INTRODUCTION
Inflammation is a general term for a pathophysiological process characterized by fever, redness, edema, and pain\(^1\). It is a part of a non-specific immune response to noxious stimuli, trauma, and infection\(^2\) and results in vasodilatation, increased blood flow, elevated cellular metabolism, release of soluble mediators, extravasation of fluids, and cellular influx\(^3\). Prolonged inflammation is implicated in the onset and progression of various pathologies including cardiovascular diseases and cancer\(^4\).

Iridoids represent a group of natural constituents with a monoterpene cyclic ring. They manifest dual facets of biological activities; one is to act as a defensive substance for certain plant species and the other is to produce a variety of pharmacological actions for animals\(^5,6\). Many medicinal plants containing iridoids such as Plantago, Cornus, Rehmanniae, Scrophularia, Gentiana, and Harpagophytum have long been used to treat various ailments in the East and the West. The pharmacological activities are summarized: treatment of hepatic dysfunction\(^7\), stimulation of bile acid excretion\(^8\), anti-microbial activities\(^9\), anti-tumor activities\(^10\), antidotal activities for noxious Amanita mushroom poisoning\(^11\), anti-viral activities against hepatitis B virus\(^12\), and anti-inflammatory activities\(^13\). A variety of iridoids including aucubin, harpagoside, catalpol, scrovalentinoside, verminoside, and ipolamiide have been reported to possess significant anti-inflammatory activities in vitro and/or in vivo assay systems\(^14\).

Harpagoside (see Figure 1) is a naturally occurring iridoid glycoside found in many medicinal plants such as Scrophularia ningpoensis, Scrophularia buergeriana, and Harpagophytum procumbens\(^15-17\).

These medicinal plants have been shown to exhibit a variety of biological activities and used as pharmaceutical products for the treatment of inflammatory ailment, rheumatoid arthritis, and osteoarthritis\(^18-20\). In particular, H. procumbens (devil’s claw) has been used to treat a wide range of ailments. H. procumbens
exhibits analgesic, anti-inflammatory, anti-oxidant, anti-diabetic, anti-epileptic, anti-microbial, and anti-malarial activities\(^{[25,27]}\). Harpagoside is believed to be a main bioactive compound related to the anti-inflammatory efficacy of these medicinal plants, and the harpagoside content is used to standardize commercial H. procumbens products, which should contain at least 1.2% of the compound according to the European Pharmacopoeia\(^{[21]}\). Harpagoside has been detected in both underground and above-ground parts of plants, but in widely varying levels. Levieille and Wilson\(^{[24]}\) reported that secondary tubers of devil’s claw accumulate ten times higher levels of harpagoside than the leaves.

This review is aimed to provide a comprehensive overview of anti-inflammatory activity of purified harpagoside and supplement the earlier reviews\(^{[22,24]}\).

**EVIDENCES FOR ANTI-INFLAMMATORY ACTIVITY OF HARPAGOSIDE**

Arthritis is a common, chronic, progressive, and disabling autoimmune disease that causes inflammation and pain in the joints\(^{[27]}\). Based on the wide recognition of anti-inflammatory potency as folk remedies for arthritis complaints, the effects of devil’s claw extracts have been investigated for nearly 60 years in animal and clinical studies.

Using mouse and rat carrageenan-induced edema model, several studies have reported anti-inflammatory action of purified harpagoside (Table 1). In intraperitoneal doses between 0.5 and 10.0 mg/kg, harpagoside dose-dependently and to a statistically significant manner inhibited the development of the carrageenan-induced inflammatory reaction in rats\(^{[28]}\). In another similar study, intraperitoneal treatment with 20 mg/kg of harpagoside ameliorated the development of zymosan-induced arthritis and reduced pathological changes in joints of mice\(^{[29]}\). Paw swelling in mice also reduced by oral administration of harpagoside (10 mg/kg) isolated from the aerial parts of Scrophularia deserti\(^{[30]}\).

There is moderate evidence for daily intake of 60 mg harpagoside in the treatment of spin, knee, and hip osteoarthritis\(^{[31]}\). A daily dose of 50 or 100 mg of harpagoside are effective for treating acute exacerbations of chronic non-specific low-back pain (NSLBP)\(^{[32]}\). In particular, significant improvement in knee osteoarthritis has been observed following the daily intake of 60 mg harpagoside as a form of Dolotefin\(^{\circ}\), a standardized devil’s claw extract for up to 54 weeks\(^{[33]}\). Furthermore, additional two clinical studies confirm the positive effects of standardized harpagoside-containing preparations in the treatment of arthritis\(^{[34,35]}\).

**UNDERLYING MOLECULAR MECHANISMS FOR ANTI-INFLAMMATORY ACTIVITY OF HARPAGOSIDE**

As for the molecular mechanism for anti-inflammatory activity of harpagoside, several in vitro studies have mainly focused on cyclooxygenase (COX), inducible nitric oxide synthase (iNOS), and nuclear factor kappa B (NF-xB) as its molecular targets (Table 2). Pure harpagoside significantly inhibits COX-2 expression in freshly excised porcine skin\(^{[36]}\). A recent molecular docking and binding study revealed that harpagoside interacts with COX-2 and acts as a potential highly selective COX-2 inhibitor\(^{[37]}\). Hydrolyzed products of harpagoside with β-glucosidase treatment show a significant inhibitory effect on COX-2 activity at 2.5-100 μM in a concentration-dependent manner\(^{[38]}\). All of these findings strongly suggest that harpagoside perturb the arachidonic acid pathway. In addition, it was reported that harpagoside inhibits lipopolysaccharide (LPS)-induced production of inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF-α) resulting from the both 1α,25-degradation and the nuclear translocation of NF-xB in RAW 264.7 cells\(^{[39]}\). Furthermore, harpagoside significantly reduces TNF-α secretion in PMA-differentiated THP-1 cells\(^{[40]}\). In addition to the effects already described, pure harpagoside inhibits COX-1/2 and NO production in peritoneal macrophages\(^{[41]}\). Interestingly, as another molecular target of anti-inflammatory action of pure harpagoside, peroxisome proliferator-activated receptor (PPAR)-γ can be activated by treatment of 10 μM harpagoside in differentiated 3T3-L1 cells, leading to the reduction of TNF-α-induced mRNA synthesis and protein production of the atherogenic adipokines including IL-6, plasminogen activator inhibitor (PAI)-1, and monocyte chemoattractant protein (MCP)-1\(^{[42]}\). Several other studies, however, showed that harpagoside had no effect on iNOS and LPS-induced TNF-α release\(^{[43,44]}\).

**CONCLUSIONS**

Taken together, harpagoside, both as the pure compound and as a major constituent of devil’s claw extracts exerts anti-inflammatory...
activities in animal and clinical studies through the inhibition of COX-2 expression, iNOS activity, and/or the nuclear translocation of NF-xB, and the subsequent reduction of inflammatory mediator production. However, for the full potential of harpagoside as a therapeutic agent, more systematic researches are required to elucidate its efficacy in rigorously controlled long-term clinical trials.

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CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

REFERENCES


