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An overview on anti-inflammatory activities of Aucubin

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Abstract
Aucubin, aniridoid glycoside present in *Aucuba japonica, Eucommiaulmoides, and Plantagoasiatica*, has been reported toshow 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 aucub in were acquired from Pubmed, Scopus, ScienceDirect, and Sci Finder. 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 pathophysiological process characterized by fever, redness, edema, and pain. It is a part of aninnate 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*, *Harpagophytum*, *Cornus,* and *Gentiana* have long been used to treat various diseases across the globe [4]. Iridoids have been reported to exhibita wide range of pharmacological activities including treatment of hepatic dysfunction, stimulation of bile acid excretion, anti-microbial activities, anti-tumor activities, antidotal 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 aucubigeninasitsaglycone form (Fig. 1). A variety of biological activities aforementioned aucubinexhibites 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 beassumed to

produce a cleavage of monoterpene rings, leading to the active form of the compound [12]. It has been suggested that an aglycone form of aucubinis 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.

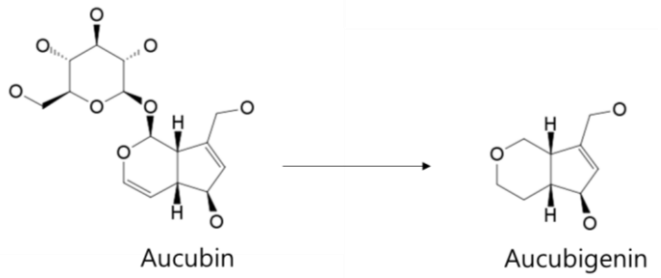

Fig 1: Conversion of the chemical structure of aucubin

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)-administrated 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 1: Anti-inflammatory activities of aucubin *in vivo*

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

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 atherogenicadipokines 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 lipoxygenase (LOX) pathway [30]. Moreover, AA also generates epoxyeicosatrienoic acids (EETs) or hydroxy eicosatetraenoic 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 LTC_4 release from murine peritoneal macrophages and TXB_2 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*

Material tested	Cell line	Maximum concentration	Effect	Ref No.
Pure aucubin	RBL-2H3 mast cells	0,01μg/ml	Inhibition of TNFα and IL-6 production via blockade of NFκB activation	[26]
Pure aucubin	3T3-L1 adipocytes	30 μM	Suppression of TNFα secretion and the atherogenicadipokine synthesis	[27]
Hydrolyzed product of pure aucubin	RAW 264.7 cells	10 μM	Inhibition of TNFα production through blocking the translocation of NFκB	[28]
Hydrolyzed product of pure aucubin	Human erythroleukemia cells & RAW 264.7 cells	100 μM	Inhibition of COX-2 activity and suppression of TNFα and NO production	[29]
Purified aucubin from *Scrophulariascorodonia*	Mouse peritoneal macrophages & Human platelet	100 μM	Reduction of LTC_4 and TXB_2 release	[32]
Pure aucubin	Rat articular chondrocytes	50 μM	Suppression of iNOS expression and NO production	[34]

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 inrigorously controlled long-term clinical trials.

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