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The Anti-Inflammatory Meroterpenes

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Abstract

The meroterpenes are one class of the natural product bearing the terpenoid structure. They have an excellent potential for various biological activities. Inflammation is a serious problem that many people face as a complication of any chronic disease or disease itself. Therefore, we have scanned the literature to compile the research about whether the meroterpenes have potential candidates for the anti-inflammatory drug. It has been mentioned many meroterpenes have IC50 values in the µM band. So, they are very active compounds according to anti-inflammatory assays tested.

Inflammation is a main immune reaction that serves survival during infection or injury and provides tissue homeostasis under a kind of risky conditions. Inflammation comes at the loss of a temporary reduction in tissue role, which can consecutively assist in the pathogenesis of diseases of changed homeostasis [1].

Inflammation is observed as the main complication in bacterial, viral, fungal, or parasitic infections; in anaphylaxis; in environmental diseases emerged with smoke inhalation, asbestos exposure, etc. like reasons, in autoimmune diseases such as rheumatoid arthritis, gout, and intestinal diseases; as well as in chronic diseases such as diabetes [2].

On the other hand in the last thirty years, it has also become clear that a much larger type of disease has revealed cellular and molecular proof for inflammation. These contain chronic arterial and venous disease [3,4], myocardial ischemia [5–7], acute cerebral stroke and Alzheimer's chronic disease (8-13), and more currently arterial hypertension [14] and cancer [15–17].

Nuclear factor-kB (NF-kB) is an essential regulator of inflammation, and activation of NF-kB stimulates inflammation-related metabolic disorders such as obesity, type 2 diabetes, and atherosclerosis [18]. Macrophages, as elemental immune cells, have been identified as essential effector cells in the starting and development of inflammation and insulin resistance [19]. Lots of papers exist using Nuclear factor-kB (NF-kB) assay as anti-inflamatory activity. Hyperinoids A and B, two polycyclic meroterpenoids from Hypericum patulum were investigated for the inhibitory activities in NF-kB pathway luciferase assay and the effects on the LPS-induced inflammatory responses in macrophages by Jia and the research group [20]. They have found Hyperinoids A and B showed powerful inhibitory activities in NF-kB pathway luciferase assay with IC_{50} values of 0.75±0.17 and 1.19 ±0.48 mmol/L, respectively. In this study, bortezomib (PS- 341) was utilized as the positive control (IC_{50} = 0.07 ± 0.01 mmol/L). Additionally, they were checked for influences on the LPS-activated inflammatory responses in RAW 246.7 macrophages and main mouse BMDM cells. The MTS assay demonstrated no noticeable cytotoxicity against RAW 246.7 cells at the analyzed concentrations. The mRNA levels of some pro-inflammatory genes, like IL-1β, IL-6, and iNOS, were downregulated by Hyperinoids A and B [20].

(+)- and (-)-gancochlearols A and B, two pairs of dimeric meroterpenoid enantiomers have been isolated from the fruiting bodies of Ganoderma cochlear by Quin and his

sresearch group. Their structures have been elucidated by spectroscopic techniques. Biological assays showed that the enantiomers of 1 and 2 are cytotoxic against three human cancer cell lines (A549, K562, Huh-7) and could inhibit COX-2 (cyclooxygenase-2) expression with IC50 values less than 10 μM [21].

Shi et all. have isolated eight pairs of meroterpenoid enantiomers and four achiral meroterpenoids from Rhododendron anthopogonoides Maxim. Compounds (+)-anthoponoid E /(-)-anthoponoid E −(+) Anthoponoid G /(-) Anthoponoid G and Anthoponoid H have been identified as NF-κB pathway inhibitors, and (+)-anthoponoid E, (-) Anthoponoid G, and Anthoponoid H further showed suppressive effects on the LPS (lipopolysaccharide)-induced inflammatory responses in RAW 264.7 macrophages [22].

Furanaspermeroterpenes A and B, with an unprecedented 6/6/6/5/5 pentacyclic skeleton, and five new analogs aspermeroterpenes D–H were co-isolated from the marine-derived fungus Aspergillus terreus GZU-31-1 by Tang et all. All of the isolates were scanned on the inhibitory activities against lipopolysaccharide-induced nitric oxide production in RAW 264.7 cells, and aspermeroterpenes D–H displayed notable anti-inflammatory activity with IC50 values ranging from 6.74 to 29.59 μM than the positive control (Indomethacin, IC50 30.98 μM) [23].

