

Review Article

Mechanistic Perspectives of Maslinic Acid in Targeting Inflammation

Wei Hsum Yap¹ and Yang Mooi Lim²

¹*School of Biosciences, Taylor's University, No. 1, Jalan Taylor's, 47500 Subang Jaya, Selangor, Malaysia*

²*Department of Preclinical Sciences, Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Lot PT 21744, Jalan Sungai Long, Bandar Sungai Long, 43000 Kajang, Selangor, Malaysia*

Correspondence should be addressed to Wei Hsum Yap; weihsum.yap@taylors.edu.my

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Chronic inflammation drives the development of various pathological diseases such as rheumatoid arthritis, atherosclerosis, multiple sclerosis, and cancer. The arachidonic acid pathway represents one of the major mechanisms for inflammation. Prostaglandins (PGs) are lipid products generated from arachidonic acid by the action of cyclooxygenase (COX) enzymes and their activity is blocked by nonsteroidal anti-inflammatory drugs (NSAIDs). The use of natural compounds in regulation of COX activity/prostaglandins production is receiving increasing attention. In Mediterranean diet, olive oil and table olives contain significant dietary sources of maslinic acid. Maslinic acid is arising as a safe and novel natural pentacyclic triterpene which has protective effects against chronic inflammatory diseases in various *in vivo* and *in vitro* experimental models. Understanding the anti-inflammatory mechanism of maslinic acid is crucial for its development as a potential dietary nutraceutical. This review focuses on the mechanistic action of maslinic acid in regulating the inflammation pathways through modulation of the arachidonic acid metabolism including the nuclear factor-kappa B (NF- κ B)/COX-2 expression, upstream protein kinase signaling, and phospholipase A₂ enzyme activity. Further investigations may provide insight into the mechanism of maslinic acid in regulating the molecular targets and their associated pathways in response to specific inflammatory stimuli.

1. Introduction

Maslinic acid is a natural pentacyclic triterpene which can be found in various natural sources including medicinal herbs [1, 2], edible vegetables and fruits [3, 4], especially in the skin of olives [5]. The amount of maslinic acid in table olives constitutes 0.8% in weight when extracted from the solid residues while the concentration in olive oil ranges from 38 mg/kg in extra virgin olive oil to 721 mg/kg in crude pomace olive oil [6]. Olives and olive oil are regular dietary components in the Mediterranean region which confers protection against chronic diseases. Daily consumption of approximately 40 g or 10 medium size olives corresponds to the intake of 28 mg maslinic acid per day [7]. It is hypothesized that this habitual consumption of olives and virgin olive oil will expose the intestinal epithelium to high concentrations of maslinic acid which confers health-protecting properties [8,

9]. On the other hand, maslinic acid can also be found in plants used for traditional Asian medicine, for example, *Eriobotrya japonica* [10, 11], *Campsis grandiflora* [12], *Geum japonicum* [1], and *Agastache rugosa* [13], which are used to treat diverse inflammatory diseases. The pharmacological effects of maslinic acid have been reported in various experimental models including their antitumour [14, 15], anti-inflammatory [16, 17], cardioprotective [18], antiviral [19], antimalarial [20], neuroprotective [21], and antioxidant [22] activities. Considering its wide distribution in the plant kingdom and biological activities, it is suggested that maslinic acid is a natural and safe molecule. Maslinic acid has been assessed for its toxicity effects in animal models fed with high doses of this triterpene and it did not produce any signs of morbidity and mortality [23]. Recent investigation further showed that maslinic acid has weak inhibitory activities on cytochrome P450 (CYP) isoforms, suggesting that it has low

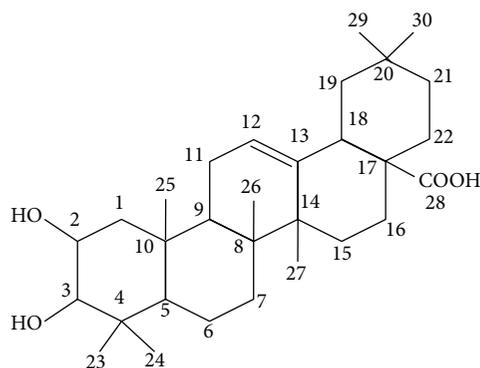


FIGURE 1: Molecular structure of maslinic acid.

potential to cause possible toxicity and drug interactions involving CYP enzymes [24].

