บทความ “A new bisanthraquinone and cytotoxic xanthones from *Cratoxylum cochinchinense*”

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Review

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The genus *Cratoxylum*: traditional use, phytochemistry and pharmacology

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Abstract

Objectives The genus *Cratoxylum* contained medicinal herbs, which are widely distributed in South-East Asia and China. Plants of this genus were consumed as a vegetable side dish, a spice, an ingredient in soup, or a substitute for tea, as well as they are traditionally appropriate for various diseases such as fever, cough, flu, diarrhoea, etc. The most aims of the current review are to highlight the ultimate information about the traditional use, phytochemistry and pharmacology of *Cratoxylum* medicinal plants.

Key findings The relevant literature data of *Cratoxylum* species have been gathered from Google Scholar, Sci-Finder, Web of Science, Science Direct and various journal websites. The most meaningful keyword '*Cratoxylum*' was used in combination or alone in the search for references.

Summary More than 150 reports have been retrieved from the search, completely written in English. Most of them are phytochemical and pharmacological studies, which determined the isolations of 277 metabolites. Xanthone derivatives (205 compounds, 74%) are essential, followed by other chemical classes such as flavonoids, anthraquinones, triterpenoids, benzophenones, phytosterols and tocopherols. *Cratoxylum* constituents possessed complexed pharmacological activities, including antioxidant, antibacterial, anti-inflammatory, antidiabetic, antihypertensive, antimalarial, antiviral, antiamoebic, protein tyrosine phosphatase 1B inhibitory, neuroprotective, hepatoprotective and gastroprotective activities, especially in terms of anticancer.

Keywords: *Cratoxylum*; xanthone; traditional use; phytochemistry; pharmacology

Introduction

The annual worldwide medication market is estimated to be valued at approximately 1.1 trillion US dollars. These remedies were derived directly or indirectly from natural items such as plants (25%), bacteria (13%) and animals (about 3%).[1, 2] Natural products are an enormously valuable resource for multinational pharmaceutical businesses developing novel treatments. They are utilized as a direct source of therapeutic agents (both pure medications and phytomedicines); a raw material source for the production of complicated semi-synthetic compounds; prototypes for the design of lead molecules; and as taxonomic markers for the discovery of new drugs.[1] Natural products or their derivatives account for almost one-third of the world's best-selling medications.[1, 2] There are numerous examples of globally best-selling natural products, which were most notably derived from terrestrial plants. For instance, several well-known antibiotic agents, such as penicillin, erythromycin and amphotericin B, were isolated from fungi.[1, 2]

Natural products provide several distinct advantages in the medication discovery and development process. They are chemical novelties that, when compared with other sources, can generate lead drug candidates for complicated targets. Furthermore, naturally occurring constituents have a chemical diversity that no manufactured chemical collection can possibly match. They can have bi- and tri-dimensional complex structures while still being able to be absorbed and metabolized in the body. Therefore, searching for new medicinal agents from natural resources is still warranted.

Cratoxylum (*Cratoxylon* Blume) is a small genus of deciduous shrubs in the family Hypericaceae, that is widely distributed in Southeast Asia and China.[3–6] About six accepted species were recorded, consisting of *Cratoxylum arborescens* (Vahl) Blume, *C. cochinchinense* (Lour) Blume, *C. glaucum* Korth, *C. formosum* subsp. *pruniflorum* (Kurz) Gogelein, *C. formosum* subsp. *formosum* (Jack) Dyer and *C. sumatranum* (Jack) Blume.[7, 8] The same morphology means that Cratoxylum plants grow as small to medium-sized trees or bushes. When the bark dries black, it exudes a yellow resinous sap.[7] The flowers range in colour from white to pink to scarlet. The ellipsoid fruits have three valves and the woods are employed for furniture.[7] *Cratoxylum* plants have been utilized for both foods and traditional medicines. As a representative example, *C. cochinchinense* leaf, stem, bark, root and resin were used in traditional Chinese medicine to treat a variety of ailments, including jaundice, oedema, cough, itch, fever, diarrhoea, hoarseness, diuretics, flu, colic, ulcer and dental conditions.[9, 10] Furthermore, the young leaf has been utilized as a herbal tea alternative and the immature fruit as a cooking spice.[10]

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Structurally Diverse Cytotoxic Polyphenols from *Garcinia gracilis*

