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Jaceosidin: A traditional herbal medicine with its wide range of pharmacological properties

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ABSTRACT

Background: Natural products of therapeutic importance are compounds derived from plants, animals, or any microorganism. Humans have been using natural products for medicinal use for ages. Jaceosidin (JAS), found in plants is used as a food and a traditional medicinal herb. In recent years, several studies noticed that the biological and pharmacological effects of JAS have attracted attention and encouraged us to review its various properties.

Objectives: This review focused on the newest scientific reports on JAS and extensively summarizes its pharmacological properties.

Methodology: Articles published by authors on JAS were analyzed for the study.

Results: JAS is known to play several pharmacological functions such as antimutagenic, angiogenesis, anti-adipogenic, immunosuppressive, anticancer, antioxidant, anti-inflammatory properties.

Conclusion: JAS has many important applications in pharmacology. Although researchers have reported multiple pharmacological applications of this compound, further experimentations covering its effects and mechanisms of action are needed to understand and extend the scope of its application.

Keywords: Natural products, Jaceosidin, pharmacological activities

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1. INTRODUCTION:

Natural products, compounds derived from plants, animals or any microorganism [1] have long been considered as promising therapeutic agents. Since ancient times, natural products, including plants and their components, have been utilized to treat and cure diseases worldwide, long before the discovery of modern drugs [2]. These compounds can be used to complement or moderate the side effects of some drugs [3]. They have been used for a long time as anti-inflammatory, antipyretic, analgesic agents and as alternatives for hormone replacement therapy [4]. Because resistance is increasing and few new antibiotics have been discovered, new classes of antibacterial compounds are urgently needed to respond to this unmet need. A significant number of compounds has been studied and played an important role in antimicrobial activities [5][6].

Flavonoids constitute the most abundant polyphenols in the diet and are metabolized to active compounds through actions of the gut flora and the liver. Since fruits and vegetables are major sources of antioxidants among other factors, previous researches hypothesized that the antioxidant effects of these foods are due to their content of flavonoids. Study evaluated on food consumption suggested that flavonoids are nutrients that provide a variety of health benefits. According to their health benefits, they display a variety of pharmacological properties of interest in the therapy of several diseases, including cancer, as cytotoxic, antiangiogenic, or antivascular agents [7]. Studies on cancer prevention have investigated the activities of a

wide variety of flavonoids and selected some of them for their efficacy in inhibiting cancer in a number of animal models. These investigations concluded that flavonoids inhibit carcinogenesis in vitro and in vivo [8] [9] [10]. Most of the regulation of transcription by flavonoids encompasses inhibition of phosphorylation signaling cascades or specific kinases. They have long been known to act as anti-inflammatory, antioxidant, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic agents [11] [12].

Jaceosidin [5,7-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-6-methoxychromen-4-one] is a natural methylated trihydroxyflavone first found in plants of the Compositae family. It is a pharmacologically active flavone isolated from medicinal herbs of the genus *Artemisia*, such as *Artemisia princeps, Artemisia argyi*, *Artemisia iwayomogi*, and *Artemisia copa* [13]. Like many flavones, jaceosidin has been found to exhibit antioxidative actions on cells in culture, antioxidant, antiinflammatory, antiallergic, and antitumor activities [13] [5]. Even though significant research findings have been made on Jaceosidin, no reviews have been published focusing on the multi-pharmacological properties of Jaceosidin against various human ailments until now. Thus, this review aims to reveal the various pharmacological/biological activities of this natural product to draw a frame for further research.

2. Natural sources of Jaceosidin

Jaceosidin, a natural methylated trihydroxyflavone, has been isolated from Vervain (*Verbena officinalis*) [14] and some medicinal herbs of the genus *Artemisia*, such as *Artemisia princeps, Artemisia argyi*, *Artemisia iwayomogi*, and *Artemisia copa* [13]. Among extracts of Artemisia species, jaceosidin is known as one of the most active ingredients [15]. Artemisia plants possess a variety of biological activities and draw considerable attention in pharmacological research due to their anti-inflammatory, anti-malarial, anti-hepatitis, and anti-cancer activities [16] [17] [18]. *Artemisia princeps* Pampanini (Family Asteraceae) has been widely cultivated in Korea, Japan, and China, and its leaves have long been used as tea, food, and traditional medicine in Korea. Extracts of *A. princeps* Pamp also possess anti-diabetic and antiallergic activities [19]. More than 500 Artemisia herbs are widespread worldwide and most Artemisia species have been used as various traditional Korean medicines for gynecologic diseases, gastrointestinal conditions, hepatitis, eczema, furuncles, inflammation, and tumours [20] [21]. Jaceosidin has also been extracted from the parts of *Saussurea medusa* and has been used for treating rheumarthritis, mountain sickness, irregular menstruation, cardiovascular disease and extending human life [22].