1.1. Bioactive Properties of Pentacyclic Triterpenoids. Triterpenoids represent a group of compounds characterized by the 30-carbon isoprenoid skeleton molecule with over 100 distinct skeletons [25]. Triterpenoids are formed from cyclization of squalene or oxidosqualene. They may be acyclic, monocyclic, bicyclic, tricyclic, tetracyclic, pentacyclic, or hexacyclic [26]. Pentacyclic triterpenes are often bioactive (antitumor, antiviral, antidiabetic, and anti-inflammatory) and have huge therapeutic potential. There are numerous examples of enzymes that can be inhibited by pentacyclic terpenoids, indicating the ability of these compounds to act broadly in a nonspecific mode on multiple targets [27]. More importantly, pentacyclic triterpenoids scaffolds also have unique safety profiles [28]. For example, corosolic acid (antidiabetic) is already on the market and several other pentacyclic triterpenes are under clinical trials or ready to be launched in the market. The anti-inflammatory effects of pentacyclic triterpenoids are largely ascribed to their ability to inhibit molecular targets such as 5-lipoxygenase (LOX), inducible nitric oxide synthase (iNOS), cyclooxygenase (COX) 2, and nuclear factor-kappa B (NF- κ B) activities.

1.2. Structure-Activity Relationship between Pentacyclic Triterpenoids and Their Effects on Inflammation. Maslinic acid (Figure 1) is a pentacyclic triterpene compound. Pentacyclic compounds comprise the most numerous classes of oxidosqualene cyclases products [26]. Their structural variety reveals that they arise through a variety of cyclization modes. Maslinic acid is synthesized from the folding and cyclization of squalene (1) to oxidosqualene (2) and subsequently to the dammarenyl ring system. Dammarenyl (3) undergoes ring expansion and additional cyclization to form lupeol (4), α -amyrin (5), and β -amyrin (6) skeletons. Further oxidation steps convert β -amyrin to erythrodiol (7), followed by oleanolic acid (8) and finally maslinic acid (9) (Figure 2).

Several studies have shown that triterpenoids significantly suppress chronic inflammation. Pentacyclic triterpenoids with well-characterized biological activities include lupane, ursane, and oleanane type of compounds, such as lupeol, ursolic acid, and oleanolic acid. Structure-activity

relationship study on the anti-inflammatory activities of triterpenoids showed that the basic carbon skeleton has no influence on the activity. The presence of C-28 or C-30 carboxylic group and an alcoholic group at C-28 increases the activity in carrageenan- and ethyl phenylpropionate-(EPP-) induced edemas, respectively [29]. There are studies reporting that the presence of functional group at C-28 in triterpenic acids is capable of acting as hydrogen bond donors [30, 31]. On the other hand, it was shown that the oleanane skeleton (β -amyrin) is more potent than the ursane skeleton (α -amyrin) in inhibiting nitric oxide production induced by interferon- γ (IFN- γ) in mouse macrophages [32]. There are studies reporting that the presence of additional hydroxyl group at the C-2 position of maslinic acid confers antioxidant properties compared to oleanolic acid [16, 22]. However, it is suggested that the mechanism by which maslinic acid mediated inhibition of inflammatory cytokines may be independent of their antioxidant activity [33]. This review will highlight on the mechanism of maslinic acid in regulating inflammation, focusing on the arachidonic acid pathway.

