REVIEW:

STUDY ON BENZOPYRANS AND OTHER ISOLATED COMPOUNDS FROM MALLOTUS APELTA

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SUMMARY

During the last decades, dozens of compounds have been isolated from Mallotus apelta. These compounds which are classified under the categories viz. terpenoids, steroids, flavonoids, cumarino-lignoids, cembrane diterpenoids, and benzopyranoids. They were known to exhibit interesting biological activities. The phytochemical investigations revealed that malloapelta B which was the major component of M. apelta, showed strong NF-κB and NFAT transcription factor inhibitory and cytotoxic activities. Numerous studies on the synthesis of some derivatives of malloapelta B were carried out. This paper reviews the progress on the isolation, structure elucidation and biological activities of secondary metabolites from M. apelta, especially, the new structures of benzopyrans. Chemical modifications of malloapelta B and structure-activity relationship were also discussed.

Keywords: Mallotus, mallotus apelta, benzopyran, malloapelta b.

I - INTRODUCTION

Ba bet (Mallotus) genus comprises about 140 species, distributed in regions from South to South-East Asia, such as in Malaysian region (about 75 species), in China (about 40 species) and in Vietnam (about 40 species) [1]. Mallotus species have been used in traditional medicine to treat various diseases. For example Mallotus apelta has been used to treat chronic hepatitis, hepatalgia, enteritis, diarrhea, lymphopathy, Mallotus repandus has been used to treat influenza and fever, Mallotus barbatus has been used in both Vietnamese and Chinese folk medicine as antipyretic, diuretic, relieving pain and curing cholera, Mallotus macrostachyus has been used to treat wounds and pimple, Mallotus paniculatus has been used to treat traumatic injuries and swelling [2, 3]. To improve the efficiency of using Mallotus species in traditional medicine, it is neccesary to know their chemical components and pharmaceutical activity. However, herbal medicine and its extracts contain hundreds of unknown components, which are often only present in a low amount. Moreover, variability usually exists within the same herbal materials [4, 5]. The chemical components may vary depending on harvest seasons, plant origins, drying processes and other factors [6]. Therefore, investigation on the chemical components of the plant is important for pharmaceutical studies. Since the
last decades the scientists have been searching for the chemical components, pharmaceutical activity of *Mallotus* species and synthesizing derivatives from isolated compounds from these species. The purpose of this review is to present an overview of the studies on *M. apelta* including the isolation and structure elucidation of bioactive compounds, chemical modifications and synthetic processes.

**II - PHYTOCHEMISTRY**

The chemistry of *M. apelta* has been widely examined and the biological activity investigations were carried out from all over of the world. The efforts have led to the isolation of a number of physiologically active compounds viz. terpenoids, steroids, flavonoids, cumarino-lignoids, cembrane diterpenoids, benzopyranoids. We are actively working on the synthesis of some new derivatives of malloapelta B, a major component of *M. apelta*, with an aim to find new derivatives having stronger bioactivity. Various compounds isolated from *M. apelta* in different areas have been classified under the categories terpenoids, steroids, flavonoids, cumarino-lignoids, cembrane diterpenoids, benzopyranoids and miscellaneous compounds as listed in figures 1-5.

![Figure 1: Terpenoids and steroids isolated from *M. apelta*](image-url)
Terpenoids and steroids

The phytochemistry of *M. apelta* has been extensively studied since the early 1980s. One of the earlier phytochemical reports was published in 1985, it described the isolation of four triterpenes 3β, 29-dihydroxylupane (1), erythrodiol-3-acetate (7), acetylursolic acid (8) and β-sitosterol (9) from the roots of this plant [7]. This plant also contains a variety of other pentacyclic terpenoids. Based on the spectral and chemical evidence, their structures were determined to be hennadiol (3), friedelin (4), friedelanol (5), epifriedelanol (6), taraxerone (12), and epitaraxerol (13) [14, 16] and a new pentacyclic triptene, named malloapelta A (2) [15, 16, 19]. From the methanol extract of *M. apelta*, daucosterol (10), stigmasterol (11), and ergosterol (14) were isolated and purified using column chromatography over silica gel [19].

Flavonoids

Two flavonoids quercitrin (15) and astilbin (16) were identified from *M. apelta* collected in Vietnam [19].

Cumarino-lignoids

A method for the isolation and purification of three coumarino-lignoids aquillochin (17), cleomiscosin A (18) and 5’-demethylaquillochin (19) from *M. apelta* has been reported by Cheng et al [12].

Cembrane diterpenoids

Recently, several cembrane diterpenoids 10-hydroxycembrene-5-one (20), 6-hydroxycembrene-5,10-dione (21) [9] 10,14-Dihydroxy-5-isopropenyl-2,8,12-trimethylcyclotetradeca-2,8,12-trienone (22) [10,11] have been isolated from *M. apelta*.