FIGURE 1: Natural sources of Jaceosidin

3. Pharmacological activities of Jaceosidin

Jaceosidin, a natural methylated trihydroxyflavone, has been found to exhibit antioxidative actions [23], antioxidant, antiinflammatory, immunosuppressive, and antitumor activities [13] [5]. It also promoted angiogenesis in endothelial cells [24], had strong antimutagenic activity and anticancer chemotherapeutic potential [25] and inhibited the functions of E6 and E7 oncoproteins of human papillomavirus (**Figure 2**). Several studies demonstrated the multi-pharmacological properties of Jaceosidin against various human ailments.

3.1. Anti-inflammatory Activity

Authors have tested jaceosidin isolated from the methanolic extracts of the aerial parts of Artemisia princeps Pampanini for its anti-inflammatory activities. Their results demonstrated that jaceosidin inhibited the generation of reactive oxygen species (ROS) concerning the regulation of NF-B signaling. Furthermore, it downregulates nuclear factor-kappa B (NF- B) activity, nitric oxide (NO) production, and suppressed expression of inducible nitric oxide synthase (iNOS) in lipopolysaccharide (LPS)-induced RAW264.7 macrophages [26].

Min SW et al, 2009 [27] showed that jaceosidin had similar activity with Eupatilin. All of them not only blocked carrageenan-induced increase in leukocyte number and protein levels in air pouch exudates, but also inhibited COX-2 expression and NF-kappaB activation. They reduced proinflammatory mediator [TNF-alpha, IL-1beta, and prostaglandin E2 (PGE (2)] levels and inhibited hind paw edema induced by carrageenan.

A research explained that three anti-inflammatory compounds such as nepetin, jaceosidin and hispidulin have been identified from Eupatorium arnottianum Griseb. Among them, jaceosidin reduced the 12-0-Tetradecanoylphorbol acetate induced-mouse ear edema by inhibiting the NF-κβ induction [28, 29] and nitric oxide production [29]. The research concludes that topical antiinflammatory activity exerted by Eupatorium arnottianum extract and the identification of active principles could support the use of this plant for the treatment of inflammatory affections [28]. In addition, in investigating its other activities, Jaceosidin was found to inhibit the secretion of the proinflammatory cytokines such as IL-2, TNF-α and IFN-γ of activated T cells. In *in vivo* study, Jaceosidin ameliorated picryl chloride - induced ear swelling, which was due to its inhibition of the STAT1/T-bet signaling pathway [30].

Acute lung injury and its more severe form known as acute respiratory distress syndrome remain the leading causes of mortality among adults in several countries. In the inflammatory response, the anti-inflammatory mediators are usually in the unbalanced state [31, 32]. The therapeutic effects of Jaceosidin on acute lung injury in mice have been tested. As results, Jaceosidin regulated the inflammatory responses by decreasing the lung wet-to-dry weight ratio and the protein concentration in bronchoalveolar lavage fluid. It down-regulates the levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β), together with up-regulating the levels of interleukin-4 (IL-4) and interleukin-10 (IL-10) in BALF. These data suggest that Jaceocidin may play the anti-inflammatory role because the levels of myeloperoxidase (MPO), lung histopathological changes, cyclooxygenase-2 (COX-2) and nuclear factor-κB (NF-κB), COX-2 mRNA and NF-κB p65 mRNA were decreased by Jaceosidin with increasing of the activity of catalase **[33]**.

3.2. Antioxidant Activity

Jaceosidin is shown to inhibit the Cu^{2+}-mediated LDL oxidation in the thiobarbituric acid-reactive substances (TBARS) assay as well as the macrophage-mediated LDL oxidation. Its antioxidant effect is exhibited not only in the conjugated diene production, relative electrophoretic mobility, and apoB-100 fragmentation on copper-mediated LDL oxidation but also in the inhibition of the the generation of reactive oxygen species concerning in regulation of NF-kappaB signaling [**23**]. Furthermore, jaceosidin exhibits antioxidant activity by decreasing the levels of complement 3 and complement 3c in serum [**33**]. In addition, its supplementation increased antioxidant capacity by enhancement of catalase and erythrocyte glutathione peroxidase activities [**34**].

