ChemistrySelect

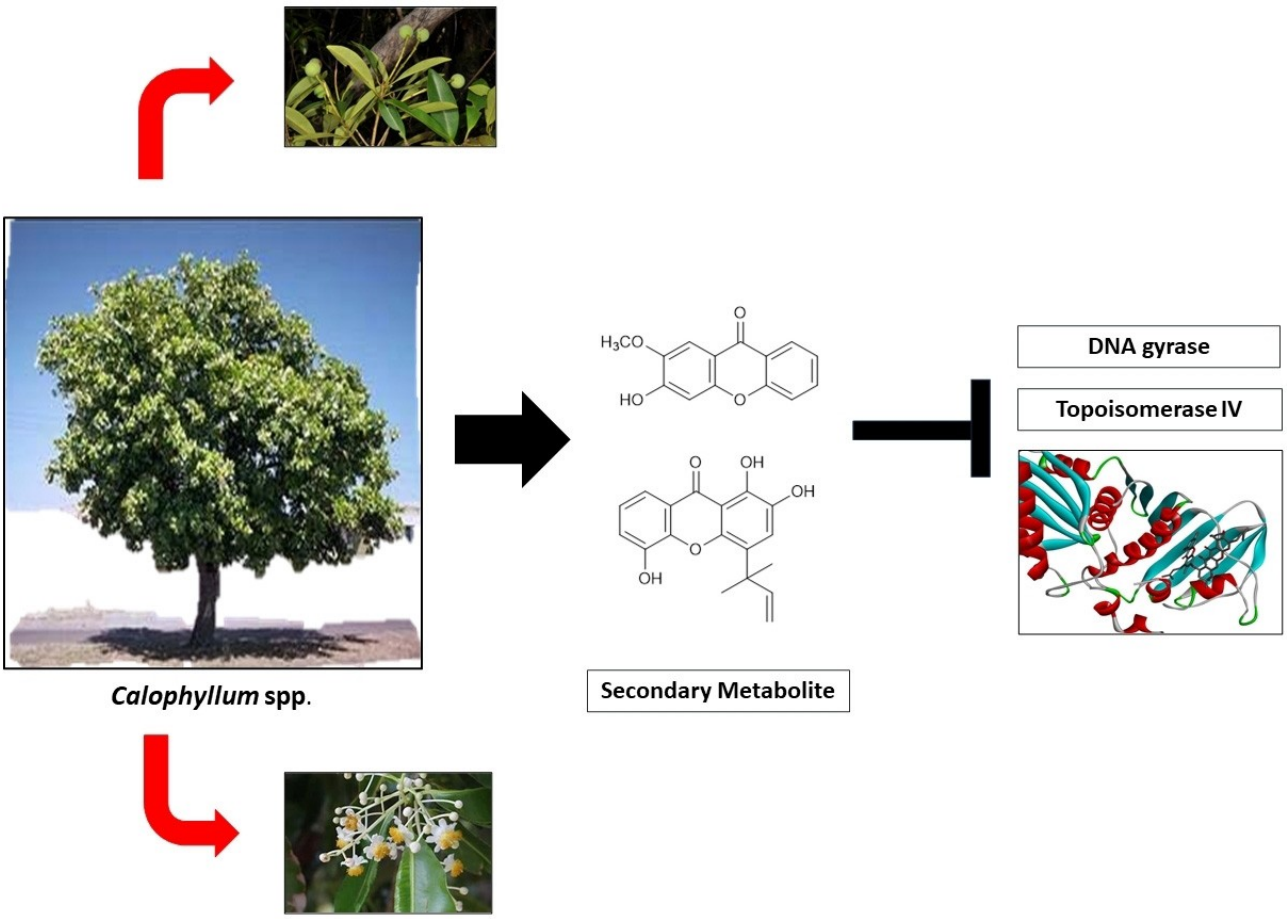
Review
doi.org/10.1002/slct.202302737

Chemistry Europe
European Chemical Societies Publishing

www.chemistryselect.org

Unlocking the Antibacterial Potential of Xanthone from Calophyllum Species: Inhibition of Nucleic Acid Synthesis

Dayang Nurul Anisa Abang Heilman,[a] Audrey Yong Chee Hui,[b] Vivien Jong Yi Mian,[c] Fasihuddin Badruddin Ahmad,[a] Lim Pei Cee,[b] Johnson Stanslas,[d] and Nor Hisam Zamakshshari*[a]



