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Review Article

From Mechanisms to Clinical Trials: Maslinic Acid, a Promising Modern Anti-inflammatory Drug?

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Abstract

Chronic inflammation plays an essential role in various severe diseases and has become a main cause of death. Anti-inflammation medications for prevention and treatment of inflammation-related diseases are urgent. Maslinic Acid (MA), a pentacyclic triterpene abundant in olives, has been on our plates for years, but its anti-inflammatory mechanism has been clarified clearly until the last five years. Subsequently, the anti-inflammatory effect of MA for inflammation-related diseases was verified in pre-clinical and clinical studies. The MA studies reported in PubMed, Web of Science, Google Scholar, Baidu Scholar, CNKI, Science Direct, Springer and Wiley databases or registered in clinical trial management platforms were searched with the following key terms: maslinic acid, inflammation, inflammatory disease, pharmacological activity. This review from the perspective of medicine combed the anti-inflammation molecular mechanisms of MA and assessed the recent clinical trials, revealing the potential therapeutic use of Maslinic Acid as a new drug for the prevention and treatment of chronic inflammation-related diseases. These results should encourage more pre-clinical and clinical studies with stringent design and more strong evidence to accelerate the drug development MA.

Keywords: Maslinic Acid; Chronic Inflammation; NF-κB

Abbreviations

AKT: Protein Kinase B; AREs: Antioxidant Response Elements; BA: Bredemolic Acid; BMI: Body Mass Index; CAIA: Collagen Antibody-induced Arthritis; COX-2: Cyclooxygenase 2; eNOS: Endothelial NOS; GM-CSF: Granulocyte-Macrophage Colony Stimulating Factor; HEAC: Human Aortic Endothelial Cells; hGIIA: Human Group IIA; HO-1: Heme Oxygenase-1; HUVEC: Human Umbilical Vein Endothelial Cells; HUVECs: Human Umbilical Vein Endothelial Cells; IFNγ: Interferon γ; IFN-γ: Interferon-γ; IKK: *IκB Kinase; IL-1*: Interleukin-1; IL-10: Interleukin-10; IL-12: Interleukin-12; IL-13: Interleukin-13; IL-1R: Interleukin-1 Receptor; IL-23: Interleukin-23; IL-4: Interleukin-4; IL-6: Interleukin-6; IL-6R: Interleukin-6 Receptor; iNOS: Inducible Nitric Oxide Synthase; IκB: Inhibitor of NF-κB; JAK: Janus Kinase; LPS: Lipopolysaccharide; MA: Maslinic Acid; MAP3: Mitogen Activated Protein 3; MAPK: Mitogen-Activated Protein Kinase; NAFLD: Non-Alcoholic Fatty Liver Disease; NF-κB: Nuclear Factor-κB; Nrf2: Nuclear Factor Erythroid 2-Related Factor 2; OA: Osteoarthritis; PI3K: Phosphatidylinositol 3 Kinase; PKB (also called Akt): Protein Kinase B; QOL: Quality of Life; RHD: Rel Homology Domain; ROI: reactive oxygen intermediates; ROS: Reactive Oxygen Species; sPLA2: Secretory Phospholipase A2; STAT: Signal Transducer and Activator of Transcription; STAT: Signal Transducer and Activator of Transcription; TAD: Carboxy-terminal Transactivation Domains; TGF-β: Transforming Growth Factor β; TLR: Toll-like Receptors; TNF: Tumor Necrosis Factor; TNFR: Tumor Necrosis Factor Receptor; TPA: 12-O-tetradecanoylphorbol-13-acetate; VOO: Virgin Olive Oil; VSMCs: Vascular Smooth Muscle Cells; WBVT: Whole-Body Vibration Training

Introduction

Inflammation is a crucial biological process in maintaining homeostasis and repairing damaged tissue. Nevertheless, chronic inflammation plays a vital role in the development of many severe diseases, including rheumatoid arthritis, asthma, chronic inflammatory bowel diseases, type 2 diabetes, neurodegenerative diseases [1], cardiovascular disease [2] and cancer. With more than 50% of all deaths being attributable to inflammatory disorders, anti-inflammation treatment is mounting concerns and interest. Anti-inflammation treatment could help suppress or alleviate disease symptoms such as seizures in epilepsies [3], inflammatory erosion, tissue hyperplasia [4], etc.