3.3. Anticancer Activity

Abnormally expressed microRNAs contribute widely to human cancer, including oral squamous cell carcinoma, by regulating their downstream targets [**35**]. Authors investigated the effects of jaceosidin in oral squamous cell carcinoma (OSCC) and initially showed selective suppression of proliferation and accumulation of cells at the sub-G1 stage of the cell cycle. Their findings showed that this natural product inhibits oral squamous cell carcinoma proliferation and increased cleavage of caspase-9 and caspase-3 in OSCC cells. In further experiments, jaceosidin downregulates Akt phosphorylation and has selective chemotherapeutic potential and that tumour-specific downregulation of Akt increases apoptosis and inhibits growth in OSCC cells [**36**]. It induces cell cycle arrest at G2/M phase and exerts induction of apoptosis in cancer cells [17], suggesting the potential roles of jaceosidin in cancer therapy.

3.4. Immunosuppressive activity

Microglias are the innate immune cells in the central nervous system, and they play a central role in the initiation and maintenance of neuroinflammation. Authors indicated that plant flavone jaceosidin is a microglial inhibitor by inhibiting activation of microglia, and attenuating microglial neurotoxicity in the microglia/neuroblastoma co-culture [**37**].

In addition, other authors aimed to investigate the immunosuppressive activity of jaceosidin on T lymphocytes both in vitro and in vivo, and further explore its potential molecular mechanism. They found that Jaceosidin exerted a significant inhibition on the T cell proliferation and activation induced by concanavalin A by down-regulating STAT1 activation and T-bet expression [**30**].

3.5. Anti-adipogenic activity

Obesity is caused by adipocyte hypertrophy. The 3T3-L1 mouse fibroblast line is a well characterized model system for preadipocyte differentiation and is commonly used in vitro studies. Therefore, inhibition of adipocyte differentiation is one potential strategy for its treatment. Thus Lee SG et al, 2018 [**38**] investigated the anti-adipogenic effects of jaceosidin. The results of their study suggest the use of jaceosidin as a treatment for obesity because the product suppressed adipocyte differentiation and cellular lipid accumulation without cytotoxicity. It also suppressed the mRNA and protein expression of adipogenesis-related genes.

3.6. Angiogenesis Activity

Angiogenesis, the growth of new blood vessels from pre-existing vasculature, plays an important role in physiological and pathological processes such as embryonic development wound healing and revascularization of tissues after exposure to ischemia. The natural flavone stimulates proliferation, migration and tubulogenesis of ECs as well as *ex vivo* sprouting from aorta rings, which are phenomena typical of angiogenesis. It also activates vascular endothelial growth factor receptor 2 (VEGFR2, FLk-1/KDR) and angiogenic signaling molecules such as focal adhesion kinase, phosphatidylinositol 3-kinase, and its downstream target, the serine-threonine kinase AKT. They resumed that jaceosidin stimulates angiogenesis by activating the VEGFR2/FAK/PI3K/AKT/NF-κB signaling pathway. This finding may be useful in developing angiogenic agents to

promote the growth of collateral blood vessels in ischemic tissues [**24**].

3.7. Antimutagenic activity

These results support the report that the antimutagenic activity of eupatilin and jaceosidin against Trp-P-2 in TA98 is a result of the inhibition of Cytochrome P450 CYP1A1-catalyzed ethoxyresorufin deethylase activity in rat liver S9 fractions. Eupatilin and jaceosidin were shown to be potent competitive inhibitors of CYP2C9 with K_i values of 1.6 and 6.4 μM, respectively, suggesting that eupatilin and jaceosidin should be used carefully with drugs metabolized by CYP2C9 such as celecoxib, diclofenac, glyburide, losartan, tolbutamide, torasemide, and *S*-warfarin to avoid drug interactions. The herbal preparations and medicinal herbs containing eupatilin and jaceosidin may affect CYP1A2 and CYP2C9 activity [**39, 40, 13**]. In addition, jaceosidin exhibited strong antimutagenic activity against Trp-P-2 and other heterocyclic amines in S. typhimurium TA98 [**39**].

4. Biological/pharmacological activities of Plants containing Jaceosidin

The biological/pharmacological activities of jaceosidin are shown in Table 1.

Table 1: Plants containing Jaceosidin with its biological/ pharmacological properties

Botanical name of the plant	Common name	Origin	Biological activities
***Artemisia iwayomogi* Kitamura**	hanin-jin dowijigi	South Korea	Anti-hepatitis[41] Anti-hypertriglyceridemia [42] Anti-cancer [43] Fat burning [44] Anti-inflammatory[45,46] Anti-apoptotic [47] Anti-fibrotic[48,49] Antioxidant[50] Antibacterial [51]
Artemisia copa	copa	Chile Spanish, Argentina	Anti-inflammatory [52] Vasorelaxant and hypotensive [53] Analgesic and topical antiinflammatory [54]
Artemisia vestita	Russian worm, wood	Russia China India	*in vitro* and *in vivo* antibacterial activity [55] anti-sepsis [56] Anti-inflammatory, antifungal, antiphlogistic, and antifebrile [57] Anti-inflammatory and immunosuppressive [58] Anticoccidal [59] Reduces contact sensitivity by down-regulating Activation, adhesion and metalloproteinase production of T lymphocytes [60] I mmunosuppressive [61] Antitumor [62] Anthelmintic [63]
Salvia tomentosa	Balsamic Sage	Greece	Antibacterial [64] Antitumoral [65] Antidiabetic [66] Antioxidant [67] Herbal tea [68] Flavoring agents [69] Anti-inflammatory, antirheumatic, antimicrobial, tranquilizing,

