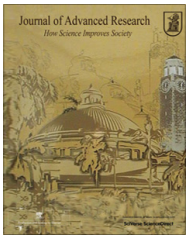
Journal of Advanced Research (2013) 4, 417–421

Cairo University

Journal of Advanced Research



SHORT COMMUNICATION

Cytotoxic effect of commercial *Humulus lupulus* L. (hop) preparations – In comparison to its metabolomic fingerprint

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Received 29 May 2012; revised 17 July 2012; accepted 17 July 2012
Available online 5 September 2012

KEYWORDS

Humulus lupulus L.;
Metabolomics;
Humulones;
Lupulones;
Anticancer activity;
Hops

Abstract Hops (*Humulus lupulus* L. Cannabaceae) is an economically important crop, that has drawn more attention in recent years due to its potential pharmaceutical applications. Bitter acids (prenylated polyketides) and prenylflavonoids are the primary phytochemical components that account for hops resins medicinal value. We have previously reported on utilizing untargeted NMR and MS metabolomics for analysis of 13 hops cultivars, revealing for differences in α- versus β-bitter acids composition in derived resins. In this study, effect of ratios of bitter α- to β-acids in hop resins to cytotoxicity of hop resins was investigated. *In vitro* cell culture assays revealed that β-acids were more effective than α-acids in growth inhibition of PC3 and HT29 cancer cell lines. Nevertheless, hop resins enriched in β-acids showed comparable growth inhibition patterns to α-enriched resins and suggesting that bioactivity may not be easily predicted by metabolomics and/or gross metabolic profiling in hops.

Introduction

The hop plant (*Humulus lupulus* L., Cannabaceae) is an economically important crop cultivated in most temperate zones of the world for its female inflorescences, commonly referred to as ''hop cones'' or ''hops''. The bitter, resinous substance produced in the glandular hairs of the strobiles (lupulin glands) is used in brewing, baking and as cattle feed for its bacteriostatic action and preservative qualities [1]. In addition, it is used in pharmaceutical applications. The resin is used as a mild sedative in European phytotherapy, and hop has been investigated for its potent estrogenic and, more recently, potential cancer chemopreventive activities [2,3]. Major class of secondary metabolites in hop lupulin glands include hop bitter acids which exhibit interesting effects on human health [4]. The hop bitter acids are resinous alicyclic phenolic acids, classified as α-acids (humulones) and β-acids (lupulones). The main α-acids are humulone, cohumulone, and adhumulone; the corresponding β-acids are lupulone, colupulone, and adlupulone (Fig. 1A). The β-acids differ structurally from the α-acids by having one extra isoprenyl group. Furthermore, hop resin contain terpenes and isoprenylated flavonoids [5–7]. There are at least 200 different hop varieties grown and cultivated worldwide and it is of increasing interest to develop accurate methods for hop

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Peer review under responsibility of Cairo University.