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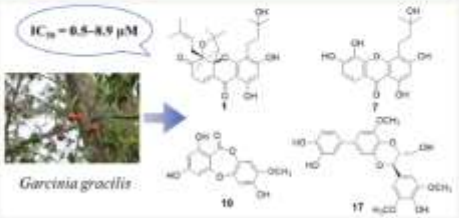
ABSTRACT: Thirty-five diverse polyphenols, belonging to seven structure classes, were isolated from *Garcinia gracilis*, a medicinal and edible plant sampled from Laos. The structures of nine new compounds, gargarcilones A−I (1−3, 5−7, 10, 12, and 17), were established using spectroscopic, X-ray diffraction, and experimental and calculated ECD methods. Additionally, we revised the stereochemical assignment of cochinchinoxanthone and cochinchinoxanthone C. The compounds were evaluated for antiproliferative activity against five human tumor cell lines (HL-60, A549, SMMC-7721, MDA-MB-231, and SW480). Compounds 1−4, 7, and 8 exhibited cytotoxic activity with IC_{50} values of 0.5−8.9 μM. Compound 3 significantly induced apoptosis in SMMC-7721 cells.



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Tropical trees of the *Garcinia* genus are mainly distributed in Southeast Asia, India, Africa, and Brazil, and many of them have medicinal and culinary uses.[1] *Garcinia* plants are an important source of polyphenols, including flavonoids, xanthones, and phloroglucinols.[2−4] In particular, caged xanthones with a partially dearomatized prenylated polyphenol core have attracted considerable attention owing to their complex carbon skeleton and potential antitumor activity.[5] The most representative caged xanthone, gambogic acid, entered clinical trials to treat colon, non-small cell lung, and renal cancers in China.[6] Therefore, the isolation of additional polyphenols from plants of the *Garcinia* genus and the evaluation of their cytotoxic potential are of much interest.

G. gracilis, known as Cha-mang or Mak-paem, is used as food and medicine in Thailand.[7] Green leaves of *G. gracilis* are used as flavoring agents to impart a sour taste to food, the ripe fruits are edible, and the roots are used as an antipyretic in Thai folk medicine.[8] To date, only three natural metabolites have been isolated from this plant.[7] In the present study, 35 phenolic compounds, including five new caged xanthones (1−3, 5, and 6), one new isoprenylated xanthone (7), one new depsidone (10), and two new biphenyl derivatives (12 and 17), have been isolated from *G. gracilis* sampled from Laos. Cochinchinoxanthone, the enantiomer of gargarcilone C (3), from *Cratoxylum cochinchinense*, was obtained as a scalemic mixture as determined after measuring its optical rotation and literature analysis. The relative configuration at C-8 of cochinchinoxanthone C was revised to the α-orientation after a detailed analysis of calculated and experimental ^{1}H NMR data. The cytotoxicity of all compounds was evaluated in five human tumor cell lines (HL-60, A549, SMMC-7721, MDA-MB-231, and SW480). Compounds 1−4, 7, and 8 presented cytotoxicity with IC_{50} values between 0.5 and 8.9 μM. Compound 3 could significantly induce apoptosis in SMMC-7721 cells. Herein, we report the isolation, structure identification, and cytotoxicity of these phenolic constituents.

RESULTS AND DISCUSSION

Isolation and Structure Elucidation. Investigation of the MeOH extract of *G. gracilis* by chromatographic techniques resulted in the isolation of 35 polyphenols, including nine undescribed structures (1−3, 5−7, 10, 12, and 17) and 26 known compounds: forbesione (4),[9] isojacareubin (8),[10] oblongixanthone A (9),[11] cowadepsidone (11),[12] multibiphenyl C (13),[13] schomburgbiphenyl A (14),[14] doitungbiphenyl A (15),[15] calophymembranside A (16),[16] quercetin,[17] naringenin,[18] volkensiflavone,[19] pancibiflavonol,[20] GB 1a,[21] fukugiside,[22] morelloflavone,[23] 1,7-dihydroxy-6-methoxyxanthone,[24] 1,6-dihydroxy-3,7-dimethoxyxanthone,[25] 1,7-dihydroxyxanthone,[26] 1,6-dihydroxy-5-methoxyxanthone,[27] 1,6,7-trihydroxyxanthone,[28] 1,3,6,7-tetrahydroxyxanthone,[29] 3,4,5-trihydroxyxanthone,[30] 1,5-dihydroxy-6-methoxyxanthone,[30] 1,2,7-trihydroxyxanthone,[31] isoathyriol,[32] and α-tocospiro A.[33]

Gargarcilone A (1) was obtained as yellow crystals. Based on the peak observed by HRESIMS at *m/z* 481.2240 $[M - H]^-$ (calcd 481.2232), the molecular formula of 1 was determined as

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Notes

The authors declare no competing financial interest.

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