Anti-Inflammatory Effects of Canthin-6-Ones

Subjects: Medicine, Research & Experimental

Contributor: Zongying Zhang, Anqi Wang, Yunhan Wang, Weichen Sun, Xiaorong Zhou, Qiuyun Xu, Liming Mao, Jie Zhang

Chronic inflammatory disease (CID) is a category of medical conditions that causes recurrent inflammatory attacks in multiple tissues. The occurrence of CID is related to inappropriate immune responses to normal tissue substances and invading microbes due to many factors, such as defects in the immune system and imbalanced regulation of commensal microbes. Thus, effectively keeping the immune-associated cells and their products in check and inhibiting aberrant activation of the immune system is a key strategy for the management of CID. Canthin-6-ones are a subclass of β-carboline alkaloids isolated from a wide range of species. Several emerging studies based on in vitro and in vivo experiments reveal that canthin-6-ones may have potential therapeutic effects on many inflammatory diseases.

Keywords: Canthin-6-one ; chronic inflammatory disease ; inflammasome

1. Introduction

Chronic inflammatory disease (CID) is a term to describe disease entities characterized by persistent inflammation. The development of this class of diseases is associated with aberrant immune responses to normal tissue substances or particular offending agents due to the occurrence of abnormalities in the immune system [1][2]. In response to injuries or some offending agents, the immune system may send out inflammatory cells and mediators to start the healing process or to eliminate infections. After this process, the inflammatory factors can be downregulated by several mechanisms. Failure of downregulation may result in persistent stimulation of inflammatory factors to the host tissues. The development of CID is usually due to persistent exposure to toxins, untreated acute inflammation, and autoimmune disorders, and may be associated with a wide range of conditions such as type 2 diabetes [3], rheumatoid arthritis [4], Alzheimer's disease [5], inflammatory bowel disease [6], and cancer [7]. Therefore, unchecked chronic inflammation may play a detrimental role to the host and mediate a variety of human diseases [8]. Appropriate management of the duration and strength of inflammation is an effective approach by the host immune system to maintain homeostasis in the body.

2. Canthin-6-Ones Suppress the Progression of Several CIDs

2.1. Inflammatory Bowel Disease (IBD)

IBD is a term to describe a class of diseases that cause inflammatory conditions in the gastrointestinal tract, primarily, Crohn's disease (CD) and ulcerative colitis (UC) [9][10]. The development of these diseases is associated with many inflammatory factors, including the increase of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12/23. The inhibition of these cytokines using neutralizing antibodies, such as infliximab and tocilizumab, has been proven to be effective in inducing remission of IBD [11][12][13], although there are also case reports showing that blockade of IL-6 may induce colitis in some patients with autoimmune diseases such as Takayasu arteritis [14][15]. Arunachalam et al. explored the role of canthin-6-one (1) in the management of colitis using a rat model induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS), a hapten that binds to tissue proteins and elicits inflammatory responses in the colon [16]. This model manifests pathological characters close to those found in patients with CD [17][18]. Using this model, the researchers found that canthin-6-one (1) can suppress TNBS-induced colitis based on macroscopic and histologic scoring data and the production of colonic pro-inflammatory mediators, including TNF-α, IL-1β, IL-12p70, and VEGF, while enhancing the level of the anti-inflammatory cytokine IL-10. Further in silico analysis of the molecular targets involved in gut inflammatory signaling revealed that canthin-6-one (1) might bind with p38α and TLR8. Moreover, in a study by Zhang et al. [19], the researchers used a strategy based on ultra-high performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) and identified a canthin-6-one alkaloid, 4-methoxy-5-hydroxy-canthin-6-one (6), from rat serum after oral administration of the Liandan Xiaoyan Formula (LXF). This compound could be rapidly absorbed following oral treatment in both dextran sulfate sodium-treated rats with UC conditions and the control animals. However, the role of this compound in UC, its intracellular targets, and inflammatory pathways need to be further studied.