2. The Arachidonic Acid Inflammatory Pathway

2.1. Inflammation: Homeostasis and Pathogenesis. Inflammatory response is initiated upon microbial infection and/or physical damage to restore the homeostatic balance of tissue structure and physiological function. Acute phase inflammation is a protective mechanism which involves coordinated actions of numerous molecular and cellular players. This process is characterized by migration of neutrophils and monocytes to the site of infection or injury, causing signs of inflammation such as swelling, pain, redness, and heat. Successful resolution of a typical acute phase inflammation requires elimination of the foreign microorganisms together with anti-inflammatory mediators that inhibit continuous recruitment of leukocytes. Persistent inflammatory response can lead to excessive tissue damage and loss of organ function. Hence, incomplete resolution of acute inflammation may predispose to chronic inflammation and autoimmunity disorders, such as multiple sclerosis, myocardial infarction, atherosclerosis, rheumatoid arthritis, stroke, Parkinson's disease, Alzheimer's disease, or cancer [34].

Local production of endogenous mediators at the site of infection and/or injury promotes the development of inflammation [35]. Prostaglandins and leukotrienes are potent mediators of inflammation derived from arachidonic acid (AA), a 20-carbon unsaturated fatty acid produced from membrane phospholipids. AA is released from the plasma membrane by phospholipase enzymes (mostly PLA₂) which are activated by interleukin-8 (IL-8), microbial peptides, phagocytic particles, and nonspecific stimuli such as damage or injury [36]. Once AA is released, they can be metabolized into various C20 unsaturated lipids derivatives, collectively known as eicosanoids. Eicosanoids are formed via three main pathways, including the prostaglandins (PGs) and thromboxanes (TXs) (collectively termed prostanoids) formed by COX,

