An overview on anti-inflammatory activities of Aucubin

Kyoung Sik Park

Abstract

Aucubin, an iridoid glycoside present in Aucuba japonica, Eucommiaulmoides, and Plantagoasiatica, has been reported to show a wide range of pharmacological activities. The present study is aimed to provide a comprehensive overview of anti-inflammatory activities of aucubin. Peer-reviewed articles on potent anti-inflammatory effects of aucubin were acquired from PubMed, Scopus, ScienceDirect, and SciFinder. This review provides a comprehensive advance on the pharmacological studies to confirm the potent anti-inflammatory effect and its underlying molecular mechanism of aucubin. Although a several of in vitro and in vivo researches have demonstrated anti-inflammatory activities of aucubin, further intensive clinical studies are required to confirm its efficacy for treating inflammatory diseases as a therapeutic agent.

Keywords: Iridoid glycoside, herbal medicine, natural product, anti-inflammatory activity

1. Introduction

Inflammation is defined as a pathophysiologic process characterized by fever, redness, edema, and pain. It is a part of the innate immune response to noxious stimuli, trauma, and infection and results in vasodilatation, increased blood flow, elevated cellular metabolism, release of soluble mediators, extravasation of fluids, and cellular influx [1]. Chronic inflammation is related with the onset and progression of various pathologies such as cardiovascular diseases and cancer. The role of pro-inflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes has been linked with chronic inflammation [2]. Iridoids represent a large group of natural compounds with a monoterpene cyclic ring. They act as a defensive substance for certain plant species and also produce a variety of pharmacological actions for animals [3]. A variety of medicinal plants containing iridoids including Plantago, Scrophularia, Rehmanniae, Harpagophytyum, Cornus, and Gentiana have long been used to treat various diseases across the globe [4]. Iridoids have been reported to exhibit a wide range of pharmacological activities including treatment of hepatic dysfunction, stimulation of bile acid excretion, anti-microbial activities, anti-tumor activities, antitodal activities for noxious Amanita mushroom poisoning, anti-viral activities against hepatitis B virus, and anti-inflammatory activities [5]. Most of iridoids including aucubin, harpagoside, catalpol, geniposide, and gentianine have been reported to exhibit significant anti-inflammatory activities in vitro and/or in vivo assay systems [6].

Aucubin (see Fig. 1) [1,4a,5,7a-tetra-5-hydroxy-7-(hydroxymethyl) cyclopenta(c)pyran-1-yl-[β-D-glucopyranoside] is a naturally occurring iridoid glycoside, found in a wide range of plants, which are used in folk medicine [7]. Although the literature on aucubin is not extensive it is sufficient to indicate a broad range of potential biological activity. This compound was found to protect against liver damage induced by carbon tetrachloride or α-amanitin in mice and rats and to inhibit the synthesis of RNA and proteins in the liver of mice [8]. It was also known to show antimicrobial activity against a range of bacteria and fungi [9]. Furthermore, aucubin has been reported to possess extensive pharmacological effects including antioxidant, anti-aging, anti-cancer, anti-inflammatory, anti-fibrotic, neuroprotective, hepatoprotective and osteoprotective properties [10].

2. Conversion of the chemical structure of aucubin into its active form

Like most of iridoids, aucubin exists usually as a glycoside form in nature. The glycosidic bond of aucubin makes the inactive compound highly susceptible to degradation and oxidation, and is cleaved by the enzymatic activity of β-glucosidase or under acidic conditions to produce aucubigeninastisaglycone form (Fig. 1). A variety of biological activities aforementioned aucubinehhibites can be revealed only when the glycoside form of aucubin is changed into its aglycone form through deglucosidation in vivo and in vitro [11]. Although no definite structure of hydrolyzed iridoid product has been determined yet, it may be assumed to
produce a cleavage of monoterpenic rings, leading to the active form of the compound [12]. It has been suggested that an aglycone form of aucubins more easily transported into the cell membrane than a glucoside form [13], which may explain the biological activation of aucubin through the hydrolysis of glucose moiety in its structure.