2.2. Alzheimer's Disease (AD)

AD is a disorder that causes the degeneration of brain cells and is the leading cause of dementia, a syndrome characterized by reduced thinking and independence abilities [20][21]. Recent studies have shown that the major pathogenesis of AD is associated with the accumulation of the β-amyloid protein and/or abnormal tau protein, which causes oxidative stress and inflammation; the latter then induces the disturbance of brain cell functions and eventually causes cell death [20]. Guo et al. isolated several canthin-6-one alkaloids from the EtOAc extract of the *Picrasma quassioides* stem in a systematic phytochemistry study. In further functional tests, they found that several canthin-6-ones, including 9-hydroxy-canthin-6-one (10), 4,5-dimethoxy-canthin-6-one (12), 4-methoxy-5-hydroxyl-canthin-6-one (20), 4,5-dimethoxy-10-hydroxy-canthin-6-one (11), and 3-methylcanthin-5,6-dione (3), exhibited protective functions for nerves and thus improve memory and cognitive abilities in mice with AD induced by the amyloid-β peptide. With respect to the mechanisms, they found that these compounds showed potential neuroprotective activity in L-glutamate-stimulated PC12 and Aβ25-35-stimulated SH-SY5Y cell models [22]. This effect may be related to the anti-inflammatory and anti-oxidative activities of the compounds. Several studies have reported the role of 3-methylcanthin-5,6-dione (3) in suppressing NO production [22][23][24][25], while 9-hydroxy-canthin-6-one (10), 4,5-dimethoxy-10-hydroxy-canthin-6-one (11), and 4,5-dimethoxy-canthin-6-one (12) have a role in suppressing the production of pro-inflammatory cytokines [22]. As a neurotransmitter, NO plays a critical role in maintaining the normal function of the neurons, while overproduction of NO may induce nitroxidative stress, which is associated with some pathological changes in AD [26][27].

2.3. Parkinson's Disease (PD)

PD is a common neurodegenerative disorder characterized by the loss of dopaminergic neurons and the presence of intracytoplasmic-ubiquitinated inclusions [28]. It has been shown that mutations in alpha-synuclein (α-syn) may contribute to the development of this disease [29][30]. A study by Yuan et al. identified canthin-6-one (1) as an α-syn inhibiting compound, which promoted both wild-type and mutant α-syn degradation in a ubiquitin–proteasome-system-dependent manner in PC12 cells [31]. using CRISPR/Cas9 genome-wide screening technology combined with the GeCKO library and flow cytometry sorting method, proteasome 26S subunit, non-ATPases 1 (PSMD1) was identified as the target gene of canthin-6-one (1). However, the role of PSMD1 in PD needs to be verified in more extensive in vitro and in vivo studies. Considering the protective effects of several canthin-6-ones identified by Guo et al. [22] in their AD study using PC12 cells, as mentioned above, it is worthwhile to verify if PSMD1 has a role in AD, since no study on this topic is available in the literature. Correspondingly, the neuroprotective role of the compounds identified in the Guo et al. study may also play a role in PD; however, in vivo studies are needed to verify this speculation. Thus, the available data support a protective role of canthin-6-one (1) in neuronal cells by targeting PSMD1 and facilitating α-syn degradation, but its potential to be a PD-treating drug needs to be further confirmed. Moreover, the α-syn degrading role of canthin-6-one (1) is similar to the function of irisin [32], a bioactive peptide induced by exercise that is beneficial for health promotion. Further studies are needed to verify if canthin-6-one (1) can act as an alternative medicine to irisin in the treatment of PD. In addition, the anti-inflammatory and anti-oxidant activities of canthin-6-one (1) may also need to be considered when evaluating its effect on PD in animal models, since both factors are considered to be major regulators of PD [33][34].

2.4. Diabetes Mellitus (DM)

DM is a term to describe a group of diseases that affect the body's glucose metabolism. Patients with DM usually do not produce enough insulin or do not respond to insulin due to the loss of functional pancreatic β cells, resulting in high blood glucose levels [35]. The role of canthin-6-ones in DM was initially reported by Agrawal et al. Using a streptozotocin–nicotinamide-induced type-II diabetes model in rats, the researchers showed that single oral administration of a partially purified alkaloid basified toluene fraction (PPABTF) isolated from the roots of *Aerva lanata* L. (Amaranthaceae) (AL) can significantly reduce the serum glucose level of rats [36]. In further studies, they identified the main bioactive compound in the PPABTF as 9-hydroxycanthin-6-one (10) using high-performance thin layer chromatography. Although no mechanistical study of 9-hydroxycanthin-6-one (10) was conducted in the Agrawal et al. study in the context of DM, the effect of this compound has been reported by many other studies. For instance, it has a role in promoting the proliferation of neuronal cells (PC12) [22]. If this effect was similarly applicable to pancreatic β cells, it may be an important mechanism to explain the protective role of this compound in DM animals. Furthermore, 9-hydroxycanthin-6-one (10) can suppress the activation of NF-κB and thereby downregulate the production of pro-inflammatory cytokines [37]. As inflammation is also a critical factor that promotes DM progression, the possible inflammatory suppressive effect of 9-hydroxycanthin-6-one (10) is probably the second arm by which this compound protects the host from DM. Therefore, the protective role of 9-hydroxycanthin-6-one (10) in DM animals might be largely dependent on its potential protection of pancreatic cells and the suppression of the inflammatory milieu. However, all these speculations need to be verified by future studies.