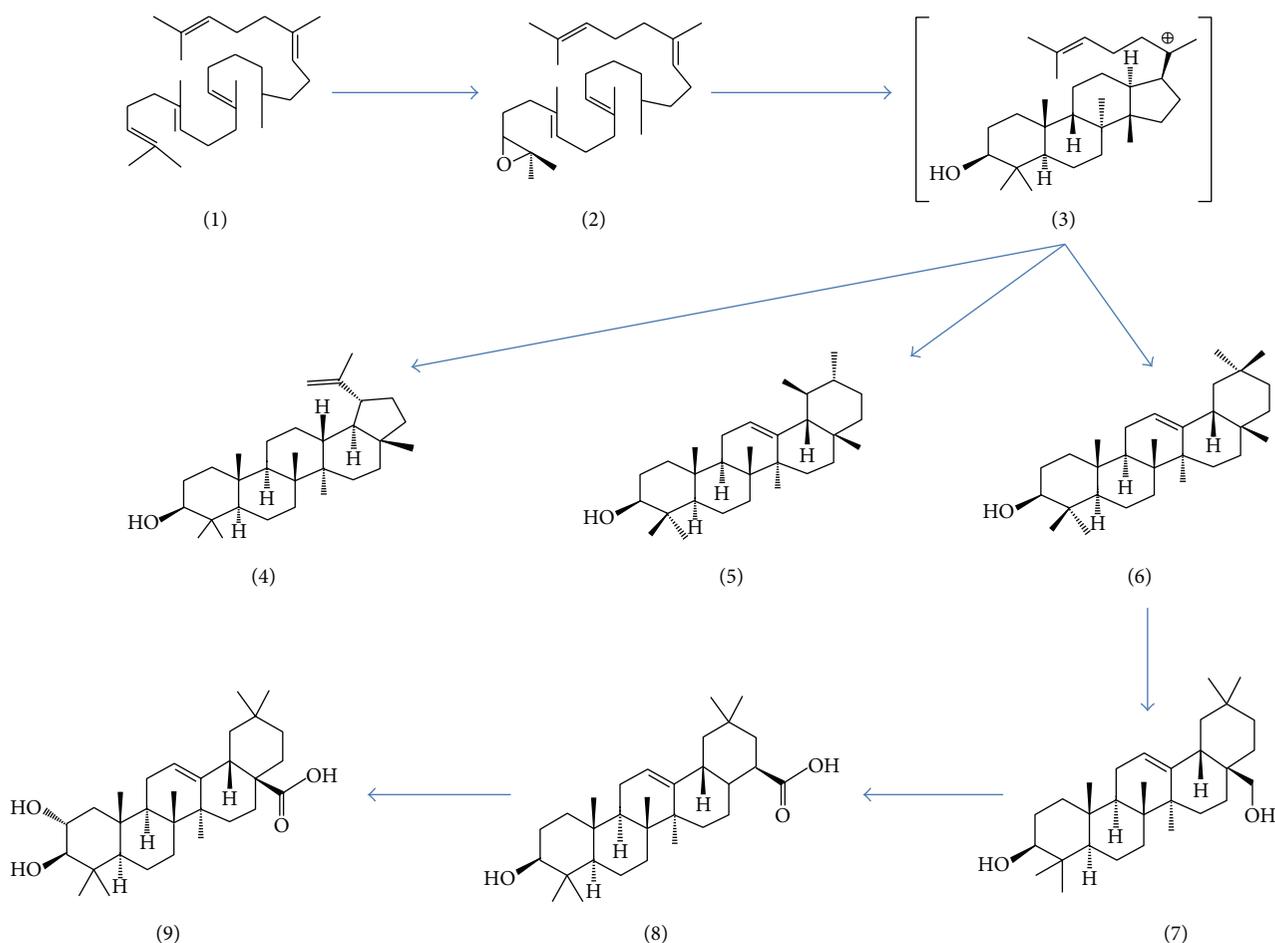


FIGURE 2: Biosynthesis of maslinic acid. Epoxidation of squalene (1) produces 2,3-oxidosqualene (2) which undergoes further cyclization into the dammarenyl cation (3). Dammarenyl cation undergoes D-ring expansion and additional cyclization to form products, such as lupeol (4), α -amyrin (5), and β -amyrin (6). Further oxidation steps convert β -amyrin to erythrodiol (7), followed by oleanolic acid (8) and finally maslinic acid (9).

leukotrienes (LTs) and lipoxins (LXs) by LOX, and epoxyeicosatrienoic acids (EETs) by cytochrome P450 enzymes [37–39].

2.2. Prostanoid Metabolism. Prostanoids are synthesized by the cyclic pathway, which is initiated through the action of COX enzyme [40], also known as the prostaglandin G/H synthase (Figure 3). COX possesses both cyclooxygenase and peroxidase activities which catalyzes the two-step conversion of AA to PGG₂ and then to PGH₂ [41, 42]. It begins by catalyzing the bisoxygenation and cyclization of AA into hydroperoxy arachidonate metabolite PGG₂ and is followed by the peroxidase element of the enzyme which reduces the hydroperoxide to its corresponding alcohol to form PGH₂. There are two COX isoforms in humans, namely, COX-1 and COX-2. COX-1 is constitutively expressed in gastric mucosa, kidney, platelets, and vascular endothelial cells while COX-2 expression is inducible primarily at the site of inflammation, especially in macrophages and monocytes [43]. PGH₂ is transformed into diverse forms of prostanoids through the action of prostaglandin D synthase, prostaglandin E synthase,

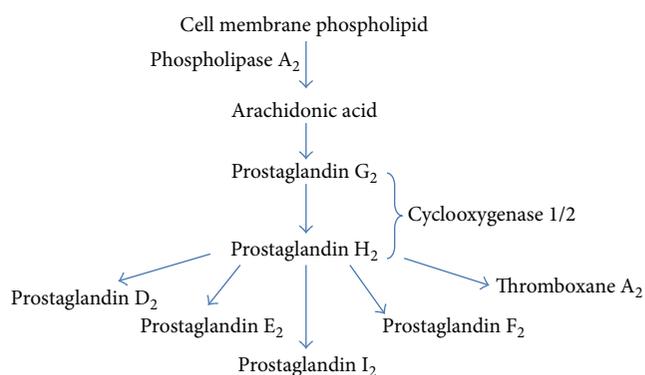


FIGURE 3: Prostanoid metabolism.

prostaglandin F synthase, prostaglandin I synthase, and thromboxane A synthase, producing PGD₂ [44], PGE₂ [45], PGF_{2a} [46], PGI₂ [47], and TXA₂ [48], respectively.

