Newman et al., 2003). Several studies have reported the anticancer property of venoms and toxins against different cancers (Gomes et al., 2010).

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The blister beetles have been used in Chinese traditional medicine for more than 2000 years (Wang, 1989). Blister beetles, *Mylabris cichorii* and *Epicauta hirticornis* (Fig. 1a and b) have been used in traditional medicine for the treatment of cancer, intestinal worms, rabies, warts and skin diseases in the ethnic community of Karbi tribes. These beetles belong to the class—Insecta, order—Coleoptera and family—Meloidea. Blister beetles have been shown to contain cantharidin, which is a terpenoid and acts as a vesicant (Moed et al., 2001). Cantharidin has been used to treat warts, piles, ulcers and molluscum through topical application and it has also found use as an abortifacient and aphrodisiac. (Wang, 1989; Moed et al., 2001).

The clinical application of cantharidin is limited by its toxicity to mucous membranes, mainly in the gastrointestinal tract, ureter and kidney (Oaks et al., 1960; Wang, 1989; Verma and Prasad, 2012). However, when cantharidin is used appropriately, complications are exceedingly rare and there is no scarring with the proper use of cantharidin (Coskey, 1984). It has been suggested that almost all effects of cantharidin are as a result of inhibition of serine/threonine protein phosphatases, PP1 and PP2A (Honkanen, 1993; McCluskey et al., 2001).

Most of the anticancer research on cantharidin has been carried out using cancer cell lines *in vitro* (Honkanen, 1993; McCluskey et al., 2001) and its effect *in vivo* needs to be further researched.

Therefore, on the basis of traditional information on zoo-therapeutic uses of these blister beetles in Karbi community, and other related literature, this study was aimed to isolate cantharidin from two different blister beetles species and evaluate its anticancer potential against murine EAC and look at the possible mode of action involving apoptosis, necrosis and autophagy cell deaths, with more emphasis on apoptosis. The novelty of the work lies on the fact that the present findings on the documentation of zoo-therapeutic value of blister beetles in Karbi tribes and possible mode of action of cantharidin against EAC *in vivo* involving apoptosis, necrosis, and autophagy cell deaths with a decrease in LDH activity are probably first of its kind in relation to cantharidin-mediated anticancer activity.

2. Materials and methods

2.1. Study area

The field survey study was carried out in Karbi Anglong district of Assam, India. This region is situated in north-eastern part of India, which is unique for its ethnic and cultural diversities coupled with biological diversity (Teron and Borthakur, 2012). Field survey sites within the Karbi Anglong district are shown in

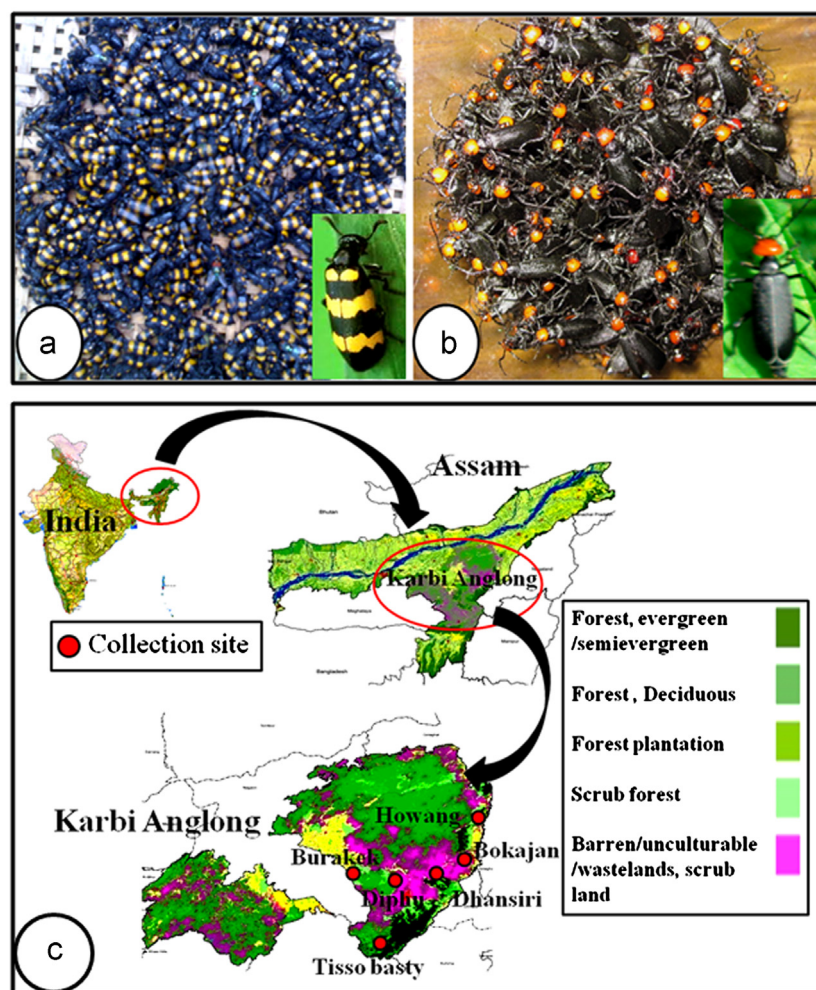


Fig. 1. Photographs of blister beetles, *Mylabris cichorii* (a) and *Epicauta hirticornis* (b). Location map of Karbi Anglong district of Assam, India showing field survey and blister beetles collection sites (red bullets) (c). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

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