2090-1232
http://dx.doi.org/10.1016/j.jare.2012.07.006

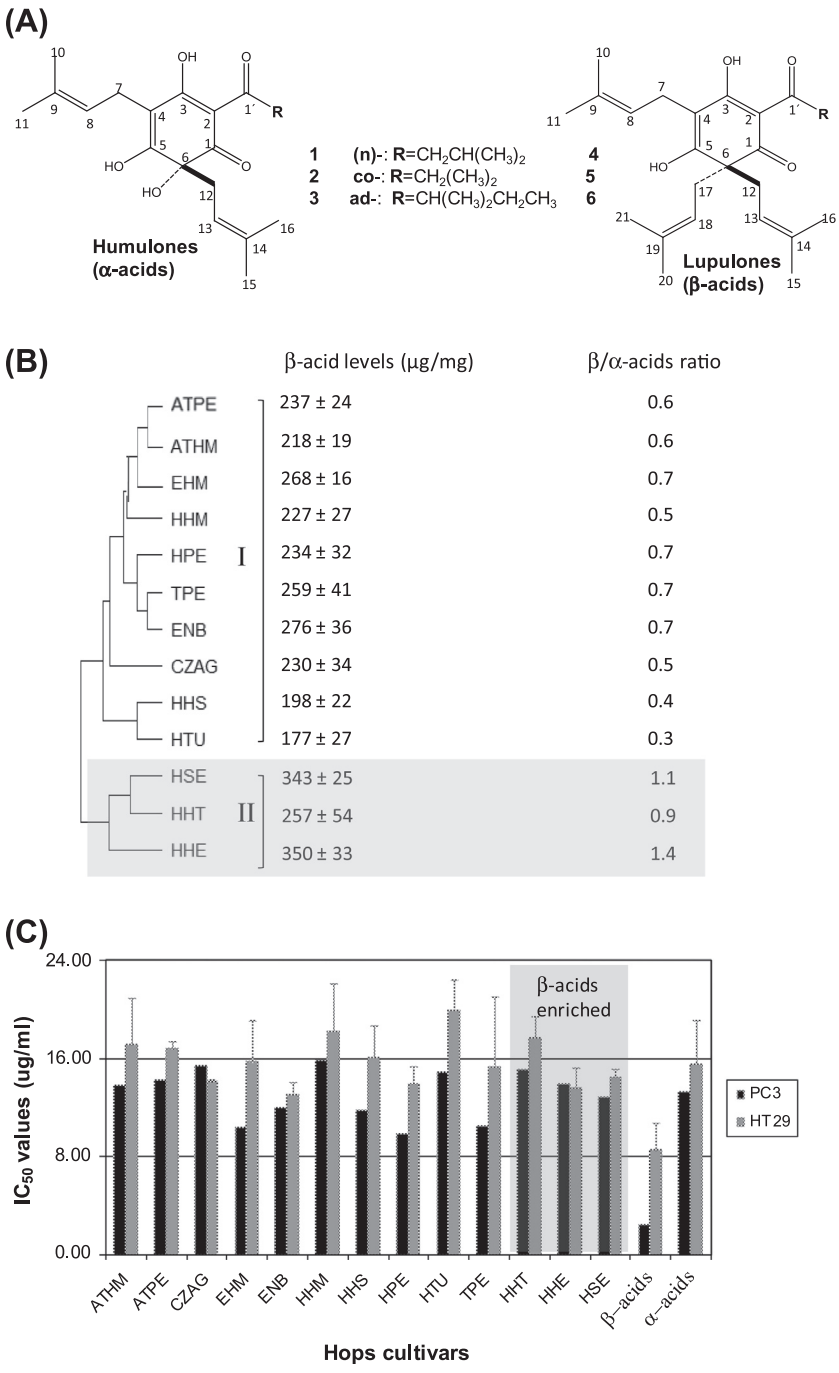

Fig. 1 Hop α/β bitter acids composition in comparison to its cytotoxic effect. (A) Chemical structures of humulones (α-bitter acids) and lupulones (β-bitter acids) series detected in hop resin. (B) Hierarchical cluster analysis (HCA) of hop cultivars based on group average cluster analysis of its biochemical profile as the analytical data showing clustering of cultivars in 2 major groups mostly influenced by its β-bitter acids levels (μg/ml) and β/α-acid ratios. Data are mean ± SE from three independent measurements. Grey box highlights β-acids enriched resins (HSE, HHE & HHT) from other cultivars. (C) Cytotoxicity data of hops resin extracts and pure α- and β-bitter acids against human prostate (PC3) and colon (HT29) cancer cell lines (IC_{50} values expressed in μg/ml). Detailed description of bitter acids standards composition is provided under materials and methods. Data are mean ± SE from four independent experiments. Note the grey box highlighting β-enriched resins (HSE, HHE & HHT) showed no significant difference in its IC_{50} values from other samples.

characterization that could be used to classify hop from different geographical origins or countries. We have recently reported on the use of LC–MS and NMR for the metabolic fingerprinting of hop. This comparative untargeted approach revealed for compositional differences in α/β bitter acids among hop cultivars [7]. Our objective from this study was to further investigate whether differences in α- and β-bitter acids composition in hop resins could influence its cytotoxic effect. A total of 13 chemically well-characterized hop resins were tested for growth inhibition effect against (mutated androgen