Biological Characteristics of Micheliolide and Its Neuroprotective / Anti-inflammatory Activity

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Abstract: Sesquiterpene lactones (SLs) isolated from natural medicinal plants have been traditionally used to treat numerous dis-eases, especially chronic inflammatory diseases in folk medicine. Dietary vegetables, such as lettuce and chicory are also important sources of SLs in daily life. Micheliolide (MCL) is a recently discovered SL from Compositae plants. MCL can also be semi-synthesized from parthenolide, and undergo a biological, chemical transformation to dimethylamino micheliolide (DMAMCL) and ACT001 for higher bioavailability and better biological function. Systematic pharmaco-kinetic researches showed that MCL and its derivatives were widely distributed in the heart, spleen, lung, kidney, brain, stomach, duodenum, testicle, fat, marrow, and muscle within 30 min, concentration reaches peak approximately at 1 h and significantly reduces 3 h later in a majority of tissues. MCL has been shown to have a good therapeutic effect on various cancers, diabetic nephropathy, nervous system disease, bacterial infectious disease, and autoimmune disease through immune response regulation, such as inhibition of NF-κB, PI3K/AKT/mTOR and MAPK signaling pathways. MCL also showed a good blood-brain barrier permeability, and have the neuroprotective effect on stroke and Alzhei-mer's disease. Yet, the exact molecular mechanism of MCL remains unclear. Identification of relevant targets (such as pyruvate kinase muscle type 2 (PKM2)) also represents a great challenge for researchers. The biological characteristics, major biological activities, and molecular mechanisms of MCL were summarized in this review, indicating the potential clinical application for inflammatory and infectious diseases.

Keywords: Micheliolide; Sesquiterpene Lactones; Anti-cancer; Anti-inflammation; Immunoregulation

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1 Introduction

Natural plants and plant constituents have been used to treat various diseases for centuries [1]. Natural products of medicinal plants are the most common sources of drug development [2]. *Sesquiterpene lactones (SLs) represent a major terpenoid class,* which are mainly extracts or secondary derivatives from plants, including *euphorbiaceae*, *umbelliferae*, *magnoliaceae*, and *compositae*, etc. [3, 4]. SLs are also widely found in microorganisms and some insects. SLs may have a highly significant role in a balanced diet [5]. Main dietary vegetables, such as lettuce

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and chicory, could also be important sources of SLs in daily life. SLs have diverse and important biological functions and physiological activities. In folk medicine, SLs are used as the active ingredient to treat diarrhea, burns, influenza, and neurodegradative disorder [6].

A large number of SLs and their derivatives have been reported every year [7, 8]. Over 5000 SLs have been discovered so far [9, 10]. These SLs display extensive structural diversity [11]. There are four types of SLs according to the main skeleton structure: germacrolide, eudesmanolide, guaianolide, and pseudoguaianolide [12]. All four types of SLs contain representative α-methylene-γ-lactones. Figure 1 displays the four SL chemical structural types [13-15]. Guaianolide is the most widely used SLs in clinical practice [15], containing a 10-membered ring with a C-4 methyl group [16]. Artemisinin [17], thapsigargin [18] and parthenolide [19] are the best-known guaianolide SL that have been investigated in several clinical trials. Another guaianolide SL, micheliolide (MCL) has drawn increasing attention over recent years due to its extensive therapeutic properties. MCL is an active component of plants in the *Magnoliae* family. Numerous studies report MCL's therapeutic applications. This review highlighted the biological characteristics and functions of MCL and explored underlying mechanisms.