2.5. Rheumatoid Arthritis (RA)

RA is an inflammatory condition causing irreversible cartilage and joint damage. Many cell types, such as joint macrophages and fibroblast-like synoviocytes (FLS), play a prominent role in the development of RA [38]. A study by Fan et al. found that a natural canthin-6-one alkaloid isolated from *Picrasma quassioides*, 4-methoxy-5-hydroxycanthin-6-one (6), suppressed the production of NO and the release of TNF-α from LPS-stimulated RAW 264.7 cells. More importantly, oral administration of 4-methoxy-5-hydroxycanthin-6-one (6) ameliorated adjuvant-induced chronic arthritis in rats. The 4-methoxy-5-hydroxycanthin-6-one (6)-treated animals also manifested reduced paw edema after treatment with carrageenan [39]. These observations suggest a possible role of 4-methoxy-5-hydroxycanthin-6-one (6) in RA-associated pathologies by regulating the production of NO and TNF-α by macrophages. It is not surprising to observe that the role of a canthin-6-one compound can suppress the production of TNF-α, since blocking signaling of this cytokine using neutralizing antibodies such as adalimumab and its biosimilars is an effective strategy for treating RA [40]. Furthermore, the inhibition of NO or iNOS using inhibitors is also efficacious for RA treatment, at least, in animal models [41]. Thus, 4-methoxy-5-hydroxycanthin-6-one (6) may be a molecule targeting both TNF-α and NO; however, its efficacy needs to be further determined in more extensive animal models.

2.6. Ulcers

Ulcers are painful sores that may appear anywhere in or on the body, such as in the blood vessels, the lining of the stomach, and the skin. Inflammation triggered by *Helicobacter pylori* (*H. pylori*) bacteria or the persistent application of nonsteroidal anti-inflammatory drugs (NSAIDs) is an important cause of ulcers, especially of those occurring in the gastrointestinal tract [42]. This disorder can also be affected by pathophysiologic events, such as impaired gastric secretions, and environmental factors, such as alcohol consumption and drug ingestion [43][44]. A recent study by De Souza Almeida et al. [45] found that the canthin-6-one alkaloid isolated from methanol-macerated rhizomes of *Simaba ferruginea A. St-Hil*. (*Simaroubaceae*), a herbal plant widely used in traditional medicine for the treatment of gastric ulcers, diarrhea, and fever, may have anti-ulcer activity. Further experiments revealed that pre-treatment of animals with canthin-6-one alkaloids reduced the generation of ulcers induced by ethanol and indomethacin in the gastric tissue in both mice and rats. Moreover, this effect of canthin-6-one (1) was partly mediated by inducing the production of NO and reducing the levels of myeloperoxidase and malondialdehyde. The decline of ulcers induced by canthin-6-one may not be mediated by the downregulation of inflammation in the local environment of the ulcer, since the inflammatory milieu might act as a beneficial factor and promote the healing of ulcers. A good example supporting this speculation is provided by the study by Freitas et al. [46], which showed that blockade of TNF-α delayed the wound healing process of ulcers in a rat model. However, the exact role of inflammation in ulcer healing needs to be further verified.