Maslinic acid (MA, 2-α, 3-β-dihydroxiolean-12-en-28-oic acid), a natural compound abundant in olives, has been widely consumed in daily diet or in traditional medicinal herbs in Europe (Mediterranean region), Asia (China, Japan, Korea, India), South America (such as Brazil), etc. [5]. A wide range of its biological activities includes anti-inflammation, antioxidant [6], antitumor, antidiabetic [7], antimicrobial [8] and growth-stimulating effects, has been observed in various research models. In recent years, mounting evidence of MA's anti-inflammatory mechanism further confirmed its anti-inflammatory effect observed in traditional usage, suggesting its potential to be applied as anti-inflammatory medication for inflammatory-related diseases. Thus, we searched the articles in PubMed, Web of Science, Google Scholar, Baidu Scholar, CNKI, Science Direct, Springer, Wiley databases and clinical trials of MA registered in clinical trial management platforms with the following terms: maslinic acid, inflammation, inflammatory disease, pharmacological activity. Here, from the perspective of medicine, we provide an overview of the recent progress made regarding the anti-inflammation mechanism of MA and assessed the recent clinical trials, hoping more strong evidence of stringent clinical studies to confirm the anti-inflammatory effect of MA alone for prevention and treatment of chronic inflammation-related disease.

Characteristics of MA

As people discover the remarkable biological properties of MA, it gradually gains attention as an excellent pharmacologically active product. MA (2-α, 3-β-dihydroxyolean-12-en-28-oic acid) is a pentacyclic triterpenoid with the olean-12-ene substituted by hydroxy groups at positions 2 and 3 and a carboxy group at position 28 (the 2α,3β stereoisomer) (Table 1). The molecular weight of MA ($C_{30}H_{48}O_4$) is 472.7 g/mol and other chemical properties are listed in table 1. Its melting point is 249~250℃. It is sparingly soluble in aqueous buffers but soluble in organic solvents such as ethanol, DMSO, and dimethylformamide, with 0.5, 20 and 15 mg/ml solubility, respectively. The water-soluble MA solution could be obtained by first dissolving it in organic solvents and then diluting the solution with aqueous buffer of choice. MA can be separated and purified from lots of natural sources, most notably pomace olive oil. Using a high-speed countercurrent chromatography, 271.6 mg MA with 86.7% purity can be isolated from 600 mg olive pulp within only 2hrs [9]. Although MA has long been a component of our food, its pharmacokinetics *in vivo* has not been clearly detected until recently. Series of MA pharmacokinetic parameters in rats were detected [10,11], confirming that MA is a safe component rapidly absorbed and widely distributed. Later, a randomized controlled trial of healthy adults found out that after ingesting 6 mg MA in 30 ml of olive oil at 2 h, the peak plasma concentration of MA could reach 30 ng/ml [12]. These data laid the foundation for the clinical application of MA as a solo medicine.

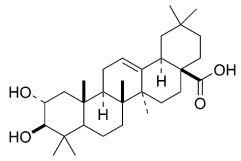
Chemical Properties	Maslinic acid
Chemical Formula	
Molecular Weight	472.7 g/mol
Hydrogen Bond Donor Count	3
Hydrogen Bond Acceptor Count	4
Rotatable Bond Count	1
Topological Polar Surface Area	77.76 Å²
XLogP3-AA	6.5
Exact Mass	472.35526 g/mol
Heavy Atom Count	34
Formal Charge	0
Complexity	919
Isotope Atom Count	0
Defined Atom Stereocenter Count	9
Covalently-Bonded Unit Count	1
Compound is Canonicalized	Yes

Table 1: Chemical properties of maslinic acid.

