BMC Complementary & Alternative Medicine

RESEARCH ARTICLE Open Access

The hexane fraction of *Ardisia crispa* Thunb. A. DC. roots inhibits inflammation-induced angiogenesis

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Abstract

Background: *Ardisia crispa* (Myrsinaceae) is used in traditional Malay medicine to treat various ailments associated with inflammation, including rheumatism. The plant's hexane fraction was previously shown to inhibit several diseases associated with inflammation. As there is a strong correlation between inflammation and angiogenesis, we conducted the present study to investigate the anti-angiogenic effects of the plant's roots in animal models of inflammation-induced angiogenesis.

Methods: We first performed phytochemical screening and high-performance liquid chromatography (HPLC) fingerprinting of the hexane fraction of *Ardisia crispa* roots ethanolic extract (ACRH) and its quinone-rich fraction (QRF). The anti-inflammatory properties of ACRH and QRF were tested using the Miles vascular permeability assay and the murine air pouch granuloma model following oral administration at various doses.

Results: Preliminary phytochemical screening of ACRH revealed the presence of flavonoids, triterpenes, and tannins. The QRF was separated from ACRH (38.38% w/w) by column chromatography, and was isolated to yield a benzoquinonoid compound. The ACRH and QRF were quantified by HPLC. The LD_{50} value of ACRH was 617.02 mg/kg. In the Miles vascular permeability assay, the lowest dose of ACRH (10 mg/kg) and all doses of QRF significantly reduced vascular endothelial growth factor (VEGF)-induced hyperpermeability, when compared with the vehicle control. In the murine air pouch granuloma model, ACRH and QRF both displayed significant and dose-dependent anti-inflammatory effects, without granuloma weight. ACRH and QRF significantly reduced the vascular index, but not granuloma tissue weight.

Conclusions: In conclusion, both ACRH and QRF showed potential anti-inflammatory properties in a model of inflammation-induced angiogenesis model, demonstrating their potential anti-angiogenic properties.

Keywords: *Ardisia crispa*, Miles vascular permeability assay, Murine air pouch granuloma, Angiogenesis

Background

Angiogenesis is the process of blood vessel formation. It is important in normal physiology and is involved in the progression of chronic diseases, particularly cancer, arthritis and cardiovascular diseases [1-7]. The advantage of targeting angiogenesis to control pathological disorders, particularly cancer, is that anti-angiogenic agents specifically target newly formed blood vessels without damaging existing blood vessels [1]. The important role of angiogenesis in the pathogenesis of chronic inflammatory diseases has led to the implementation of anti-angiogenic strategies for treating these diseases [8].

Drugs are increasingly being developed from natural products, offering a very promising approach to identify novel anti-angiogenic and anti-cancer agents [9]. A considerable number of bioactive compounds derived from functional and medicinal foods have been identified as potential anti-angiogenic agents based on the results of experimental and clinical studies. Compounds such as curcumin in turmeric [10], naringenin in citrus [11], humulone in beer hop [12], betulinic acid in almond hull [13], capsaicin in pepper [14] and resveratrol in grapes [15,16] were reported to inhibit angiogenesis by targeting the cyclooxygenase-2 (COX-2) and 5-lipoxygenase

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