The anti-inflammatory and anticancer properties of eight meroterpenoids isolated from the brown seaweed Cystoseira usneoides have been evaluated by Zbakh and his research group. The algal meroterpenoids usneoidone Z, 11-hydroxy-1′-O-methylamentadione, cystomexicone B, cystomexicone A, 6-cis-amentadione-1′-methyl ether, cystodione A, and cystodione B.were assayed for their inhibitory effects on the production of the pro-inflammatory cytokines tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), and the expression of cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) in LPS-stimulated THP-1 human macrophages. All compounds remarkably reduced the production of TNF-α, IL-6, and IL-1β, and suppressed the COX-2 and iNOS expression, in LPS-stimulated cells ($p < 0.05$) [24].

An uncommon austinoid, 1,2-dehydro-terredehydroaustin, has been isolated from the mangrove endophytic fungus Aspergillus terreus, and its' anti-inflammatory activity was tested and the new compound displayed feable inhibition effect against the production of nitric oxide (NO) in lipopolysaccharide (LPS)-induced RAW 246.7 mouse macrophages with an IC50 value of 42.3 μM [25].

In another study, six farnesyl meroterpenes, consisting of two new meroterpenoids, chrysogenester and 5-farnesyl-2-methyl-1-O-methyl hydroquinone, were found in the jellyfish-related fungus Penicillium chrysogenum J08NF-4. Chrysogenester managed to suppress the in vitro inflammatory answer by joining in the peroxidase proliferator-activated receptor (PPAR-γ)/NF-κB signaling line [26,29].

Brasilianoids B–C which isolated from sponge-derived fungus Penicillium brasilianum exhibit moderate anti-inflammatory activity (NO-Nitric oxide) in RAW 264.7 cells (IC50 = 37.69/33.76 μM) [27,29].

The research of a marine algae-associated fungus Pleosporales sp. resulted in the obtaining of four new merosesquiterpenoids (pleosporallins A–D); pleosporallins A–C showed average anti-inflammatory against the lipopolysaccharide (LPS)-induced intracellular IL-6 production of murine macrophage cell line RAW264.7 [28, 29].
Berkeleyacetal C (BAC) isolated from Penicillium sp. from a soil sample collected in Fukushima, suppressed NO production and induction of iNOS protein in RAW264.7 cells triggered by the Toll-like receptor (TLR) 2 ligand, peptidoglycan (PGN) or TLR4 ligand, lipopolysaccharide (LPS). BAC inhibits LPS- and PGN-induced NO generation and iNOS expression by lessening the level of the translocating of NF-kB in nuclear through preventing the kinase activity of IRAK-4 in inflammatory cells. [30]

Amestolkolides A-D was isolated from the mangrove endophytic fungus Talaromyces amestolkiae YX1 by Chen's research group. Amestolkolide B displayed powerful anti-inflammatory activity in vitro by suppressing nitric oxide (NO) generation in lipopolysaccharide-induced RAW264.7 cells with an IC50 value of 1.6 ± 0.1 mM [31].

A phytochemical investigation of the alga Cystoseira usneoides has come out to obtaining the of six new meroterpenoids, cystodiones A−F, and also six known derived compounds: 6-cis-amentadione-1′-methyl ether, amenta- dione-1′-methyl ether, cystomexicone A, cystomex- icone B, usneoidone Z, and its corresponding 6E isomer. In anti-inflammatory tests, usneoidone Z and its' 6E isomer exhibited remarkable activity as inhibitors of the generation of the proinflammatory cytokine TNF-α in LPS-induced THP-1 human macrophages [32].

Three antioxidant and anti-inflammatory oxygenated meroterpenoids, 1-(3-methoxypropyl)-2-propylcyclohexane (C13), 3-(methoxymethyl)heptyl 3-(cyclohex-3-enyl) propanoate (C18) , and 2-ethyl-6-(4-methoxy-2-((2-oxotetrahydro-2H-pyran-4-yl)methyl)butoxy)-6-oxohexyl 5-ethyloct-4-enoate (C29) were isolated from the methanol:ethyl acetate fraction of red seaweed Kappaphycus alvarezii by Makkar & Chakraborty. The compound 2-ethyl-6-(4-methoxy-2-((2-oxotetrahydro-2H-pyran-4-yl)methyl)butoxy)-6-oxohexyl 5-ethyloct-4-enoate showed strong in vitro inhibitory activities against pro-inflammatory 5- lipoxidase (IC50 1.04 mg/mL), which pointed out its potential anti-inflammatory features against promoted inflammatory mediators ledding an inflammatory reply. [33].

The meroterpenes have been isolated from Ganoderma lucidum (lucidumins A-D, lingzhine C, ganocochlearin B, fornicin B, cochlearin I, ganocochlearine A, lucidimine A) by Shuang-Yang and the research team. All meroterpenes were tested for anti-inflammatory activity by determining LPS-induced nitric oxide (NO) generation in RAW264.7 macrophages. The outcomes displayed that lucidumins A-D, can significantly inhibit NO production with IC50 values 8.06 ± 0.51, 10.98 ± 0.15, 15.49 ± 0.40, 9.39 ± 0.21, respectively, which exhibited stronger activity than the positive control L-NMMA [34].