2.7. Erectile Dysfunction (ED)

ED is a condition that can be affected by both organic and psychogenic factors. It is also closely associated with inflammatory factors, such as those induced by infections [47]. Previous studies showed that the inhibition of phosphodiesterase-5 (PDE-5) using Tadalafil, a commercially available-carboline medication, is an effective treatment for ED, probably by suppressing PDE-5-mediated inflammatory responses [48][49]. Choonong et al. isolated several canthin-6-one alkaloids from *Eurycoma longifolia Jack* (EL) and *Eurycoma harmandiana Pierre* (EH), including canthin-6-one (1), 9-methoxycanthin-6-one (8), and 9-hydroxycanthin-6-one (10), and found that these canthin-6-ones show potent PDE-5 inhibitory effects [50]. Moreover, it has been shown that ED patients display an increased level of pro-inflammatory cytokines in their blood. Thus, inhibition of these cytokines is one of the common effects through which ED-treating drugs achieves their functions. For instance, sildenafil, a common PDE5 inhibitor used to treat ED, could suppress the blood concentration of many inflammatory mediators, including IL-6 and TNF-α [51]. In agreement with this finding, Sahin et al. [52] showed that blockade of TNF-α could normalize the circulating and cavernosal concentration of many inflammatory mediators, such as TNF-α, CRP, MCP-1, ICAM-1, and testosterone, and proposed that the inhibition of TNF-α may be a promising strategy for treating age-related ED. In addition, the inhibitory role of canthin-6-ones toward NO and iNOS may suggest a potential role of these compounds in improving ED by reducing oxidative stress, which acts as a promoting factor for ED development. A

2.8. Tumors

The occurrence and progress of tumors are highly associated with chronic inflammation in the tissues [53]. Many canthin-6-ones showing anti-tumor activity may also have potential anti-inflammatory effects. A previous study showed that canthin-6-one (1) had a strong anti-proliferation effect on many tumor cell lines, such as human prostate adenocarcinoma PC-3 cells, with low toxicity [54]. Several canthin-6-one derivatives may also have anti-tumor activity. For instance, Yunos et al. found that 9-methoxycanthin-6-one (14) manifests significant anti-tumor effects using a Sulphorhodamine B assay

[55]. Their further studies revealed that the effect of this compound is exerted by inducing tumor cell apoptosis. Furthermore, three other canthin-6-ones, including 9-hydroxycanthin-6-one (10), 9-methoxycanthin-6-one-N-oxide (16) and 9-hydroxycanthin-6-one-N-oxide (17), isolated from roots of *Eurycoma longifolia*, were cytotoxic to tumor cells [56]. Jiang et al. showed that four canthin-6-ones isolated from the stem of *Picrasma quassioides* Bennet (Simaroubaceae), including 5-hydroxy-4-methoxycanthin-6-one (15), 4,5-dimethoxycanthin-6-one (12), 8-hydroxycanthin-6-one(18), and 4,5-dimethoxy-10-hydroxycanthin-6-one (11), have a role in reducing cell growth and exhibit significant cytotoxicity to human nasopharyngeal carcinoma (CNE2) cells [23]. In addition, using in silico molecular docking studies, Bultum et al. found that several canthin-6-ones derived from *Brucea antidysentrica*, including canthin-6-one (1), 1-methoxycanthin-6-one (19), 1,11-dimethoxycanthin-6-one (20), and 2-methoxycanthin-6-one (21), are candidates for preventing acute myeloid leukemia (AML) [57]. Along the same line of evidence, Torquato et al. revealed that 10-methoxycanthin-6-one (22) had cytotoxicity toward malignant AML cells by activating necrotic and apoptotic processes, stress-activated MAPKs, and DNA damage pathways. Canthin-6-ones are therefore anticipated to be brand-new weapons in the struggle against leukemia [58].

All these observations may indicate a possible application of these canthin-6-ones as chemotherapy drugs for cancers, since drug-induced cytotoxicity is one of the common mechanisms by which chemotherapy drugs kill cancer cells [59][60]. Although few studies have been conducted to investigate their potential effects on inflammation, their roles in cell death may indicate an effect of these compounds on inflammatory responses. During regulated cell death, many caspases can be activated and thereby regulate inflammatory responses. Supporting this line of evidence, studies have shown that exposure to canthin-6-one (1) may induce caspase-8, caspase-9, and caspase-3 activation [61], which are regulators of apoptosis in cancer cells. At the same time, the activation of these caspases, such as caspase 8, may promote activation of the NLRP3 inflammasome, which subsequently induces GSDMD-mediated pyroptosis of the cells [62]. Both inflammasome and pyroptosis are critical regulators of CIDs. This may be one way that canthin-6-ones with anti-tumor activity exert their regulatory roles in CID. Moreover, canthin-6-one (1) can suppress the production of COX2 [63], a critical regulator of autophagy. Studies have shown that COX2 expression is inversely correlated with autophagy [64]. Exposure to canthin-6-one (1) may induce a decline in COX2 levels and a corresponding increase in autophagy. While the effect of autophagy on cancer cells and whether it has a tumor-suppressive or tumor promoting role is dependent on the context and stage of cancer development, enhanced autophagy can suppress inflammatory responses in CID [65].