			anticancer, antidiabetic, hepatoprotective [70,71,72]
Eupatorium arnottianum	Clavel	Argentina and Bolivia	Antiinflammatory [73] Leishmanicidal and trypanocidal activity [73] spasmolytic role in gastrointestinal motility [74]
Artemisia princeps	Japanese mugwort" or "yomogi"	China Korea Japan	Anti-inflammatory, Anti-diarrheic, Anti-circulatory disorders [41]
Verbena officinalis	vervain	Europe	Antitussive [75] Analgesic, anti-inflammatory [76] Neuroprotective [77] Antiradical [78] Antioxidant, antifungal [79] Anti-tumor [80] Antibacterial [81] Antiproliferative [82] Antidepressant [83] Anticonvulsant, anxiolytic and sedative [84]
Eupatorium perfoliatum	herbe à fièvre boneset	North America	Immunomodulatory, anti-inflammatory [85] Antiplasmodial [86] Anti-influenza [87]
Artemisia argyi	Gaiyou	China	Herbal medicine for conditions of the liver, spleen and kidney [88] Antimicrobial [89] Anti-histaminic and antifungal activity [90] Antibacterial [91]
Saussurea medusa	Snow Lotus	Northern and central Europe, northwest Asia	Anti-tumor-promoting [92] Anti-inflammatory, analgesic, anti-fungal, anti-tumor, anti-Anoxia, anti-oxidation, and anti-fatigue [93]
Artemisia asiatica	Japan	Titeypati, Asian mugwort	Neuroprotective, gastroprotective, anti-oxidative, anti-inflammatory, and anti-cancer [94] Anti-photoaging, anti-apoptotic, skin remodeling, moisturizing, anti-inflammatory and anti-melanogenesis [95] Anti-inflammatory [96]
Eupatorium cannabinum	Hemp agrimony	North America and eastern South America	Anti-inflammatory [97] Antitumour [98] Antibacterial, immunological, cytostatic, anti-inflammatory, fungicidal, anti-diarrheal [99] Cytotoxic, antimicrobial, antioxidant, antiinflammatory, immunological, choleretic, hepatoprotective, insecticidal and repellent [100]

5. Conclusion and future perspectives

Plants materials are tremendous source of natural drugs and they are used for the treatment of different ailments. Plant-derived products act as a promising agent in the health care for the treatments of different disorders because they can be used against microorganisms and several diseases. Many drugs as quinine, ibuprofen, and morphine are used in the medicine and now day's researchers are using natural products for better medicine development. Jaceosidin is one of natural products promising pharmacological and biological roles. In this retrospective study, we collected information about pharmacological effects of jaceosidin (Figure 2). Although several applications of the drug have been identified, further experimentations are still mandatory; the outcome will be a great of importance and helpful to researchers for the development of natural products in the future.

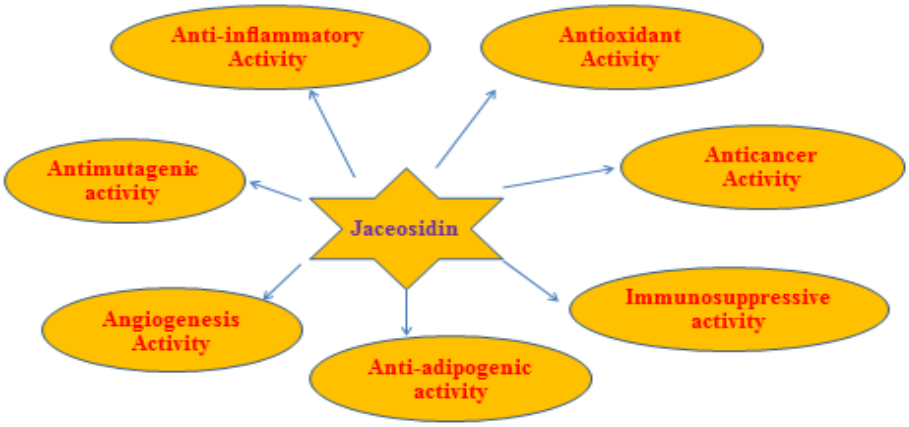

Figure 2: Pharmacological activities of Jaceosidin

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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