Aspertetranones A−D was obtained from the marine algal-related

fungus Aspergillus sp. ZL0-1b14. They were assayed for anti-inflammatory activity in LPS- activated RAW264.7 macrophages. Aspertetranone D showed an inhibitory effect towards IL-6 production with 69% inhibition at 40 μM. [35].

Anti-inflammatory activity has been assayed on bakuchiol isolated from the species Ulmus davidiana var. Japonica by Choi et. all. Bakuchiol powerfully suppressed the production of nitrogen oxide activated by lipopolysaccharide (LPS), and prostaglandin E2 (PGE2) in line 264.7 macrophages, without exhibiting cytotoxicity [36]. In another bakuchiol study, it was exhibited to inhibit degranulation of human neutrophils in vitro. The same effect was also confirmed in vivo in mice administered with zymosan causing tissue inflammation. It was also determined that bakuchiol fully inhibited myeloperoxidase activity, hence restraining the formation of oxidizing compounds such as hypochlorite. As a result, bakuchiol caused a diminishing in tissue damage caused by hydrolytic enzymes and some oxidizing compounds that existed in human leukocytes [37-38].

Xiao and the research group have found a new meroterpene, psoracorylifol F from Psoralea corylifolia fruits, together with two common meroterpenes (psoracorylifol A and bakuchiol), All the three meroterpenes possessed evaluated by TLC bioautography against O2•− radicals. They have strong inhibitory activity against LPS-induced NO production in RAW 264.7 cells with IC50 values varying from 7.71 to 27.63 μM [39].

The COX-1 and COX-2 IC50 for bakuchiol were found to be 14.7 μg/mL and 514 μg/mL, respectively by Chaudhuri & Marchio [40].

Chen et. all. have isolated nine unidentified shikimate-conjugated meroterpenes, as well as nine known compounds from solid cultures of the fungus Guignardia mangiferae. Nine undescribed meroterpenes suppressed nitric oxide (NO) production in LPS-activated RAW 264.7 cells with IC50 values in between 4.7 and 40.0 μM [41].

Zbakh and the research group have studied the anti-inflammatory actions of the algal meroterpene 11-hydroxy-1'-O-methylamentadione (AMT-E) in a murine model of dextran sodium sulphate (DSS)-promoted colitis. To perform the test, AMT-E was orally subjected daily (1, 10, and 20 mg/kg animal) to DSS-treated mice (3% w/v) for 7 days. AMT-E inhibited body weight loss and colon shortening and efficiently weakened the size of the colonic damage. Likewise, AMT-E increased mucus generation and decreased myeloperoxidase activity (a marker for anti-inflammatory activity). Furthermore, the algal meroterpene reduced the tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-10 levels, and caused an important reduction of the expression of promotable nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [42].

Conclusion:

As a result of the literature survey, a limited number of papers are present about the anti-inflammatory research on meroterpenes from different sources. Five of them (Hypericum patulum, Psoralea corylifolia, Ulmus davidiana var. Japonica, Rhododendron anthopogonoides Maxim., Ganoderma cochlear) is about the meroterpenes obtained from the plants, one is on the meroterpenes isolated from mushroom (Ganoderma lucidum). Five research is focused on the meroterpenes from marine-derived fungus (Aspergillus sp. ZL0-1b14., Pleosporales sp., Penicillium brasilianum., Penicillium chrysogenum J08NF-4. Aspergillus terreus GZU-31-1). Marine meroterpenes studies are the investigations belonging to Zbakh and the research group, Makkar & Chakraborty, De Los Reyes, and his co-workers, Zbakh and his research group. Plant- related endophytic fungus papers are about Talaromyces amestolkiae YX1, Aspergillus terreus. Additionally, there is one research on Penicillium sp. from a soil sample and one is the meroterpenes from solid cultures of the fungus Guignardia mangiferae. To measure the anti-inflammatory activity, the production of NO, IL-6, IL-1ß, TNF-α in LPS- and prostaglandin E2 (PGE2)-induced RAW 264.7 cells, in LPS-induced THP-1 human macrophages, the inhibitory effect of COX-1 and COX-2, 5- lipoxidase, nitric oxide synthase (iNOS), peroxidase proliferator-activated receptor (PPAR-γ)/NF-κB signaling line and in NF-kB pathway luciferase assay have been performed in the papers we selected. The majority of the meroterpenes in the manuscripts mentioned have extreme anti-inflammatory activities in the μM range. It shows us that meroterpenes have the capability of an anti-inflammatory agent.

Conflicts of Interest:

The authors declare that they have no conflicts of interest.

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