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A new bisanthraquinone and cytotoxic xanthones from *Cratoxylum cochinchinense*

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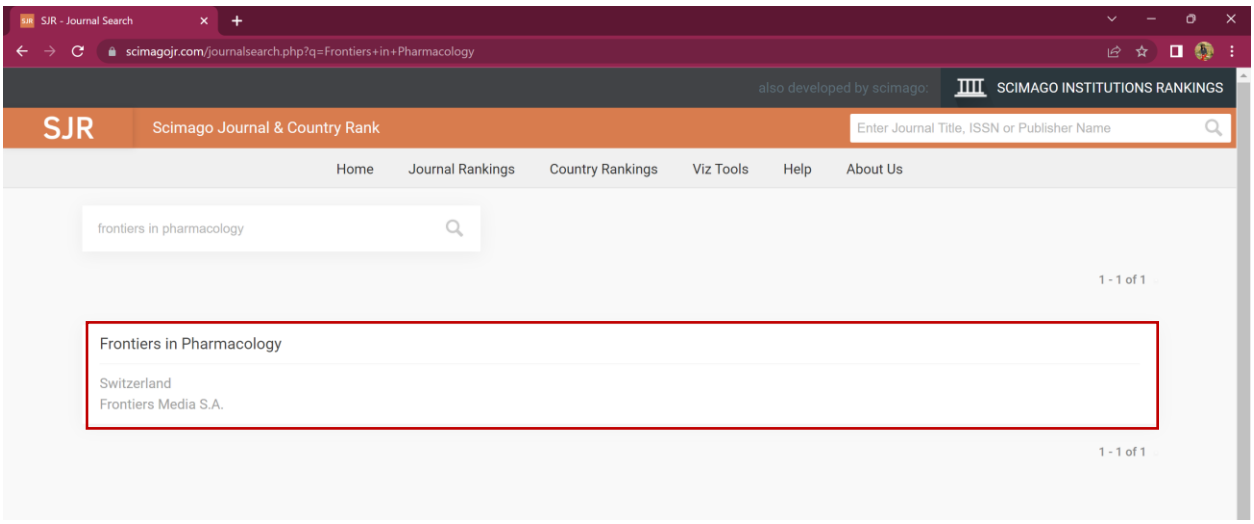

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Cratoxylumxanthone C, a natural xanthone, inhibits lung cancer proliferation and metastasis by regulating STAT3 and FAK signal pathways

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To discover phytochemicals as lead compounds for cancer treatment, cratoxylumxanthone C, a natural xanthone, was obtained from *Cratoxylum cochinchinense* (Lour.) Bl., for which there have been no reports on the biological effects against cancer. Our study revealed that cratoxylumxanthone C had significant anti-tumor activity by inducing apoptosis, augmenting cellular reactive oxygen species (ROS), and arresting cell circle. The mechanistic examination showed the inhibition of A549 cell proliferation and metastasis by cratoxylumxanthone C was coupled with the signal transducer and activator of transcription 3 (STAT3) and focal adhesion kinase (FAK) signaling pathways. Furthermore, the zebrafish models confirmed its significant *in vivo* anti-tumor activity, in which cratoxylumxanthone C inhibited tumor proliferation and metastasis and suppressed the angiogenesis. Comprehensively, these cellular and zebrafish experiments implied that cratoxylumxanthone C may have the potential to become an anti-tumor agent for lung cancer, especially non-small cell lung cancer (NSCLC).

KEYWORDS

cratoxylumxanthone C, anti-tumor, stat3, FAK, natural xanthone, zebrafish

Introduction

Lung cancer, accounting for about 11.4% of all cancers, is a common malignant tumor all over the world (Sung et al., 2021). Lung cancer can be divided into two categories, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) according to different growth and diffusion modes (Lemjabbar-Alaoui et al., 2015). NSCLC accounts for over 80% of lung cancers and is the most common and deadly form of primary lung cancer (Singh et al., 2021). Currently, surgery, radiotherapy, and chemotherapy have been

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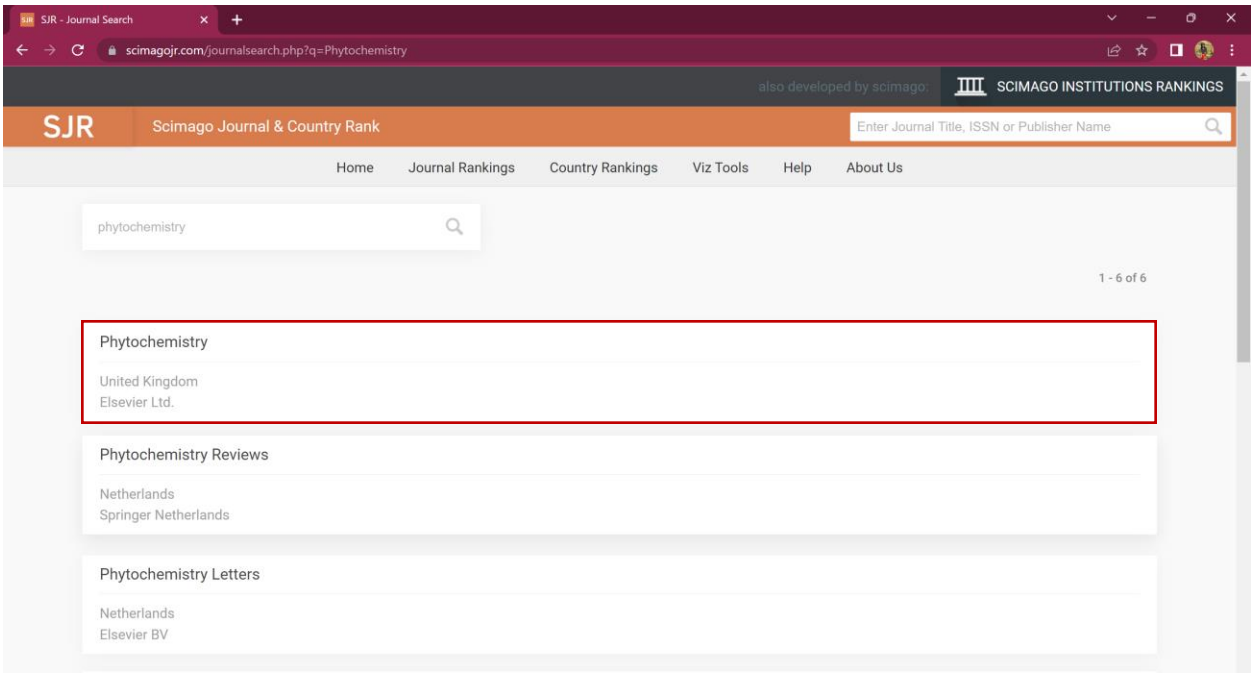