PGs play important roles in inflammatory response. PGE₂ is one of the PGs which is of particular importance in

regulating inflammation. PGE₂ acts locally by binding to one or more of its respective receptors known as EPI-EP4 [49]. Under physiological conditions, PGE₂ controls immune responses, blood pressure, gastrointestinal integrity, and fertility. Dysregulated PGE₂ synthesis or degradation has been associated with a wide range of pathological conditions [50]. PGE₂ enhances vasodilation and production of cAMP and decreases T-cell proliferation and lymphocyte migration and secretion of IL-1 α and IL-2 [51, 52]. Knockout mouse studies further established the involvement of EP in inflammatory exudation [53]. PGE₂ also mediates hyperalgesia through EPI receptor signaling that plays important role in peripheral sensory neuronal signaling at the site of inflammation [54]. Other studies have also implicated the EP3 receptor in the inflammatory pain response mediated by low doses of PGE₂ [55]. There are studies reporting that the release of PGE₂ is mediated via activation of NF- κ B [56], a transcription factor which regulates numerous inflammatory genes and is considered as a possible target for therapeutic intervention. In fact, various studies have implicated NF- κ B in the transcriptional regulation of COX-2 [57, 58].

2.3. COX and Inflammation. Prostanoids as important mediators of inflammation are further supported by the fact that their biosynthesis is the target of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs such as ibuprofen, indomethacin, and aspirin all act upon the cyclooxygenase activity of both COX-1 and COX-2 enzymes. Both COX-1 and COX-2 may contribute to inflammatory response depending on the type of inflammatory stimulus and target tissue. It was shown that each isoform displays differential contribution to the development of inflammatory response depending on the experimental models used. For example, deletion of COX-2 inhibits synovial inflammation and joint destruction in collagen-induced arthritis model while COX-1-deficient mice showed no significant response [59, 60]. COX-1-derived PGs however contribute to development of arthritis in K/BxN serum-transfer arthritic model [61]. Specific COX-2 inhibitor was being developed because inhibition of COX-1 activity in the gut is associated with NSAID-induced ulcerations [62]. Targeted inhibition of COX-2 however increased the risk of cardiovascular disease [63]. It is reported that cardiovascular risk is dependent on the balance between vasodilating PGI₂ and prothrombotic TXA₂. These findings highlight the importance of pharmacological drug development in regulation of prostanoids profile.

3. Role of Maslinic Acid in Targeting Inflammation and Related Diseases

3.1. Inflammatory Modulating Effects of Maslinic Acid. Maslinic acid shows promising anti-inflammatory effects in several *in vivo* and *in vitro* experimental models. The anti-inflammatory effect of maslinic acid was first evaluated by Banno et al. in a model of 12-*O*-tetradecanoylphorbol-13-acetate- (TPA-) induced inflammation ear edema in mice [11]. Maslinic acid was applied topically to the tip of the mice ear 30 minutes before TPA treatment and the ear

thickness was measured before treatment and 6 h after TPA treatment. Maslinic acid exhibited strong inhibitory effects (ID₅₀ = 0.13 mg/ear) on TPA-induced inflammation. The same study also showed that triterpenes possessing more than one oxygen-bearing functional group such as both hydroxyl and carboxyl group have higher inhibitory activities on TPA-induced inflammation in mice. Maslinic acid which has one additional hydroxyl group compared to its parent compound oleanolic acid has lower ID₅₀ for inhibition of inflammation.

Studies investigating the mechanism of maslinic acid in the *in vitro* models of inflammation showed that it regulates reactive species production and its corresponding inflammatory enzyme expressions. In a study evaluating the effect of maslinic acid in reactive oxygen and nitrogen-derived species and proinflammatory cytokines, it showed that maslinic acid significantly suppressed lipopolysaccharide- (LPS-) induced production of nitric oxide (NO) and iNOS gene expression, secretion of inflammatory cytokines interleukin-6 and tumour necrosis alpha (TNF- α), and the generation of hydrogen peroxide in murine peritoneal macrophages [16]. Qian et al. also observed that maslinic acid protects cortical neuron against oxygen-glucose deprivation-induced injury by inhibiting the level of NO, which was correlated with reduced iNOS protein and mRNA levels [21]. NO has a variety of regulatory mechanisms ranging from vasodilatation and blood pressure control to neurotransmission. High levels of NO produced from iNOS are an important mediator which lead to the production of reactive nitrogen oxide species, contributing to a wide range of chronic inflammations and infectious diseases [64]. Inhibition of NO production by blocking iNOS expression may be a strategy for treatment of chronic inflammation.