3. Mechanism of Action and Pathways for Canthin-6-Ones

3.1. NF-κB Pathway

The transcription factor NF-κB is a central regulator of inflammation and immune responses. It can be activated by a variety of environmental cues, including inflammatory cytokines, pattern recognition receptor ligands, and endogenous danger signals [66]. Overactivation of NF-κB can lead to serious diseases such as CIDs, autoimmune diseases, and cancers. Recent studies have shown that inhibition of NF-κB is an effective approach for the management of numerous diseases [67]. A recent study by Yue et al. showed that canthin-6-one (1) pretreatment could significantly inhibit LPS-induced activation of molecules in the NF-κB pathway, such as the phosphorylation of IκBα, IKKα/β, and NF-κB p65 in astrocytes [68]. Thus, canthin-6-one (1) may provide significant benefits by suppressing astrogliosis via the regulation of NF-κB signaling in neurodegenerative disorders. Moreover, Tran et al. reported that canthin-6-one derivatives may also work as NF-κB inhibitors. They showed that IC50 values of 9-methoxy-canthin-6-one (8) and 9-hydroxycanthin-6-one (10) for NF-κB inhibition were 3.8 μM and 7.4 μM, respectively, which were higher than that of the standard drug, valuliolide, with an IC50 of 1.5μM [37]. Moreover, Cho et al. demonstrated that canthin-6-one (1) without a hydroxyl group in the D ring could downregulate NF-κB activity in LPS-stimulated macrophages [69].

3.2. MAPK Pathway

MAPKs are a group of serine/threonine protein kinases that play a role in regulating cell growth and death in response to a range of stimuli, such as osmotic stress, and inflammatory cytokines [70]. The three members of MAPKs, including extracellular signal-regulated kinase (ERK), p38, and c-Jun NH(2)-terminal kinase (JNK), can be activated by many cellular signals and act as ligands of cytokine receptors and stress sensors in inflammatory responses [71][72][73]. Regarding the effects of canthin-6-ones on MAPKs, in a study by Yue et al. [68], the authors found that canthin-6-one (1) treatment dramatically suppressed the phosphorylation of ERK, p38, and JNK. However, whether the derivatives of canthin-6-one (1) have a role in MAPK suppression needs to be determined. Moreover, it is worthwhile evaluating the significance of MAPK inhibition by canthin-6-one (1) in inflammatory diseases in future studies.

3.3. JAK/STAT Pathway

The JAK/STAT pathway is a signaling cascade that transduces signals from many cytokine receptors and is involved in the pathogenesis of a wide range of CIDs and cancers. JAK inhibitors are effective in treating many CIDs, such as rheumatoid arthritis and psoriasis [74]. In investigating the effects of canthin-6-one (1) on MAPKs, Yue et al.'s study also showed that this compound has a role in suppressing the phosphorylation of STAT3 [68], indicating an impact of canthin-6-one (1) in regulating the JAK/STAT pathway. Whether the suppression of this pathway by canthin-6-one (1) can be applied to treating an inflammatory disease need to be further determined.

3.4. PI3K–AKT Pathway

The PI3K–AKT pathway is an intracellular mechanism that transduces signals to regulate several physiological processes. The activation of this pathway can be induced by several events, which primarily include the binding of ligands such as growth factors. Previous studies have shown that the PI3K–AKT pathway inhibits LPS-induced inflammatory mediators in monocytes, microglia cells, and endothelial cells [75][76]. As mentioned above, Cho et al. [69] provided evidence that the anti-inflammatory effect of canthin-6-one (1) without a hydroxyl group in the D ring could be partially attributed to its role in suppressing the AKT pathway in LPS-stimulated macrophages. Meanwhile, the study by Yue et al. [68] found that treatment with canthin-6-one (1) can suppress the phosphorylation of AKT and increase endothelial nitric oxide synthase (eNOS) expression, indicating an inhibitory role of canthin-6-one (1) in the PI3K–AKT pathway. This impact is inconsistent with the anti-inflammatory role of the compound. Thus, the negative regulation of the PI3K–AKT pathway may be a concomitant event that occurs simultaneously with the inhibition of other inflammatory pathways induced by canthin-6-one (1). Its physiological significance needs to be further investigated.