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Review of lignans from 2019 to 2021: Newly reported compounds, diverse activities, structure-activity relationships and clinical applications

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ABSTRACT

Lignans, with various biological activities, such as antitumor, antioxidant, antibacterial, and antiviral activities, are widely distributed in nature and mainly exist in the xylem of plants. In this paper, we summarized the structures and bioactivities of lignans reported in recent years (2019–2021) from five parts, including (1) a summary and classification of newly reported compounds; (2) the pharmacological activities of lignans; (3) molecular resources and activity distribution; (4) the structure-activity relationships; and (5) the clinical application of lignans. This review covers all undescribed compounds that were reported within the covered period of time and all bioactivity data about previously isolated lignans. The distribution of lignans in different plants and families is visualized, which improves the efficiency of searching for specific molecules. The diverse activities of different types of lignans provide an important reference for the rapid screening of these compounds. Discussion about the structure-activity relationships of lignans provides a direction for the structural modification of skeleton molecules. Combined with the clinical application of such molecules, this work will provide a valuable reference for pharmaceutical chemists.

1. Introduction

Lignans, natural compounds polymerized by two phenylpropanoid (C_6–C_3) derivatives in different ways, mostly exist as dimers, while a few exist as trimers and tetramers. In nature, they are mostly free, and a few are glycosides. It is well known that phenylpropane dimers are classified as lignans or neolignans based on the presence or absence of the 8,8′-bond between phenylpropanoid monomers. Lignans, formed by different polymerization positions and modes of dehydration condensation of oxygen-containing groups of side chains, can be divided into "norlignans" and "polymeric lignans". Lignans, a large group of specialized metabolites with a long study history, widely exist in nature. Lignans have received considerable attention from both chemists and pharmacologists over the past few decades because of their intriguing structures and potent biological activity, which is exemplified by their antitumor and anti-inflammatory activities. These structural motifs also serve as an important starting point in the development of anticancer drugs (Mukhija et al., 2022). In recent reports, dietary lignans have been demonstrated to regulate intestinal flora and metabolites by targeting the NF-kappa B pathway (Li et al., 2022). Some reviews have summarized the structural diversity and biosynthesis of active dibenzylbutyrolactone, furofuran and diarylbutane lignans (Mori, 2018; Solyomvary et al., 2017). Notably, in 2015, Lau et al. discovered six enzymes from mayapple that complete the biosynthetic pathway to the etoposide aglycone and published in *Science*, which is a milestone in the study of lignans (Lau and Sattely, 2015). In 2019, Zalesak et al. reviewed 413 lignans and neolignans isolated between 2016 and 2018, covering their source, structure elucidation, and bioactivity (Zalesak et al., 2019).

In recent years, originative and more selective extraction technologies combined with more sensitive separation and identification technologies have greatly enriched the amounts of such natural products. Thus, approximately 356 previously undescribed lignans have been

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REVIEW ARTICLE

Genus *Morinda*: An insight to its ethnopharmacology, phytochemistry, pharmacology and Industrial Applications

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Abstract *Background of the study:* The genus *Morinda* of the Madder family, (Rubiaceae) has been widely documented in traditional medicine due to its therapeutic properties and also, contributed a great deal in chemical industry. Different parts of *Morinda* species have traditionally been used to treat malaria, diabetes, memory loss, cancer, inflammation, skin infections, and typhoid fever.

Aim and Objectives: The review provide a critical and innovative information on the traditional uses, phytochemical constituents, and industrial applications of the genus *Morinda*. This will help researchers understand future research trends by bridging the gap between documented literature and contemporary uses.

Methodology: All the systematic literature data or information on the genus *Morinda* was collected via selected electronic databases, including Scopus, PubMed, Web of Science, Springer, Medline, ChemSpider, Taylor and Francis, Google Scholar, SciFinder, ScienceDirect and Wiley. Relevant book chapters, Wikipedia and books were also explored.

Results: The study reveals that different parts of *Morinda* plants have been extensively used for folkloric therapeutic purposes and are a plethora of mineral or nutritional benefits and secondary metabolites. Several classes of bioactive compounds have been elucidated from *Morinda* plants via spectroscopic and chromatographic phytochemical analyses. Compounds such as terpenoids, glycosides, anthraquinones, polyphenols, steroids, saponins and reducing sugars are among the bioactive

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