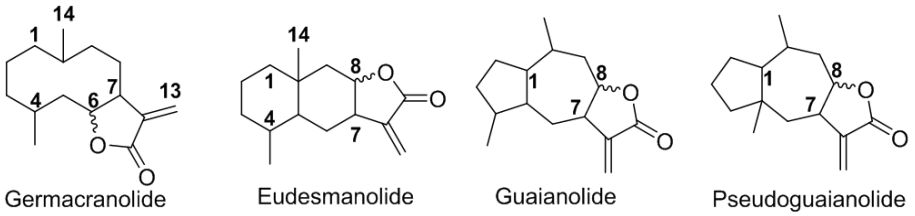

Figure 1 Type and structure of sesquiterpene lactones (SLs)

2 Biological Characteristics of MCL

2.1 The Structure and Synthesis of MCL

MCL is a typical guaianolide SL, and the molecular formula is $C_{15}H_{20}O_3$ with a molecular weight of 248.32 Da. Its systematic name is (3aR,9R,9aR,9bS)-9-hydroxy-6,9-dimethyl-3-methylene-1,3,3a,4,5,7,8,9,9a,9b-decahydro-2H-cyclopenta[e]azulen-2-one. The colorless MCL crystals formed from ethyl acetate-hexane solution and its structure were described by Acosta *et al* in 1991 [20], The two 5-membered rings are in half-chair conformation while the 7-membered ring is in a distorted-chair conformation. With the pseudomirror bisecting the double bond, the C-14 methyl group exhibits disorder between two rotamers, featuring a 7-membered ring trans-fused to the lactone. Molecules form dimers about two-fold axes through a weak hydrogen bond. The disordered H atom enables a hydroxyl group to form a bifurcated hydrogen bond with both lactone ring O atoms [20]. MCL can be extracted from the root bark of *Michelia compress* [21] and *Michelia champaca* [22]. However, drugs extracted from natural plants are often trace natural products, making semi-synthesis from abundant precursors essential. Parthenolide (PTL) is a prominent member of guaianolide SL, possessing a trans-6α,12-lactone moiety, making it a suitable precursor for the synthesis of guaianolide SL and its derivatives [23]. It has been reported that the MCL structure is similar to PTL (both consist of α-methylene-γ-lactone). The yield of MCL obtained from PTL by semi-synthesis can reach 90% [24, 25]. The synthesis process from PTL to MCL is the following (Figure 2): (1) *p*-Toluenesulfonic acid was dissolved in CH_2Cl_2 (the mixture named solution A). (2) PTL was dissolved in CH_2Cl_2 (the mixture named solution B). (3) Solution B was added drop by drop into solution A; the mixed solution was placed at 20 ℃ for 8 h. (4) After stirring the mixture at 25 ℃ for 15 h (5), the reaction was quenched with $NaHCO_3$. The organic layer was isolated and washed with saturated brine. (6) Activated carbon decolorization followed by reduced-pressure concentration gave crude MCL, recrystallized from acetone, and the purity of MCL was 90% [26].

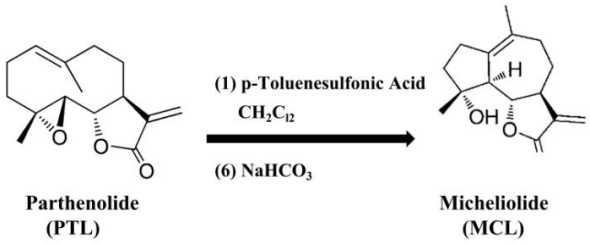

Figure 2 Structure of PTL and MCL and the semi-synthesis of MCL from PTL

2.2. Biological Chemical Transformation from MCL to DMAMCL

Due to the poor solubility of MCL crystal, Mai *et al* carried out derivatization to synthesize dimethylamino Micheliolide (DMAMCL) [27]. DMAMCL, a water-soluble dimethylamino michael adduct of MCL, has the molecular formula $C_{21}H_{31}NO_7$ (MW 409.21 Da). It has been demonstrated that the C-4 hydroxyl group of MCL might be a suitable position for structural modification. The DMAMCL synthesis process with etherification or esterification of the hydroxyl group at the C-4 position in MCL is the following (Figure 3): (1) a mixture with $Me_2NH·HCl$, K_2CO_3, and CH_2Cl_2 was stirred at room temperature (the mixture named solution C) until $Me_2NH·HCl$ dissolved; then, the solution C was immediately filtered. (2) MCL was added to solution C and stirred at 25 ℃ for 3 h. (3) The mixture was concentrated in vacuo (4) and the residue was collected. CH_2Cl_2 addition and saturated brine wash preceded isolation of the organic layer. After drying (Na_2SO_4) and concentration, DMAMCL purity reached 82% [26].