Molecular mechanism of anti-inflammatory activity of MA

MA directly inhibits NF-κB activity via targeting IκB

Inflammation is an innate immune response to harmful stimuli, including pathogens, toxic compounds, irradiation, damaged cells, and endogenous stress signals. These extracellular stimuli are mainly divided into two categories: the antigen receptors and the pattern-recognition receptors such as TLRs and cytokine receptors, including interleukin-1 receptor (IL-1R), interleukin-6 receptor (IL-6R) and tumor necrosis factor receptor (TNFR) to trigger intracellular inflammatory signaling pathways, most commonly the Nuclear Factor-κB (NF-κB), the mitogen-activated protein kinase (MAPK) and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways.

NF-κB is a protein complex that controls the transcription of target genes, which regulate a wide variety of fundamental processes, including cell proliferation, differentiation, and survival. There are five proteins in the mammalian NF-κB family: NF-κB1 (also called p105/p50), NF-κB2 (also called p100/p52), RelA (also called p65), RelB and c-Rel. NF-κB1 and NF-κB2 are synthesized as large precursors, p105 and p100, then degraded by ubiquitin into the mature NF-κB subunits, p50 and p52, respectively. All the members have a Rel homology domain (RHD) in their N-terminus, a domain that is required for dimerization, DNA binding, and nuclear translocation. In addition, RelA (p65), RelB, and c-Rel contain carboxy-terminal transactivation domains (TAD), necessary for the target gene transcription. p50 and p52, due to lack of TAD, need to bind with other members to from Rel/p50 and Rel/p52 heterodimers to trigger transcription. NF-κB dimers keep inactive "resting" state in the cytoplasm through binding with inhibitor of NF-κB (IκB) proteins. Once stimuli trigger the activation of the IκB, IκB undergoes phosphorylation, ubiquitination, and degradation to release NF-κB dimers, thus NF-κB dimers turn to "active" state: translocating to the nucleus and binding specific DNA sequences to promote transcription of target genes including inflammatory and adhesion cytokines, prostaglandins, inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2). Therefore, NF-κB activation depends on IκB degradation (Figure 1).

MA could not only prevent IκB-α phosphorylation to keep from IκB degradation but also upregulate the IκB-α expression [13], which, in turn, reduces NF-κB nuclear localization, phosphorylation and the DNA binding activity, finally inhibit inflammatory pathways [14] (Figure 1). The inhibition of inflammation via regulating IκB degradation by MA was further confirmed in the collagen

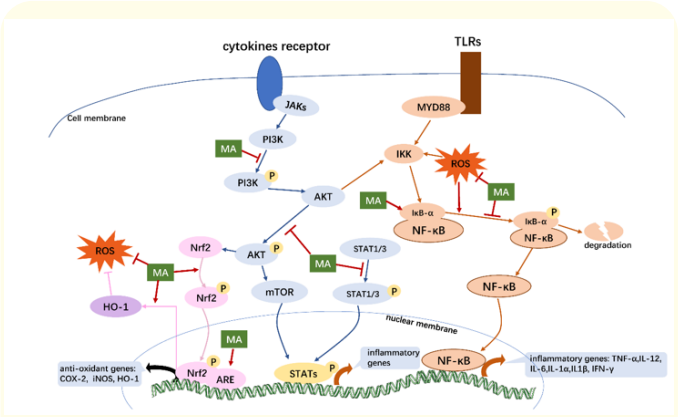


Figure 1: Scheme of the anti-inflammatory and antioxidant mechanisms of Maslinic acid. Brown lines and ellipses indicate NF-κB signal pathway. Blue lines and ellipses indicate PI3K/AKT and JAK/STAT pathways. Pink lines and ellipses indicate anti-oxidation-involved Nrf2/HO-1 pathway. Arrows denote activation or upregulation and T-shaped lines indicate inhibition. Abbreviations: TLR, Toll like receptor; MYD88, Myeloid differentiation primary response 88; IKK, IκB kinase; IκB, inhibitor of NF-κB; NF-κB, Nuclear Factor-κB; JAK, Janus kinase; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, rapamycin; STAT, signal transducer and activator of transcription; Nrf2, nuclear factor erythroid 2–related factor 2; ARE, antioxidant response elements; HO-1, heme oxygenase-1; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; IL-12, interleukin-12; IL-6, interleukin-6; IL-1α, interleukin-1α; IFN-γ, interferon-γ.