In another similar study, maslinic acid was shown to inhibit the expression of iNOS and COX-2 as well as the release of proinflammatory mediators including NO and TNF- α in LPS-induced cortical astrocyte cultures [17]. The inhibitory effects of COX-2 expression and enzyme activity by maslinic acid were also observed in several other culture systems including human macrophages, B lymphocytes, primary human chondrocytes, primary rat astrocytes, and SK-S-NH neuroblastoma type cell line [64]. The release of PGE₂, an enzymatic product derived from COX-2, was also downregulated in primary human chondrocyte, primary rat astrocytes, and neuroblastoma type cell line. A thorough clinical study of patients with COX-2-related pathologies such as arthrosis, arthritis, or fibromyalgia reported the effectiveness of maslinic acid given in simple topical treatments in the affected areas, showing reduction of discomfort and considerable increase of flexibility of the joint [65]. Interestingly, complete remission of symptoms was observed in patients younger than 60 years old in less than one month of maslinic acid treatment. These findings collectively showed that maslinic acid has beneficial effects in modulating COX-2-related chronic inflammatory diseases.

3.2. Modulatory Effects of Maslinic Acid on Other Inflammation-Related Diseases. Inflammatory cells and cytokines also contribute to tumor growth and progression. Previously

published literature has indicated that COX-2 creates a tumor-promoting environment which transforms epithelial cells. COX-2 is also inducible by oncogenes ras and scr, IL-1, hypoxia, ultraviolet light, epidermal growth factor, transforming growth factor-beta (TGF- β), and TNF- α [66]. Maslinic acid has been shown to inhibit the metastatic capacity of DU145 human prostate cancer cells. It reduces epidermal growth factor-induced DU145 cell migration via down-regulation of both matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (uPA) systems. The study showed that maslinic acid inhibits hypoxia inducible factor-1 α (HIF-1 α), one of the regulators of angiogenesis in response to oxygen deficiency which has been associated with inducing expression of MMP-2, MMP-9, and uPA [67]. The protective effect of maslinic acid was also reported in a spontaneous intestinal polyposis animal model. The results showed that maslinic acid-enriched diet inhibited the formation of polyps in the small intestines of Apc^{Min/+} mice by regulating genes associated with inflammation pathways. It is suggested that maslinic acid suppress chronic inflammation which contributed to the development and sustainability of intestinal adenomatous polyps in Apc^{Min/+} mice [15].

4. Molecular Targets of Maslinic Acid in Regulating Inflammatory Pathway

Considering that maslinic acid regulates inflammation through inhibiting iNOS and COX-2 expression, it is postulated that it inhibits the activity of NF- κ B, a transcription factor which binds to the promoter sequence of these two enzymes. Li et al. proved that maslinic acid affects the NF- κ B pathway by inhibiting I κ B α phosphorylation, thus preventing NF- κ B translocation to nucleus and its DNA-binding activity to the COX-2 promoter in pancreatic cancer cells, Panc-28 [14]. NF- κ B is recognized as a stress-regulated transcription factor, which plays a key role in the control of inflammatory responses [68]. NF- κ B transcription factors are dimer proteins (typically p65/p50 heterodimer) retained in the cytosol by inhibitory proteins, including inhibitory-kappa B (I κ B) proteins I κ B α , I κ B β , I κ B ϵ , and I κ B γ [69]. After receiving a stimulatory signal such as LPS or TNF- α , the I κ B α inhibitory protein is phosphorylated by I κ B kinases (IKKs), which allow NF- κ B to translocate from the cytoplasm to the nucleus, where it binds to the promoter region and transcribes its target genes [70]. The inhibitory effect of maslinic acid on NF- κ B activation was also shown in Raji B lymphoma cells where it was correlated to the inhibition of COX-2 expression in a concentration-dependent manner. In addition, the authors also showed that maslinic acid was able to suppress activation of activator protein (AP-1) [71].