![Figure 2: Flavonoids isolated from *M. apelta*](image)

![Figure 3: Cumarino-lignoids and cembrane diterpenoids isolated from *M. apelta*](image)
**Benzopyranoids**

In 2001, An et al have isolated seven benzopyran derivatives 4-hydroxy-2,6-dimethyl-6-(3,7-dimethyl-2,6-octadienyl)-8-(3-methyl-2-butenyl)-2H-1-benzopyran-5,7(3H,6H)-dione (23), 4-hydroxy-2,6,8-trimethyl-6-(3,7-dimethyl-2,6-octadienyl)-2H-1-benzopyran-5,7(3H,6H)-dione (24), 5-hydroxy-2,8-dimethyl-6-(3-methyl-2-butenyl)-8-(3,7-dimethyl-2,6-octadienyl)-2H-1-benzopyran-4,7(3H,8H)-dione (25), 5-hydroxy-2,8,6-trimethyl-8-(3,7-dimethyl-2,6-octadienyl)-2H-1-benzopyran-4,7-(3H,8H)-dione (26), 2,3-dihydro-5,7-dihydroxy-2,6-dimethyl-8-(3-methyl-2-butenyl)-4H-1-benzopyran-4-one (27), 2,3-dihydro-5,7-dihydroxy-2,8-dimethyl-6-(3-methyl-2-butenyl)-4H-1-benzopyran-4-one (28), and 2,3-dihydro-5,7-dihydroxy-2,6,8-trimethyl-4H-1-benzopyran-4-one (29) from the leaves of *M. apelta* [13].

Figure 4: Benzopyranoids isolated from *M. apelta*

In recent years, a number of biologically active secondary metabolites have been isolated from *M. apelta* which is widely distributed in the northern areas of Vietnam. From the methanol extract of the *M. apelta*, a new chromene derivative with benzopyran skeleton was isolated and identified as 1-(5,7-dimethoxy-2,2-dimethyl-2H-chromen-8-yl)-but-2-en-1-one or malloapelta B (30) with high yield. Different chromatographic techniques were applied to purify compounds 8-(1'-oxo-3'(R)-hydroxybutyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-
benzopyran (31), 8-(acetic acid 1’-oxo-3’(R)-hydroxy-butyl ester)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (32); 6-(1’-oxo-2’-en-butyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (33), 6-[1’-oxo-3’(R)-hydroxybutyl]-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (34), 6-[1’-oxo-3’(R)-methoxybutyl]-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (35), and 6-(1’-oxo-2’-3’-epoxybutyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (36) from the leaves of *M. apelta* which were named as malloapelta C, D, E, F, G, and H, respectively [17, 18]. These compounds were evaluated their NF-κB inhibitory, NFAT transcription factor inhibitory and cytotoxic activities (The cytotoxic assay was evaluated on two cancer cell lines (Human hepatocellular carcinoma, Hep-G2) and rhabdosarcoma, RD). Interestingly, malloapelta B showed strong NF-κB inhibitory activity, NFAT transcription factor inhibitory and cytotoxic activities (The cytotoxic assay was evaluated on two cancer cell lines (Human hepatocellular carcinoma, Hep-G2) and rhabdosarcoma, RD). The other compounds showed significant cytotoxic activities against the two mentioned human cancer cell lines [17, 18].

**Miscellaneous compounds**

Recently, the Chinese scientists carried out an extensive screening for effective anti-HIV natural products. Notably, the extract of the roots of *M. apelta* showed significant activity [8]. Based on the bioassay guided fractionation, malloapeltine (37), 4-methoxy-3-cyano-pyridine 1-oxide (38), along with 4,5,4’-trimethyl-ellagic acid (39) were purified from the roots of this plant [9]. These compounds were evaluated for their anti-HIV activity, among them 37 demonstrated a significant inhibitory activity [9]. The following phytochemical examination of the *M. apelta* by Cheng et al led to the isolation of two compounds named as 2α,4β,15,16-tetrahydroxydolabrand (40), malloapeltin (37) [10,11]. By repeated chromatography on silicagel column, isopimpinellin (41), α-tocopherol (42), trans-phytol (43), squalene (44) β-carotene (45), lutein (46), and betulaprenol 10 (47) were isolated from the methanol extract of this plant which were identified by comparison with the spectral data reported in the literatures [15, 16, 19].

![Figure 5: Other compounds isolated from *M. apelta*](image-url)
III - CHEMICAL MODIFICATIONS AND SYNTHESSES

To investigate the relationship between the structure and their bioactivity as well as to find new derivatives having stronger effect, Binh et al synthesized the derivatives of malloapelta B by using electro organic synthetic method (see scheme 1). As a result, a new compound named as bimalloapelta (48) and a known compound 8-[1’-oxo-3’(R)-methoxy-butyl]-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (49) were afforded (see scheme 2) [22, 23].

Scheme 1: Modifications of malloapelta B to produce 48 [22]

Scheme 2: Modifications of malloapelta B to produce 49 [23]

Scheme 3: Modifications of malloapelta B to produce 49 - 52 [25]

Scheme 4: Modification of malloapelta B to produce 53 [25]
As part of our ongoing studies to look for new derivatives having stronger bioactivities, nine benzopyrans 8-[1'-oxo-3'(R)-methoxy-butyl]-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (49), 8-[1'-oxo-3'(R)-ethoxy-butyl]-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (50), 8-[1'-oxo-3'(R)-propoxy-butyl]-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (51), 8-[1'-oxo-3'(R)-isopropoxy-butyl]-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (52), 8-[1'-oxo-2'-en-butyl]-5,7-dimethoxy-3-nitro-2,2-dimethyl-2H-1-benzopyran (53), 8-[1'-oxo-3'(R)-methyl-4'-acetyl-5'-oxo-hexyl]-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (54), 8-(1'-oxo-3'(R)-methyl-4'(S/R)-(methylformiate)-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (55), 8-(1'-oxo-3'(R)-methyl-4'(S/R)-(ethylformiate)-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (56), and 1-(5,7-dimethoxy-2,2-dimethyl-2H-chromen-8-yl)butan-1-one (57) were synthesized by addition, nitration and Michael reactions from malloapelta B [24, 25, 26].

Scheme 5: Modifications of malloapelta B to produce 54 - 56 [24]

Scheme 6: Modifications of malloapelta B to produce 57 - 63 [26]