In acidic HEPES (pH<5.0), solubility decreases significantly, DMAMCL was stable, and in HEPES with pH 7.4, DMAMCL was released into MCL slowly and consistently. In mouse plasma, MCL ($t_{1/2}$ = 2.64 h) exhibits superior pharmacokinetic stability against PTL ($t_{1/2}$ = 0.34 h) [28]. Surprisingly, DMAMCL has a much longer half-life than MCL. DMAMCL releases into MCL steadily for more than 8 h with very low acute toxicity in mice [27, 29]. This structural optimization from PTL to MCL, even to DMAMCL, has prolonged the sustained concentration of the active compound. DMAMCL's enhanced properties may translate to greater therapeutic potential than MCL, and are currently being used in clinical studies for acute myelogenous leukemia (AML).

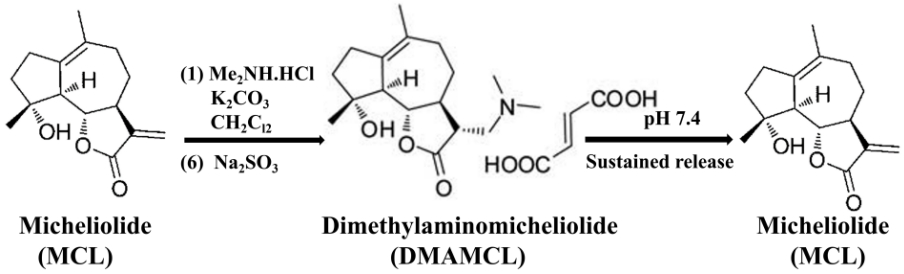

Figure 3 Chemical transformation from MCL to DMAMCL

2.3 Systematic Pharmacokinetic Research of MCL and Its Derivatives

Systematic pharmacokinetics research is essential to evaluate the efficacy and safety of natural compounds. Drug bioavailability is primarily governed by absorption and metabolism. Following single-dose i.v. administration (150 mg/kg DMAMCL aqueous solution in mice), plasma concentrations of both DMAMCL and MCL peaked rapidly before declining. The oral bioavailability of DMAMCL is 75% [29]. ACT001, the fumarate salt of DMAMCL, has the molecular formula $C_{17}H_{27}NO_3$ $C_4H_4O_4$, and its molecular weight is 409.47 Da. Xi et al. [30] characterized ACT001's rat pharmacokinetics (oral bioavailability = 50.82%), including distribution, excretion, and metabolism. After a single dose of 20 mg/kg ACT001 *i.v.* administration, the plasma concentration of ACT001 quickly reaches a peak and then gradually declines. ACT001 is absorbed into the liver and ovary within 5 min. ACT001 is widely distributed in the heart, spleen, lung, kidney, brain, stomach, duodenum, testicle, fat, marrow, and muscle within 30 min, concentration reaches peak approximately at 1 h and significantly reduces 3 h later in a majority of tissues.

Numerous SLs demonstrate blood-brain barrier permeability and some studies have proved that MCL shows the neuroprotective effect [31]. In C57BL/6 mice receiving 40 mg/kg MCL i.p., serum and brain concentrations peaked at 2 h (unpublished data).

2.4 Biological Function of MCL and Its Derivatives

The exocyclic double bond in MCL dictates its bioactivity via nucleophile-targeting reactivity [32]. It has been reported that MCL and its derivatives are used to treat many kinds of cancers, bacterial infectious diseases, and autoimmune diseases. The anti-cancer activity of MCL

and its Derivatives is further discussed in the following paragraph.