4. Major Inflammatory Mediators Regulated by Canthin-6-Ones

4.1. Pro-Inflammatory Cytokines

Pro-inflammatory cytokines are mediators predominantly produced by antigen-presenting cells that play a key role in upregulating inflammatory reactions. Studies have shown that several major pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, contribute to the host's response against infections and also play a role in the development of many chronic diseases. Some of the canthin-6-ones may affect the production of pro-inflammatory cytokines. For instance, Zhao et al. showed that β-carboline alkaloids can inhibit the release of TNF-α and IL-6 in lipopolysaccharide (LPS)-activated RAW 264.7 macrophage cells [77]. Yue et al. found that canthin-6-one (1) from *Picrasma quassioides* (D.Don) Benn can suppress LPS-induced astrocyte activation and the associated production of pro-inflammatory cytokines, including that of TNF-α, IL-6, and IL-1β [68]. Fan et al. also revealed that 4-methoxy-5-hydroxy-canthin-6-one (6) can significantly suppress the production of TNF-α [39].

4.2. NO

NO is a biological messenger molecule and neurotransmitter synthesized by NO synthases such as iNOS in multiple cells [78]. The NO synthase iNOS acts as a key mediator of immune responses and inflammation [79], and its expression can be induced by extracellular stimulation such as LPS [80]. The dysregulation of iNOS has been linked to several diseases. It has been shown that β-carboline alkaloids, including quassidine F, 6-methoxy-3-vinyl-β-carboline, and 6,12-dimethoxy3-vinyl-β-carboline, have a role in suppressing the production of NO in LPS-activated RAW 264.7 macrophage cells. Moreover, 3-methylcanthin-5,6-dione (3), a derivative of β-carboline that has antioxidant activity, inhibited LPS-stimulated NO production in RAW264.7 cells [24][25]. The impact of these alkaloids is largely mediated by regulating iNOS since downregulation of iNOS protein expression or inhibition of the iNOS enzymatic activity blocks the inhibitory role of these alkaloids on NO production [77]. Thus, blockade of iNOS has been suggested to be the theoretical basis for using β-carboline analogs in the treatment of CIDs.

As a subtype of β-carboline alkaloids, it is reasonable to assume that canthin-6-ones may also have an inhibitory effect on NO production. For example, Fan et al. evaluated the anti-inflammatory effect of a canthin-6-one derivative, 4-methoxy-5-hydroxycanthin-6-one (6), and found that this compound significantly inhibited LPS-induced NO release while downregulating iNOS expression in RAW264.7 cells [39]. Canthin-6-one (1) and 9-methoxy-canthin-6-one (8) isolated from Simaroubaceae plants have been shown to suppress NO production in LPS-activated RAW 264.7 macrophages. Another study by Yue et al. showed that canthin-6-one (1) could suppress the production of NO from astrocytes and thus play a neuroprotective effect [68]. Moreover, Liu et al. [63] found that canthin-6-one (1) displayed significant inhibitory activity against NO production and the expression of iNOS in a dose-dependent manner in LPS-activated RAW264.7 macrophages. In addition, Kim et al. [81] identified three new canthin-6-one type alkaloids from the stem barks of *Ailanthus*

altissima, including canthin-6-one-1-O-β-D-apiofuranosyl-(1→2)-β-D-glucopyranoside, canthin-6-one-1-O-(6-O-(3-hydroxy-3-methylglutaryl))-β-D-glucopyranoside, and canthin-6-one-1-O-(2-β-D-apiofuranosyl-6-O-(3-hydroxy-3-methylglutaryl))-β-D-glucopyranoside, and found that they all suppress the production of LPS-induced NO in RAW 264.7 cells. Zhang et al. isolated two new canthin-6-one alkaloids, 4,9-dimethoxy-5-hydroxycanthin-6-one and 9-methoxy-(R/S)-5-(1-hydroxyethyl)-canthin-6-one, from the roots of Thailand *Eurycoma longifolia* Jack and found that both compounds could inhibit NO release from RAW264.7 cells [82].

4.3. PGE2

Prostaglandins (PGs) are the major lipid mediators in animals and are biosynthesized from arachidonic acid by cyclooxygenases as rate-limiting enzymes. PGE2 is the most abundant PG in various tissues and performs a variety of physiological and pathological functions [83]. PGE2 plays an important role in cell growth and causes inflammatory symptoms. Two cyclooxygenases (COX-1 and COX-2) are responsible for catalyzing the initial steps of arachidonic acid metabolism and prostaglandin synthesis and act as the primary agent of inflammation in mammalian cells. COX-2 is mainly expressed in inflammatory cells and is significantly upregulated in chronic and acute inflammation, becoming a key target for many drug inhibitors [84].

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