antibody-induced arthritis (CAIA) mice model: MA upregulated IκB-α expression to suppress the NF-κB signaling pathway and to downregulate the proinflammatory cytokines IL-1β, IL-6, interleukin-12 (IL-12) [15], tumor necrosis factorα (TNF-α), IL1β, and interferon γ (IFNγ). Thus, MA could alleviate carrageenan-induced paw edema and decreased the arthritis score of CAIA mice-fewer inflammatory cells in the knees of MA treated mice with no knee injury [16]. Mice models of other diseases verified this anti-inflammation molecular mechanism of MA. In the osteoarthritis mice model established by the medial meniscus, MA, in a dose-dependent manner, strongly inhibited p65 translocation and IκBα degradation in IL-1β-stimulated cells [17]. In the LPS-induced acute liver injury mice model, MA attenuated NF-κB activation by increasing the levels of phosphorylation of p65 and IκB-α in liver tissues. MA ameliorated acute liver injury [18] and relieved arthritis [17] in the mouse model, suggesting it may use as a potential agent for the anti-inflammation treatment.

MA indirectly inhibits NF-κB activity via the PI3K/AKT and JAK/STAT pathways

MA could inhibit other inflammatory signaling pathways such as the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) [17] and JAK/STAT [19] to indirectly modulate NF-κB signaling (Figure 1). The PI3K/AKT pathway, an intracellular signal transduction pathway that promotes cell proliferation, cell survival, and growth, is the upstream pathway of NF-κB. AKT activates the NF-κB pathway through direct activation of IκB kinase (IKK). Yan-Lin Chen., *et al*. observed that MA could not only inhibit p65 translocation and IκBα degradation but also inhibit the phosphorylation of IL-1β-induced PI3K and AKT at the same time. Consequently, MA decreases the expression of inflammatory mediators such as cyclooxygenase-2, IL-6, TNF-α, and prostaglandin E2 in a concentration-dependent manner in human osteoarthritis (OA) chondrocyte. They further observed in the surgically induced OA mice model by medial meniscus that MA could ameliorated OA development via inhibition of AKT and PI3K phosphorylation, suggesting MA is a potential therapeutic agent against OA [17].

MA can also inhibit JAK/ signal transducer and activator of transcription (STAT) signaling (Figure 1), which is essential for signal transduction resulting from cytokine and growth factor receptors [20]. In the *in-vitro* model of human umbilical vein endothelial cells (HUVECs) treated with lipopolysaccharide (LPS), MA not only reduced NF-κB activity but also induced HO-1 expression to down-regulate the STAT1 phosphorylation [19]. In the *in-vivo* mice skin tumor model treated by 12-O-tetradecanoylphorbol-13-acetate (TPA), MA significantly inhibited STAT3 phosphorylation on its tyrosine 705 and serine 727 residues and the downstream signaling of STAT3, resulting in reducing skin inflammation and inhibiting skin tumor promotion [21].

MA indirectly inhibits NF-κB activity by activating Nrf2/HO-1 pathway to decrease ROS level

Besides anti-inflammatory effect, MA exerts anti-oxidation effect through the protein kinase B (Akt)/nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signal pathway (Figure 1). Xiaofei., *et al*. found that MA induced Akt activation in a dose- and time-dependent manner, leading to an elevated expression of Nrf2 and HO-1 promoter, consequently increasing HO-1 expression in vascular smooth muscle cells (VSMCs) and protecting VMSCs from oxidative stress [22]. Ampofo, E., *et al*. found that MA induced Nrf2 transfer from cytoplasm to nucleus and increases the activity of antioxidant response elements (AREs) to activate the expression of HO-1 [23]. Another study observed that MA significantly increased the expression of antioxidant enzymes HO-1 and endothelial NOS (eNOS) and reduced oxidative DNA damage [24]. In addition, some evidence showed that MA could decreased the reactive oxygen species (ROS) level to show the antioxidant potential and improve cellular tolerance to oxidative stress. For example, MA could decrease the ROS level significantly in the impaired human aortic endothelial cells (HEAC) endothelial cell by high glucose, inhibited the inflammatory cytokines expression induced by high glucose and suppressed the cellular apoptosis ratio induced by high glucose [24]. Khalida Mokhtari., *et al*. found when B16F10 melanoma cells cultured without fetal bovine serum, Low concentration MA (0.44μM) could decreased ROS levels to improve tumor cell tolerance to oxidative stress [25]. In fact, ROS may activate NF-κB through alternative IκBα phosphorylation, which result in the degradation of IκBα [26]. Therefore, MA decreases ROS level, also resulting in inhibition of the IκBα phosphorylation and NF-κB activity, exerting anti-inflammatory effect [27]. The cardioprotective effect may be attributed to the ability of MA to ameliorate antioxidants [28].