© 2023 Wiley-VCH GmbH

Plants are valuable resources for the development of novel pharmaceutical products. The increasing threat to global health caused by antibiotic resistance remains a serious concern, driven a need to discover and evaluate novel anti-bacterial agents. *Calophyllum* species are known for having excellent biological activity due to its secondary metabolites, such as xanthone. Numerous xanthones have been found to possess anti-bacterial properties that are effective against plant pathogens, hence can be applied to fight human pathogens. Topoisomerase enzymes (DNA gyrase and topoisomerase IV) are DNA metabolism enzymes that possess distinct roles as unlinking enzymes during DNA replication. Nucleic acid synthesis inhibition reduces bacteria proliferation through the inhibition of topoisomerase enzymes that are essential for bacterial growth. The xanthone isolated from *Calophyllum* and its anti-bacterial were discussed in this review. Besides, molecular docking simulations were applied to explore the potential binding mode of xanthones to DNA metabolism enzymes. The docking study displayed that biscaloxanthone is a good topoisomerase enzymes inhibitor compared to their co-cystalize ligand, novobiocin and BDBM50198240. The complied information and molecular docking simulations suggested that xanthone isolated possesses potential anti-bacterial agents inhibiting nucleic acid synthesis. Besides, it suggested that the anti-microbial activity of xanthone contributes from the topoisomerase enzyme's inhibition.

1. Introduction

The increasing threat to global health caused by antibiotic resistance remains a serious concern and has driven a need to discover and evaluate novel anti-bacterial agents. People have utilized plants to treat and cure illnesses since the beginning of civilization.[1] The significance of some genus, such as *Calophyllum*, has increased given that it has been proven to be a potential source of lead compounds for discovering and developing new drugs. This genus has been used in old folk medicine to treat peptic ulcers, blood pressure, pain, and inflammation.[2] The scientific study of the genus *Calophyllum* revealed that it is a rich source of bioactive secondary metabolite.[3] The genus *Calophyllum* belongs to the *Calophyllaceae* family, where the plants are widely renowned for being abundant in secondary metabolites such as xanthones. Xanthones, one of the most significant compounds in natural product chemistry, have gradually risen to great importance due to their medicinal properties. Xanthones, polyphenolic compounds, are one of the most important classes in natural products as they exhibit a variety of pharmacological and health benefits. Several studies have shown that xanthones isolated from *Calophyllum* possess a broad spectrum of interesting biological properties, such as anti-cancer, anti-viral, anti-oxidant, anti-inflammatory, anti-fungal, anti-allergy and anti-bacterial activities.

Nucleic acid synthesis inhibition is one of the targeted strategies by inferring the anti-bacterial mechanism and thus reduces bacteria proliferation.[4] The nucleic acid synthesis inhibition could be done through the inhibition of the topoisomerase enzyme. The topoisomerase enzymes are DNA gyrase and topoisomerase IV. Both enzymes are essential for bacterial growth.[5] DNA gyrase is used to relax supercoiled DNA in the DNA replication process.[6] At the same time, topoisomerase IV is used for chromosome decatenation during DNA replication.[7] Gyrase and topoisomerase IV have similarities in their conserved active sites, subunit organization, and antibiotic sensitivity to a small molecule inhibitor such as coumarins and quinolones. These similarities suggest that a small-molecule inhibitor of active sites would be an excellent strategy to inhibit these two enzymes, thus increasing the anti-bacterial activity.[8]

In recent years, in silico methods such as molecular docking has been frequently applied at the early stages of the drug design process.[9] Molecular docking is a computational strategy involving the implementation of a search algorithm, which generates plausible ligand-target structures and a scoring function. This parameter calculates the binding energies between the ligand and therapeutic target to identify which plausible complex structures are of most interest.[10] There are several molecular docking software available such as AutoDock, DOCK, FlexX, and GOLD; the difference between these softwares is the algorithm embedded inside the packages.[11] Once the ligand conformation is predicted, the confirmation will be scored and evaluated. The high binding energies score will indicate that the ligand has a strong interaction with the therapeutic target.[12]

Owing to the importance of the genus and good biological activity of xanthone, this review compiled and discussed the xanthone derivatives isolated from the *Calophyllum* and their anti-bacterial activities. Additionally, molecular modeling simulations were applied to explore the potential binding mode of xanthone to two important therapeutic targets: DNA gyrase enzyme and topoisomerase IV.

2. Xanthone from *Calophyllum* species

The name xanthones designate a group of secondary metabolites usually obtained in a restricted assembly of higher plants, fungi and lichens. The word "xanthone" comes from the word

[a] *D. N. A. A. Heilman, F. B. Ahmad, N. H. Zamakshshari*
Faculty of Resource Science and Technology, Universiti Malaysia Sarawak 94300 Kota Samarahan, Sarawak, Malaysia
E-mail: znhisam@unimas.my
[b] *A. Y. C. Hui, L. P. Cee*
Faculty of Pharmacy, MAHSA University, Jln SP 2, Bandar Saujana Putra, 42610 Jenjarom, Selangor, Malaysia
[c] *V. J. Y. Mian*
Faculty of Applied Sciences, Universiti Teknologi MARA, Samarahan Campus 2, 94300 Kota Samarahan, Sarawak, Malaysia
[d] *J. Stanslas*
Pharmacotherapeutics Unit, Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia
Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202302737

© 2023 Wiley-VCH GmbH