2.5 Anticancer Activity of MCL and Its Derivatives

It has been found that the methylene-butyrolactone ring is an effective group to endow some SLs with anti-cancer biological activity [33]. To date, MCL's anticancer efficacy is best characterized in leukemia. MCL reduces primary AML stem cell populations. Cancer metabolic reprogramming (e.g., Warburg effect) requires PKM2, the pace-limiting glycolytic kinase [34], in which pyruvate kinase M2 (PKM2), the last pace-limiting kinase of glycolysis, has a critical role. PKM2 knockdown impairs podocyte energy metabolism and differentiation [35]. MCL suppresses leukemia growth and tumorigenesis in zebrafish xenografts by promoting the formation of PKM2 tetramer, thus inducing the retention of PKM2 tetramer in the cytoplasm, blocking PKM2 nuclear translocation [36].

Dynamic associated protein 1 (Drp1) is an essential protein for mitochondrial fission. The overexpression of Drp1 can inhibit mitochondrial fission, thereby inhibiting and slowing down cell apoptosis. MCL upregulates the expression of Drp1, thus promoting apoptosis of human breast cancer cell MCF-7 [37]. In addition, MCL triggers apoptosis of liver cancer cells *in vivo* and *in vitro* by activating caspase-3 and releasing mitochondrial ROS [38]. Moreover, other studies have shown that MCL induces Drp1-mediated apoptosis in MCF-7 breast cancer cells. MCL inhibits ovarian cancer proliferation (NF-κB suppression) and promotes apoptosis (caspase-9 induction) [39]. Via IL-6/STAT3 blockade, MCL exerts pro-apoptotic and anti-proliferative effects in gastric cancer in vitro and in vivo [40].

In brief, MCL inhibits the proliferation of malignant cells by reducing energy metabolism and promotes apoptosis by inhibiting the cell cycle. It is reasonable to expect that MCL could be used in clinical trials as a useful therapeutic agent for cancer treatment.

3 Cardioprotective Activity of MCL

Chronic anticancer drug use induces cardiotoxicity. MCL has a cardioprotective effect. Doxorubicin (anthracycline class) treats breast and lung cancers and hematopoietic malignancies [41]. Myocardial biopsies reveal cardiotoxicity even at low doxorubicin doses [42]. MCL confers cardioprotection against doxorubicin toxicity in mice via PI3K/Akt/NF-κB pathway modulation [43].

4 Neuroprotective Activity of MCL

Microglia-driven neuroinflammation accelerates neurodegeneration [44]. Targeting microglial overactivation offers therapeutic potential for neurodegenerative disorders [45]. MCL suppresses inflammatory responses in bacterially infected mice. MCL achieves significant brain accumulation by crossing the blood-brain barrier, which is a key CNS drug delivery challenge. ACT001, a derivative of MCL, was detected in the brain [30]. Sun *et al* [31] demonstrated that in LPS-stimulated BV-2 microglia, MCL downregulates iNOS and COX-2, suppresses IL-1β, IL-6 and TNF-α transcription via IκBα/NF-κB, AKT, JNK, P38 and ERK1/2 inhibition, and induces anti-oxidant protein heme oxygenase-1 (HO^{-1}) through Nrf2 transcriptional activation. Collectively, MCL demonstrates neuroprotective efficacy against neuroinflammation-mediated neurodegeneration.

5 Anti-inflammatory Activity of MCL and Its Derivatives

Inflammation drives pathogenesis in multiple pathologies, including infections and autoimmune disorders. MCL's potent anti-inflammatory activity underscores its therapeutic potential for inflammation-associated diseases.

6 Anti-bacterial Inflammatory Activity of MCL

MCL ameliorates LPS-induced inflammation and bacterial immune responses in established models. Gram-positive (G^+) bacteria (e.g., Staphylococcus) are predominant sepsis pathogens [46]. Jiang *et al* [47] found that MCL improved the survival rate of mice, which were challenged with a lethal dose of *Staphylococcus aureus* by reducing the secretion of inflammatory mediators. In the MRSA infection mouse model, MCL ameliorated the organ damage of liver and kidney and down-regulated the expression of CCL2, IL-6, IFN-γ, MCP-1, and TNF-α by inhibiting the activation of PI3K/AKT and NF-κB path-

ways, indicating it can also treat G^- bacterial infection.