The effect of MA on inflammatory cells

Inflammation, as a complex biological response to harmful stimuli, involves a variety of cells including neutrophils, macrophages, lymphocytes, and plasma cells. Macrophages play a central role in the development and maintenance of the inflammatory response. Macrophages have two distinct types, identified as M1 (or classically activated macrophages) and M2 (or selectively activated macrophages). M1 macrophages can be activated by lipopolysaccharide (LPS) or be induced by interferon-γ (IFN-γ), TNF-α, or granulocyte-macrophage colony stimulating factor (GM-CSF). M1 exerts pro-inflammatory response through secreting inflammatory cytokines such as IL12、IL-1β、IL-6、interleukin-23 (IL-23) and TNF-α and producing inducible nitric oxide synthase (iNOS) and reactive oxygen intermediates (ROI). M2 macrophages can be induced and activated by interleukin-4 (IL-4), interleukin-13 (IL-13), interleukin-10 (IL-10), transforming growth factor β (TGF-β), glucocorticoids, immune complexes, etc. It has anti-inflammatory, angiogenesis, and tissue repair functions [29]. Macrophages constantly shift M1 or M2 functional phenotype to regulate tissue homeostasis. It has become a major target in the treatment of many

diseases. Cristina., *et al*. found that MA could increase IFN-γ production, which leads to M1 polarization and a decrease in IL-4 and IL-6 production. This then leads to M2 polarization in THP-1 (human acute monocytic leukemia) macrophages. Meanwhile, MA increased cytokines related to macrophages recruitment such as IL-8, IL-1α, IL-1β, and pro-inflammatory cytokine IL-6 [30]. A recent study gave a similar conclusion with the effect of MA on THP-1 macrophages that MA increases IL-1β cytokines and inhibits TNF-α production in LPS-induced human U937 macrophage [31].

MA also acts on monocyte and neutrophil to inhibit inflammation. Yap, WH., *et al*. found that MA could bind with human group IIA (hGIIA)-secretory phospholipase A2 (sPLA2) enzyme to inhibit the access of catalytic calcium ion for enzymatic reaction and to block hGIIA-sPLA2 to bind with membrane phospholipid, leading to reduce hGIIA-sPLA2-induced THP-1 monocyte adhesive and migratory capabilities [32]. Subsequently, Yap, WH., *et al*. confirmed that MA could inhibit THP-1 monocyte adhesion to human umbilical vein endothelial cells (HUVEC) cells but induce trans-endothelial migration only at low concentration. Meanwhile, MA down-regulates both gene and protein expression on VCAM-1 and MCP-1 in HUVECs, thus to further reduce monocytes adhesion to endothelial cells [33]. Thiele., *et al.* found MA could reduce dermatitis edema caused by croton oil in mouse ears by reducing neutrophil infiltration [34].