The NF- κ B transcriptional activity can be modulated through phosphorylation by various members of the mitogen-activated protein kinase (MAPK) family. Majority of the studies investigated the effect of maslinic acid in mediating apoptosis via activation of JNK and p38 MAPK [72, 73]. Meanwhile, others have shown that maslinic acid inhibited osteoclastogenesis by downregulating phosphorylation of MAPKs and AP-1 activity, inhibited the

I κ B α phosphorylation and degradation, and blocked NF- κ B phosphorylation, nuclear translocation, and DNA-binding activity by downregulating receptor activator of NF- κ B (RANK) expression and blocking RANK interaction with tumor necrosis factor receptor-associated factor 6 (TRAF6) [74]. Maslinic acid also suppressed the expression of PKC β I, δ , and ζ in tumour promoter phorbol 12-myristate 13-acetate-(PMA-) induced Raji cell model [75]. The authors proposed that the inhibition of PKC activity by maslinic acid may explain the regulation of downstream targets in the signaling cascade including NF- κ B and downstream gene expression such as COX-2, VEGF, cyclin D1, and MMP-9 [14, 75]. Other natural triterpenoids such as α -amyrin have been reported to inhibit PMA-induced mouse skin inflammation through suppressing PKC α [76]. Table 1 summarizes the various inflammatory modulating effects of maslinic acid.

A recent study showed that phospholipase A₂ (PLA₂) may be a potential binding target of maslinic acid [20]. PLA₂ is responsible for hydrolyzing membrane phospholipids and releasing AA which serves as a substrate COX-2-mediated prostaglandins production [77]. There is evidence that AA release also occurs through different PKC isoforms activation [78]. Inhibition of PLA₂ would decrease formation of AA and production of PGs. PLA₂ inhibitors are currently being developed as a therapeutic strategy, focusing on the development of specific PLA₂ isoform inhibitors for treatment of inflammatory diseases. Mammalian tissues contain many secretory PLA₂s (sPLA₂s) including group I/II/V/X [79]. The enzyme sPLA₂-GV has been involved in prostanoids production in inflammatory cells such as macrophages and mast cells [80, 81]. A preliminary study by Yap et al. showed that maslinic acid inhibited sPLA₂-GV enzyme activity in a concentration-dependent manner. The sPLA₂-GV enzyme inhibitory activity shown by maslinic acid is more potent compared to ursolic acid. Molecular docking study further showed that maslinic acid binds to the sPLA₂-GV interfacial phospholipid binding site via hydrogen bonding and hydrophobic interaction, thereby inhibiting the enzymatic activity of sPLA₂-GV [82].

5. Future Prospects

Maslinic acid has been widely accepted as a natural compound with anti-inflammatory effects. Recent studies have elucidated its molecular mechanism and potential binding targets (Figure 4). Nevertheless, it is still unknown how maslinic acid regulates the PKC/NF- κ B inflammatory signaling pathways which contribute to the inhibition of iNOS/COX-2 activity and NO/PGE₂ release. Further studies are required to unravel the mechanism of maslinic acid in regulating upstream protein kinases or transcriptional targets in response to specific inflammatory stimuli which leads to the reduction of proinflammatory enzyme expression and activity. Direct interaction and inhibition of the PLA₂ enzyme upstream the arachidonic acid pathway may also be one of the mechanisms of maslinic acid which reduces substrate availability for COX-2-mediated PGE₂ formation. It is hoped that future studies will provide insight into the

TABLE 1: Inflammatory modulating effect of maslinic acid.