Mycobacterium tuberculosis (Mtb) induces granulomatous lung inflammation and systemic responses, posing persistent global health risks [48]. In Mtb-induced inflammatory response in Raw264.7 cells, MCL decreased the secretion of IL-1β, TNF-α, iNOS, COX2, and NO through inhibiting PI3K/Akt/NF-κB pathway [49]. By modulating host immunity, MCL represents a promising anti-infective therapeutic candidate.

7 Anti-autoimmune Inflammatory Activity of MCL

Autoimmune disease is a kind of disease in which the tissue and organs are damaged because the autoimmune tolerance is broken, the immune system is activated, and the body attacks its own organs [50]. The traditional glucocorticoid and immunosuppressant can timely control the diseases, but long-term use of these drugs will bring a series of side effects, which seriously affect the life quality of patients and could even be life-threatening [51]. Diabetic nephropathy predominates among chronic kidney diseases amid rising diabetes prevalence [52]. Systemic and renal inflammation characterize diabetic nephropathy [53]. A low dose of DMAMCL has been found to exert its renal protective role by reducing the serum levels of IL-1, IL-6, MCP-1, and TNF-α in the diabetic nephropathy mouse model [54]. Peritoneal fibrosis drives ultrafiltration failure in long-term dialysis patients [55]. MDAMCL halted the progression of peritoneal fibrosis in a peritoneal dialysis-related peritoneal fibrosis mouse model by promoting autophagy and inhibiting extracellular matrix deposition [56].

Inflammatory bowel disease (IBD) involves chronic gastrointestinal inflammation. In a mouse model of DSS-induced colitis, both MCL and DMAMCL administered intraperitoneally, attenuated colitis and decreased colitis-associated cancer incidence rate by inhibiting the expression of IL-1β, IL-6, and TNF-α [26]. Collagen-induced arthritis (CIA) models rheumatoid arthritis (RA), a systemic autoimmune disorder [57]. MCL attenuates paw swelling and articular cartilage degeneration by suppressing M-CSF, TIMP-1, and C5a expression [58]. Ankylosing spondylitis (AS) progressively inflames the axial skeleton [59]. Impairment of negatively regulating the immune response in AS patients might be its etiology [60]. MCL ameliorates AS via NLRP3 inflammasome inhibition and Th1/Th2 balance modulation through NF-κB regulation [61]. MCL also alleviated hepatic steatosis in Db/Db mice by inhibiting inflammation and promoting autophagy via inhibiting NF-κB and AMPK/mTOR signaling pathway [62]. These results suggest that MCL might be considered for use as a novel treatment against autoimmune diseases.

8 Functional Mechanisms of MCL

Combined with the research results of other research groups, MCL may inhibit NF-κB, PI3K/AKT/mTOR and MAPK pathways. The biological function of MCL and its derivatives were summarized in Table 1.

Table 1 Schematic diagram of MCL functional mechanism

Disease	Animal	Administration	Dose	Mechanism	Ref
Leukemia	zebrafish	*i.p.*	10 μg/mL	Inhibiting PKM2 nuclear translocation	[36]
Liver cancer	mouse	*i.p.*	20 mg/kg	Inducing apoptosis	[38]
Cardiotoxicity	mouse	*i.p.*	12.5, 25, 50 mg/kg	Regulating PI3K/AKT/NF-κB signaling	[43]
Diabetic kidney disease	mouse	*i.p.*		Inhibiting renal inflammation	[54]
Renal fibrosis	mouse	*i.g.*	25 mg/kg	Suppressing Mtdh/BMP/MAPK signaling	[63]
Hepatic steatosis	mouse	*i.g.*	12.5, 25, 50 mg/kg	Inhibiting inflammation and promoting autophagy through PPAR-γ-mediated NF-κB and AMPK/mTOR pathways	[62]
Peritoneal fibrosis	mouse	*i.p.*	50 mg/kg	Activation of autophagy	[56]
Colitis and colitis-associated cancer	mouse	*i.p.*	5, 40 mg/kg	Inhibiting inflammation	[26]
Rheumatoid arthritis	mouse	*i.p.*	30 mg/kg	Inhibiting inflammation	[58]
Ankylosing spondylitis	mouse	*i.g.*	20, 50 mg/kg	Suppressing NLRP3 inflammasome while maintaining Th1/Th2 balance via NF-κB regulation	[61]