Figure 1: Conversion of the chemical structure of aucubin

3. Evidences for anti-inflammatory activity of aucubin in animal models
Table 1 summarizes the animal studies demonstrating anti-inflammatory activity of aucubin in vivo. Carrageenan-induced mouse paw edema is one of the most popular tests used in the screening of anti-inflammatory agents. The anti-inflammatory activity may also be assayed using themouse model of 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced ear edema [14]. Recio et al. reported the anti-inflammatory activity of aucubin in animal models, in which the either oral or topical administration of aucubin reduced the chemical-induced mouse edema significantly [15]. Using a mouse model with pulmonary fibrosis induced by intratracheal injection of bleomycin (BLM), two studies have reported anti-inflammatory action of aucubin. Treatment of aucubin for 21 days after BLM injection reduced the intrapulmonary collagen disposition and inflammatory injury induced by BLM [16]. In addition, aucubin inhibited pro-inflammatory cytokines and nuclear factor kappa B (NF-κB) expression in lipopolysaccharide (LPS)-administered mice [17].

In an animal model with neurological diseases, the levels of interleukine (IL)-1β, high mobility group box (HMGB), tumor necrosis factor (TNF)-α were dramatically reduced with aucubin treatment [18]. In another similar study, aucubin exerted neuroprotective effects by reducing inflammation in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-treated parkinsonism mouse model [19].

<table>
<thead>
<tr>
<th>Material tested</th>
<th>Animal model</th>
<th>Administration route</th>
<th>Dose</th>
<th>Effect</th>
<th>Ref No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure aucubin</td>
<td>Mice with carrageenan-induced paw edema Mice with TPA-induced ear edema</td>
<td>Oral administration</td>
<td>100 mg/kg</td>
<td>Reduction of the chemical-induced mouse edema</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical administration</td>
<td>0.5 mg/ear</td>
<td></td>
<td></td>
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<tr>
<td>Personally provided</td>
<td>Mice with pulmonary fibrosis induced by bleomycin</td>
<td>Intraperitoneal injection</td>
<td>5 mg/kg</td>
<td>Attenuation of pulmonary fibrosis</td>
<td>[16]</td>
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<tr>
<td>aucubin</td>
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<tr>
<td>Pure aucubin</td>
<td>Mice with acute pulmonary injury induced by LPS</td>
<td>Intraperitoneal injection</td>
<td>10, 20 mg/kg</td>
<td>Mitigation of pulmonary inflammation and oxidative stress</td>
<td>[17]</td>
</tr>
<tr>
<td>Purified aucubin from</td>
<td>Li-pilocarpine-induced epileptic mice</td>
<td>Intraperitoneal injection</td>
<td>50, 100 mg/kg</td>
<td>Inhibition of neuroinflammation</td>
<td>[18]</td>
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<tr>
<td>Eucommia ulmoides</td>
<td></td>
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<tr>
<td>Pure aucubin</td>
<td>MPTP-induced parkinsonian mice</td>
<td>Intraperitoneal injection</td>
<td>50 mg/kg</td>
<td>Preservation of dopaminergic neurons</td>
<td>[19]</td>
</tr>
</tbody>
</table>

4. Underlying molecular mechanisms for anti-inflammatory activity of aucubin
The anti-inflammatory effect of aucubin is in large part at the origin of the extensive use of plant extracts containing it in folk medicine for the treatment of rheumatism, hepatitis, inflammatory bowel disease, glomerulonephritis, dysentery and other inflammatory diseases [20]. As for the molecular mechanism for anti-inflammatory activity of aucubin, several in vitro studies have mainly focused on nuclear factor kappa B (NFκB), cyclooxygenase (COX), and inducible nitric oxide synthase (iNOS) as its molecular targets (Table 2). Tumor necrosis factor (TNF) was originally known as its anti-tumor activity, however it is now recognized to be one of the most important pleotropic cytokines acting as a host defense factor in immune and inflammatory responses [21]. While anti-inflammatory and anti-tumor effects mediated by TNF could be beneficial to the host, overproduction of TNF may be the basis for the development of various diseases. There is now overwhelming evidence to suggest that TNF plays pivotal roles in the development of pathologies such as intravascular coagulation, septic shock in humans, cerebral malaria] and a range of inflammatory diseases including asthma, dermatitis, multiple sclerosis, inflammatory bowel disease, cystic fibrosis, rheumatoid arthritis and immunological diseases [22]. It is thus clear that suppression of TNF production or inhibition of its function could be beneficial in the treatment of TNF-mediated diseases. It is now well established that the most critical step in the transcriptional activation of TNF gene is the mobilization of nuclear factor (NFκB), a transcription factor [23]. NFκB is sequestered in the cytoplasm by inhibitory proteins IκB, which can be phosphorylated by a cellular kinase leading to degradation and subsequent translocation of free NFκB to the nucleus [24]. The potential target of NFκB in TNF-mediated diseases is evident as inappropriate regulation of NFκB has shown to be associated with diseases such as septic shock, graft versus host reaction, acute inflammatory condition, radiation damage, atherosclerosis and cancer [25]. In antigen-stimulated mast cells, aucubin inhibited TNFα and IL-6 expression through blocking nuclear translocation of NFκB and degradation of IκB [26]. A similar anti-inflammatory effect of aucubin has been demonstrated by the report showing that it significantly inhibited TNF-α-induced secretion and mRNA synthesis of the atherogenic adipokines including plasminogen activator inhibitor (PAI)-1, adipose-tissue-derived monocyte chemoattractant protein (PAI)-1, and IL-6 by suppression of extracellular signal-regulated kinase (ERK) activation, IκB degradation, and subsequent NFκB activation in differentiated 3T3-L1 adipocytes [27]. Notably, the hydrolytic product of aucubin with β-glucosidase treatment suppressed mRNA synthesis of TNF-α and subsequent TNF-α production in LPS- and IFN-γ-stimulated RAW 264.7 cells [28]. Another study has also observed that conversion of aucubin into the aglycone form with β-glucosidase treatment induced the
inhibition of cyclooxygenase (COX)-2 activity and the significant suppression of both TNFα and nitric oxide (NO) formation [29].