Inflammatory model	Modulatory effect of maslinic acid	References
12-O-Tetradecanoylphorbol-13-acetate- (TPA-) induced ear edema	Maslinic acid reduced TPA-induced ear edema at the concentration of 0.13 mg per ear	[11]
Spontaneous intestinal polyposis animal model	Maslinic acid-enriched diet inhibited the formation of polyps in the small intestines of Apc ^{Min/+} mice by regulating genes associated with inflammation pathways	[15]
Lipopolysaccharide- (LPS-) induced murine macrophages	Maslinic acid suppressed production of nitric oxide (NO) and inducible nitric oxide synthase (iNOS) gene expression, secretion of inflammatory cytokines interleukin-6, and tumour necrosis alpha (TNF- α)	[16]
LPS-induced cortical astrocyte cultures	Maslinic acid inhibits the expression of iNOS and COX-2 as well as the release of proinflammatory mediators including NO and TNF- α	[17]
Oxygen-glucose deprivation-induced cortical neuron injury	Maslinic acid reduced NO levels and iNOS mRNA and protein expression	[21]
COX-2-related pathologies such as arthrosis, arthritis, or fibromyalgia	Maslinic acid given in simple topical treatments showed reduction of discomfort and considerable increase of flexibility of the joint	[65]
Phorbol 12-myristate 13-acetate- (PMA-) induced Raji B lymphoma cells	Maslinic acid suppresses PKC β I, δ , and ζ , COX-2 expression, NF- κ B, and AP-1 activation	[71, 75]
Osteoclastogenesis and bone loss	Maslinic acid suppresses osteoclastogenesis by regulating receptor activator of NF- κ B ligand- (RANKL-) mediated NF- κ B and mitogen-activated protein kinase (MAPK) signaling pathways	[74]

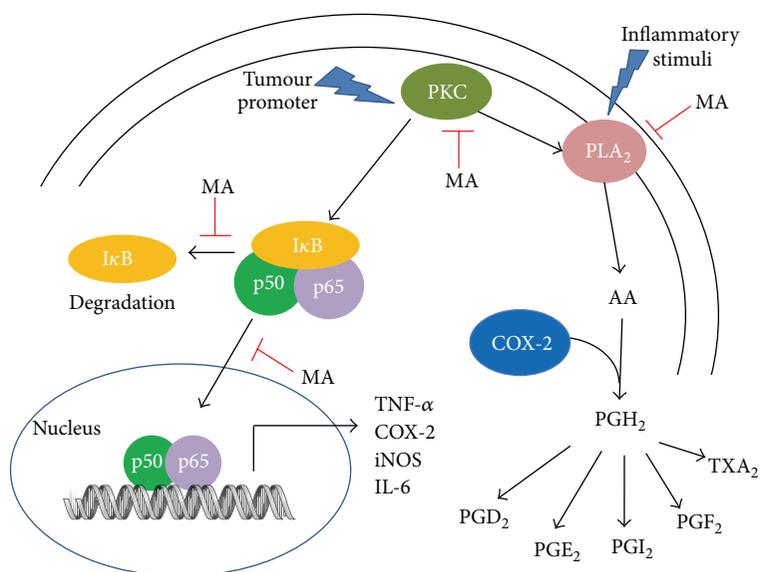


FIGURE 4: Molecular mechanism of maslinic acid in targeting inflammatory pathways. PKC plays a central role in the activation of NF- κ B (p50/p65). Once activated, the I κ B protein is degraded which allows NF- κ B to translocate from cytoplasm to the nucleus, where it transcribes the expression of downstream proinflammatory genes such as TNF- α , COX-2, iNOS, and IL-6. It was shown that maslinic acid inhibited PKC activation, I κ B α degradation, and NF- κ B nuclear translocation, which might correlate to its anti-inflammatory properties. In addition, evidence also demonstrated the role of PKC in mediating PLA₂ phosphorylation and AA release. Once released from membrane phospholipids, AA can be converted into prostanoids through the action of COX enzymes. Considering that prostanoids are important mediators of inflammation, the anti-inflammatory effect of maslinic acid may be explained through its effect in inhibiting PKC activation and/or PLA₂ enzyme activity which reduces the substrate availability for COX-2-mediated prostanoids biosynthesis in inflammatory cells.

anti-inflammatory mechanism of maslinic acid and further develop maslinic acid as a potential dietary nutraceutical.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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