9 Discussion and Perspective

Molecular biology advances enable cellular/molecular-level research on natural product active components. MCL demonstrates established anticancer, anti-inflammatory, and immunomodulatory activities. Their precise molecular mechanisms remain largely uncharacterized. The diversity of chem-

ical structure and broad pharmacological activities of MCL and its derivatives represent a big challenge in identifying their targets, thus leading to a lack of in-depth studies on the mechanisms of MCL. Thus, a lot of effort is still being put into exploring the biological function and mechanism of MCL. Although one recent study reported that MCL bound covalently to PKM2 at the cysteine 424 (C424) residue of PKM2 [36], there are still many questions about the target of MCL. One question is whether MCL has a therapeutic role in many diseases by regulating multiple target molecules in cells. Another question is whether MCL may have a therapeutic role in a variety of diseases by acting on a ubiquitous intracellular target molecule (such as PKM2), thereby affecting multiple downstream signaling pathways. Due to the deficiency of evidence on the regulation of the above-mentioned signaling pathways by PKM2, we could not draw a conclusion and answer these questions.

At present, many difficulties are encountered in the treatment of many diseases. For example, targeted drugs cannot accurately aim at cancer cells alone. The treatment of infectious diseases is faced with the problem of multiple drug resistance. There is a lack of effective clinical drugs for autoimmune diseases. MCL may have great application prospects in these diseases due to its extensive anti-inflammatory and immunomodulatory effects. For MCL regulation of immune inflammation, there is also ongoing research on stroke and Alzheimer's disease. It was also found that the immunoregulatory mechanism of MCL may affect the functional state of macrophages and neutrophils.

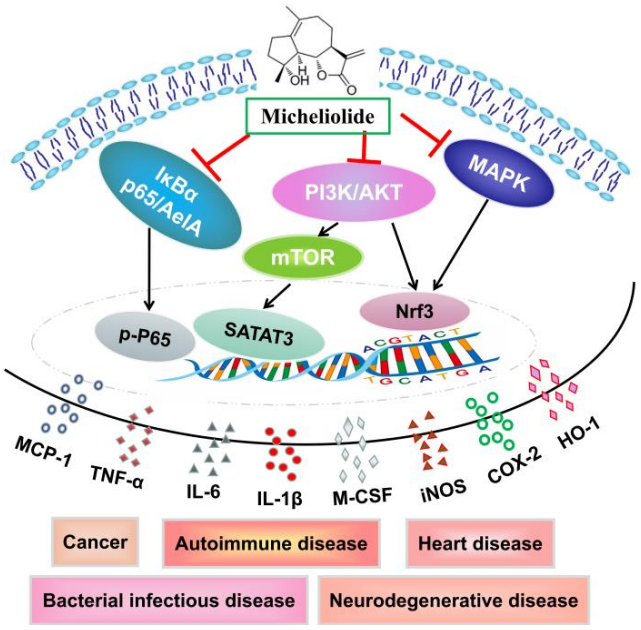

Figure 4 Graphical abstract

Therapeutic applications of MCL similarly require further exploration. MCL derivatives show significant promise as novel therapeutics for inflammation-associated disorders and malignancies.

MCL and its derivatives treat cancers, bacterial infectious disease, and autoimmune disease by inhibiting the activity of NF-κB, PI3K/AKT/mTOR and MAPK signal pathways.

Conflict of Interest

The authors confirm that this article has no conflict of interest.

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