MA Clinical trials for inflammation-related diseases

The NF-κB pathway is usually aberrantly activated in a sustained inflammatory response which contributes to the pathophysiology of many chronic diseases and the development of inflammation-associated cancer. Inhibition of the NF-κB signaling became a promising strategy for the treatment of type 2 diabetes, rheumatoid arthritis, metabolic syndrome, cardiovascular disease, ischemia/reperfusion injury, and cancer. For example, metformin, a first-line medication of type 2 diabetes, ameliorates the proinflammatory state via downregulation of NF-κB signaling in type 2 diabetes and in cancer. Salsalate, an IκB kinaseβ-NF-kB inhibitor, could decrease C-reactive protein and expediate blood glucose, and promote insulin secretion in diabetes clinical trials [35]. Preclinical rodent studies extended the application of this strategy to target NF-κB to other disease models. For example, NF-κB downregulation could reduce ischemia/reperfusion brain injury and significantly reduce inflammation and infarct size, alleviating ischemic stroke [36]. By inhibiting the heme oxygenase-1(HO-1)/nuclear factor erythrocyte 2-related factor 2(Nrf-2) pathway, NF-κB activated could also significantly relieve inflammatory symptoms in rheumatoid arthritis murine model [37]. Strategies to target NF-κB pathways as such have led to some encouraging pre-clinical outcomes in cancer treatment [38]. IMD-0560, An IκB kinaseβ Inhibitor that could hold NF-κB dimers in the "resting" state, showed potent therapeutic efficacy in the ovarian cancer xenograft mice model.

The anti-inflammatory and antioxidative properties of MA has been confirmed in a wide variety of animal disease models (Summarized in table 2). Besides MA, some derivatives of MA were investigated regarding their anti-inflammation properties in some *in vivo* inflammation models. Benzyl (2α, 3β) 2,3-diacetoxy-oleann12-en-28-amide (EM2), a benzylamide derivative of MA, also showed anti-inflammatory property in TPA-induced local acute inflammation model [39].

Following the encouraging results of these pre-clinical studies, clinical studies on the anti-inflammatory effects of maslinic acid are gradually carried out. The earliest clinical trial exploring the benefits of MA was on arthritis, a disease highly related with chronic inflammation. In 2016, Satoshi F., *et al*. performed a randomized, double-blind, placebo-controlled trial on 20 volunteers with mild knee joint pain in Japan to investigate the effects of consuming orally administered 50 mg MA daily for 12 weeks. The results showed that MA was most likely to improve joint condition and quality of life (QOL) by reducing pain and inflammatory response, resulting in significant decrease of the body weight and body mass index (BMI) [46]. Subsequently, they performed an open-label community residents-based clinical study on an isolated island with 29 elderly residents (mean 70.0±10.1 years). They were given 30 mg of MA daily for 16 weeks. The results showed that intake of MA could decrease knee joint pain (VAS and JKOM score), body weight, BMI, and could improve physical-related QOL [47]- a conclusion in accordance with the previous trial. Later, another research team in Japan performed a double-blinded, placebo-controlled, randomized intervention study that enrolled women aged 65-85 years with knee osteoarthritis (OA). The results showed that whole-body vibration training (WBVT) in conjunction with ingesting three 50 mg MA capsules (16.7 mg of MA) at breakfast for 20 weeks could reduce knee OA and remarkably improve knee and muscle function. This suggests the anti-inflammatory supplement MA is an effective treatment when used in combination with WBVT for improving knee muscle strength [48]. In 2018, a parallel, double-blind, randomized, placebo-controlled trial with 36 partici-

Chronic Disease	Animal Model	Dose MA (mg/kg)	Notable Changes Observed	Reference(s)
Arthritis	Collagen antibody induced in arthritis DBA/1J mice	200 mg/kg	Reduced paw edema Reduced TNF-α, IL-1b levels Inhibited TLR and NF-κB signaling pathways Upregulated gene expression of type III collagen Inhibited leukotriene biosynthesis pathway	[15]
	Collagen antibody induced in arthritis DBA/1J mice	100 mg/kg	Reduced the gene expression of TNF-α, IL-1β, and IFN-γ Decreased the paw arthritis score Reduction in inflammatory cells Reduced joint destruction	[16]
Ischemia/ reperfusion	I/R model of injury of blood vessel in BALB/c mice	20 mg/kg	Increased the number of rolling leukocytes Stabilize volumetric blood flow Reduced leukocyte adherence during the early I/R	[23]
Osteoarthritis	DMM surgical induced in C57BL/6 mice	10 mg/kg	Reversed hypocellularity Reduced cartilage cauterization Reduced proteoglycan degradation	[17]
Sepsis	Cecal ligation and puncture induced sepsis in C57BL/6 mice	0.7 mg/kg	Improved the survival rate of mice Reduced impairment of the lung tissue	[40]
Obesity	High fat diet induced obesity in C57BL/6J mice	38 mg/kg	Improved insulin sensitivity and lipid homeostasis Enhanced glucose tolerance Reduction on body weight Reduced pro-inflammatory genes in liver and adipose tissue Restored vascular function	[41]
	High fat diet induced obesity C57BL/6 mice	20 mg/kg	Reduced liver weight and lipid accumulation Improved hepatocyte steatosis Reduced leptin, and free fatty acid concentrations	[42]
Leukemia	Injected(i.p.) WEHI-3 cells induced leukemia in BALB/c mice	32 mg/kg	Enhanced macrophage phagocytosis Improved NK cell activities	[43]
Seizure	kainic acid induced seizure in C57BL/6 mice	40 mg/kg	Improved the survival rate of mice Reduced seizure scores Reduced hippocampal inflammatory and apoptotic injury Alleviated oxidative injury	[44]

