

Article

Xanthenes with Potential Anti-Inflammatory and Anti-HIV Effects from the Stems and Leaves of *Cratoxylum cochinchinense*

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Abstract: Four new xanthenes, cratocochinones A–D (1–4), together with eight known analogues (5–12), were isolated from the stems and leaves of *Cratoxylum cochinchinense*. The chemical structures of cratocochinones A–D (1–4) were elucidated by comprehensive spectroscopic analyses and the known compounds were identified by comparisons with the spectral data reported in the literature. All isolated compounds 1–12 were evaluated for their anti-inflammatory activities and anti-HIV-1 activities. Compounds 1–12 showed remarkable inhibitory activities on nitric oxide (NO) production induced by lipopolysaccharide in mouse macrophage RAW 264.7 cells in vitro, with IC₅₀ values in the range of 0.86 ± 0.05 to 18.36 ± 0.21 μM. Meanwhile, compounds 1–12 exhibited significant anti-HIV-1 activities with EC₅₀ which ranged from 0.22 to 11.23 μM. These findings indicate that the discoveries of these xanthenes, isolated from the stems and leaves of *C. cochinchinense*, showing significant anti-inflammatory and anti-HIV-1 effects could be of great importance to the research and development of new natural anti-inflammatory and anti-HIV agents.

Keywords: *Cratoxylum cochinchinense*; xanthenes; cratocochinones A–D (1–4); anti-inflammatory effects; anti-HIV-1 effects



Citation: Zhang, Y.; Guo, J.-M.; Zhang, M.-M.; Wang, R.; Liang, C.-H.; Zhao, Y.-M.; Deng, Y.-Y.; Liu, Y.-P.; Fu, Y.-H. Xanthenes with Potential Anti-Inflammatory and Anti-HIV Effects from the Stems and Leaves of *Cratoxylum cochinchinense*. *Molecules* **2023**, *28*, 6050. <https://doi.org/10.3390/molecules28166050>

Academic Editor: Kemal Husnu Can Baser

Received: 4 July 2023

Revised: 31 July 2023

Accepted: 9 August 2023

Published: 14 August 2023



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1. Introduction

The genus *Cratoxylum* belonging to the Hypericaceae family consists of approximately six species, which are distributed in India, Myanmar, Thailand, through the Indo-China Peninsula, the south of China to Malaysia, Indonesia, and the Philippines, all in the south of 24 degrees north latitude. There are two species and one subspecies in China, mainly growing in Guangdong, Guangxi, and Yunnan provinces or regions [1]. Previous chemical investigations on the plants from the genus *Cratoxylum* have caused the isolation and identification of a variety of natural products including xanthenes [2–15], triterpenoids [2], tocotrienols [2], bisanthraquinones [3], phloroglucinol benzophenones [15], and anthraquinobenzophenones [3], which display various biological activities, such as anti-tumor [3,6,8–10,14], anti-inflammatory [10,15], anti-bacterial [8,12], anti-oxidant [7,12], anti-malarial [6,9], anti-HIV [4], α-glucosidase inhibitory [15], vascular protective [7], retinoid X receptor-α transcriptional [11], protein tyrosine phosphatase 1B inhibitory [13], and NF-κB inhibitory activities [10]. Among the genus *Cratoxylum*, *C. cochinchinense* (Lour.) Blume, a deciduous shrub or tree, is widely distributed in Hainan, Guangdong, Yunnan, and Guangxi provinces or regions in Southern China. The roots, barks, and tender leaves of

new xanthenes 1–4 is not only a further addition to diverse and highly aromatic array of xanthenes, but also, their presence as characteristic markers might be helpful in chemotaxonomical classifications. All isolated xanthenes 1–12 were also investigated for their anti-inflammatory effects and anti-HIV-1 activities, and were proven to be very powerful. In particular, among these isolated compounds, compounds 1–3 and 11 displayed stronger inhibitory effects against NO production with IC_{50} values ranging from 0.86 ± 0.05 to $3.16 \pm 0.18 \mu\text{M}$, which were below that of hydrocortisone. These remarkable inhibitory activities against nitric oxide (NO) production of xanthenes 1–12 might be used as an explanation of the folk applications of the stems and leaves of *C. cochinchinense*, which are applied as an anti-inflammatory ethnic drug in China. These findings also indicate that these isolated xanthenes, isolated from the stems and leaves of *C. cochinchinense* with notable inhibitory activities on nitric oxide (NO) production and anti-HIV-1 effects, could be used for the research and development of new anti-inflammatory and anti-HIV agents.

Supplementary Materials: The following supplementary materials can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules28166050/s1>. Anti-inflammatory bioassays, anti-HIV-1 activity bioassays as well as 1D and 2D NMR spectra of new compounds 1–4 are available online as Supplementary Materials.

Author Contributions: The list authors contributed to this work as follows: Y.Z., J.-M.G., M.-M.Z., R.W., C.-H.L., Y.-M.Z. and Y.-Y.D. performed the isolation, structure elucidation of the chemical constituents and the bioassay experiments; Y.-P.L. and Y.-H.F. wrote this manuscript; and the entire research was performed based on the planning of Y.-P.L. and Y.-H.F. All authors have read and agreed to the published version of the manuscript.

Funding: This work was financially supported by the Hainan Province Science and Technology Special Fund (No. ZDYF2022SHFZ028), the Hainan Provincial Natural Science Foundation of China (Nos. 222RC655), the National Natural Science Foundation of China (Nos. 21967008, 22067005 and 32070390), and the Key Research and Development Project of Haikou City (Nos. 2020054 and 2017050).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article or its Supplementary Materials.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of all isolated compounds 1–12 are available from the authors.

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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, antiamebic, 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.^{3,4} Natural products or their derivatives account for almost one-third of the world's best-selling medications.⁵

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.^{6,7}

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.^{8–11} 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.^{12,13} 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.¹³ The flowers range in colour from white to pink to scarlet. The ellipsoid fruits have three valves and the woods are employed for furniture.¹³ *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.^{14,15} Furthermore, the young leaf has been utilized as a herbal tea alternative and the immature fruit as a cooking spice.¹⁶

Received: March 10, 2023; Editorial Acceptance: July 25, 2023

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