Arachidonic acid (AA) is mainly present in the form of phospholipids in the cell membrane. AA is released from the phospholipids as free arachidonic acids, which become the precursor of pro-inflammatory bioactive mediators. Through the cyclooxygenase (COX) pathway, which is inhibited by nonsteroidal anti-inflammatory drugs, AA can be metabolized into prostaglandins (PGs) and thromboxanes (TXs). AA can also be converted into leukotrienes (LTs) and lipoxins (LXs) by the lipoxgenase (LOX) pathway [30]. Moreover, AA also generates epoxyeicosatrienoic acids (EETs) or hydroxyeicosatetraenoic acids (HETEs) through the cytochrome P450 (CYP450) pathway. Together, these AA metabolites are widely involved in a variety of physiological and pathological processes [31]. Aucubin isolated from plant extracts exerted the inhibitory effects on both LTC4 release from murine peritoneal macrophages and TXB2 release from calcium ionophore-stimulated human platelets [32]. Nitric oxide (NO) production due to cytokine-mediated enzyme induction of inducible nitric oxide synthase (iNOS) is largely involved in the pathophysiology of inflammation [33]. Aucubin significantly down-regulated the elevated gene and protein expression level of iNOS and suppressed the NO production induced by IL-1β challenge in rat chondrocytes [34].

### Table 2: Anti-inflammatory activities of aucubin in vitro

<table>
<thead>
<tr>
<th>Material tested</th>
<th>Cell line</th>
<th>Maximum concentration</th>
<th>Effect</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure aucubin</td>
<td>RBL-2H3 mast cells</td>
<td>0.01 µg/ml</td>
<td>Inhibition of TNFα and IL-6 production via blockade of NFκB activation</td>
<td>[26]</td>
</tr>
<tr>
<td>Hydrolized product of pure aucubin</td>
<td>RAW 264.7 cells</td>
<td>30 µM</td>
<td>Suppression of TNFα secretion and the atherogenic adipokine synthesis</td>
<td>[27]</td>
</tr>
<tr>
<td>Hydrolyzed product of pure aucubin</td>
<td>Human erythroleukemia cells &amp; RAW 264.7 cells</td>
<td>10 µM</td>
<td>Inhibition of TNFα production through blocking the translocation of NFκB</td>
<td>[28]</td>
</tr>
<tr>
<td>Purified aucubin from Scrophularia nodosa</td>
<td>Mouse peritoneal macrophages &amp; Human platelet</td>
<td>100 µM</td>
<td>Inhibition of COX-2 activity and suppression of TNFα and NO production</td>
<td>[29]</td>
</tr>
<tr>
<td>Pure aucubin</td>
<td>Rat articular chondrocytes</td>
<td>50 µM</td>
<td>Reduction of LTC4 and TXB2 release</td>
<td>[32]</td>
</tr>
</tbody>
</table>

5. Conclusions
Taken together, aucubin, especially as the hydrolyzed product of an intact form, exerts anti-inflammatory effects in in-vitro and in-vivo studies through the inhibition of COX-2 activity, NO production, and/or the nuclear translocation of NF-κB, and the subsequent reduction of inflammatory mediator production. However, for the full potential of aucubin as a therapeutic agent, more systematic researches are required to elucidate its efficacy rigorously controlled long-term clinical trials.

6. Acknowledgments
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