Myocardial infarction	Isoprenaline induced in albino wistar rat	15 mg/kg	Reduced heart edema Reduced infiltrated inflammatory cells NO necrosis of cardiac fibers Preserved the structural integrity of myocardium Attenuated the increase of tumors and lesions	[28]
Colon Tumor	Azoxymethane/dextran sulfate sodium induced colon tumor in C57BL/6J mice	30 mg/kg	Reduced tumor volume, weight and number	[45]
	HCT116 xenograft tumor induced colon tumor in BALB/c nude mice	30 mg/kg	Reduction in inflammatory cytokines	
Liver injury	LPS/D-gal induced acute liver injury in BALB/c mice	50 mg/kg	Attenuated liver histopathologic changes Reduced inflammatory cytokines in serum and liver tissues Attenuated oxidative stress Reduced neutrophil infiltration	[18]
Pulmonary injury	LPS induced in C57BL/6 mice	0.7 mg/kg	Suppressed the levels of TNF-α and iNOS Alleviated lung tissue injury	[19]

Table 2: Overview of animal models used to study the anti-inflammatory and anti-oxidation properties of MA.
Note: DMM: Destabilization of the medial meniscus, I/R: Ischemia/reperfusion, LPS: Lipopolysaccharide, i.p.: Intraperitoneally, D-gal: D-galactosamine.

pants in Japan came to the same conclusion that MA combined with resistance training could significantly improve muscle mass and grip strength, and reduce knee pain [49]. Although these clinical studies had limited statistical power with small sample size, they evaluated the anti-inflammatory effect of MA with randomized controlled trial design. More clinical studies of MA treatment with large sample size and even for other inflammation-related diseases are still needed in the future.

In addition to treatment of inflammation-related diseases, daily supplement of MA for health benefits has been tried to evaluate in clinical trials. A randomized, double-blind, crossover, controlled study with 54 healthy volunteers (aged 20 to 50) was carried out to compare three kinds of olive oil consumption: virgin olive oil (VOO), OVOO (VOO with a high phenolic content), and FOO (OVOO with oleanolic and maslinic acids) for coronary heart disease (ClinicalTrials.gov ID: NCT02520739) [50]. Three years later, the results of this NUTRAOLEUM Study become a first-level evidence on the *in vivo* health benefits of olive oil triterpenes (oleanolic and maslinic acids) in healthy human-decreasing DNA oxidation via CoQ9 and CoQ10 and plasma inflammatory biomarkers such as IL-8 and TNF-α after three weeks of supplementation [6]. From this study, we confirmed the health benefits of the consumption of oleanolic and maslinic acids, but the benefits of MA alone still need to be confirmed by other clinical trials with rigorous design.

Conclusion

Inflammation is involved in various severe diseases and is recognized as a deadly symptom that is becoming increasingly prevalent. To inhibit the inflammation becomes necessary. MA is a natural anti-inflammatory ingredient in the Mediterranean diet and in the Traditional Chinese Medicine. As the mechanisms underlying the anti-inflammatory and antioxidant role of MA has gradually been elucidated and more clinical trials data would be obtained, the application of MA in the prevention and treatment of chronic inflammation-related diseases would become more and more extensive in the future.

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