

A Review of the Ethnomedicinal, Phytochemical, and Anticancer Properties of *Melicope* Species

Idris Adewale Ahmed,^[a] Md. Sanower Hossain,^[b] Lim Pei Cee,^[c] and Nor Hisam Zamakshsharia^{*[d]}

The genus *Melicope*, which consists of 230 species, stands out as the largest genus within the Rutaceae family. *Melicope* species are characterized by their evergreen nature and can range from shrubs to predominantly dioecious trees. The *Melicope* species have been utilized in traditional medicine to address a wide range of ailments, including fever, colds, cramps, and inflammation. These plants have gained significant attention due to their noteworthy ethnopharmacological and ethnomedicinal significance. Researchers have isolated numerous biologically active secondary metabolites from different *Melicope* species, which include polymethoxylated flavonoids, furanocoumarins, acetophenones, benzenoids, and quinolone alkaloids. These compounds exhibit diverse biological activities,

such as antibacterial, antidiabetic, antifungal, and antiproliferative properties against human cancer cell lines. This review provides an update on the chemical constituents of the selected species of *Melicope*. The study also highlights the anticancer and cytotoxicity properties of the plant extracts and phytochemical constituents from *Melicope* species. Furthermore, the molecular mechanisms underlying the anticancer effects are elucidated. Overall, this review contributes to understanding the significant pharmacological potential of *Melicope* species and unlocking their chemical composition, emphasizing their relevance in the development of therapeutic agents, particularly in the field of cancer research.

1. Introduction

The genus *Melicope* belongs to the family Rutaceae. This family comprises about 160 genera and 1650 species.^[1] *Melicope* is derived from Greek, meaning “a division of honey,” referring to the bottom of the ovary glands.^[2] It is the largest genus in the *Rutaceae* family, with about 230 species, due to its close relationship with the genera *Tetradium* Lour. and *Euodia* J. R. Forst, where in some cases, they are synonyms.^[3] They are widely distributed in Asia, Australia, the Indian Ocean Islands, Madagascar, and the Pacific Islands.^[4] The species in the genus are evergreen and vary from shrubs to mostly dioecious trees. Depending on the species, the leaves are trifoliolate or unifoliolate, with dry to fleshy fruits.^[5] The flowers are bisexual or unisexual, and the number of stamens can be the same or twice that of the petal. The shiny and smooth seeds remain attached to dehiscent fruit.^[6] *Melicope* species are notable for their ethnopharmacological activities and have been traditionally used for

various ailments. This species has been used to treat fever, colds, cramps, and inflammation.^[7,8] The activity is because *Melicope* species produce many biologically active secondary metabolites, including polymethoxylated flavonoids, furanocoumarins, acetophenones, and quinolone alkaloids.^[9–11] These secondary metabolites possessed biological activities such as antibacterial, antidiabetic, antifungal, and antiproliferative toward human cancer cell lines.^[12–13]

Cancer is one of the leading causes of death worldwide, accounting for nearly 10 million deaths in 2020.^[14] There is an urgent need to find an anticancer drug to combat this disease. Around half of the medicines in clinical use are from natural products.^[15–17] The exorbitant costs, safety issues, and adverse side effects of most synthetic medications have made compounds from natural products with minimal toxicity more acceptable and popular as potential drug candidates.^[18–21] Additionally, religious scripts have long referenced the importance of plants in treating diverse ailments, which has prompted increased scientific interest in evaluating the veracity of traditional medicinal claims.^[22–24] As a result, identifying natural sources of safer alternatives to conventional chemotherapeutic drugs has become a critical and worthwhile area of research. Therefore, this review examines and presents the potential of the *Melicope* genus as an anticancer lead agent. The mechanisms of the anticancer activities of reported isolated compounds at the molecular level were also postulated.

[a] Dr. I. Adewale Ahmed
Department of Biotechnology, Faculty of Applied Science, Lincoln University College, 47301, Petaling Jaya, Selangor, Malaysia

[b] Dr. Md. S. Hossain
Centre for Sustainability of Mineral and Resource Recovery Technology (Pusat SMarRT), University Malaysia Pahang Al-Sultan Abdullah, Kuantan 26300, Malaysia

[c] Dr. L. Pei Cee
Department of Medicinal Chemistry, Faculty of Pharmacy, MAHSA University, 42610 Jenjarom, Selangor, Malaysia

[d] Dr. N. Hisam Zamakshsharia
Department of Chemistry, Faculty of Resource Science and Technology, University Malaysia Sarawak, 94300, Kota Samarahan Sarawak, Malaysia
E-mail: znhisam@unimas.my