



Biological and Biomedical Journal

Journal homepage: <https://bbj.journals.ekb.eg>



Harnessing isosaponarin: A multifaceted bioactive and therapeutic potential compound from nature

Kaynat Firdos¹, Saddam Hussain¹, Basim. S. A. AL Sulivany², Muhammad owais³, Muhammad J. Iqbal⁴, Rizwan N. Paracha⁵, Rana M. Fazal^{*6}

¹ Department of Zoology, Faculty of Basic Sciences, University of Agriculture, Dera Ismail Khan, KPK, Pakistan

² Department of Biology, College of Science, University of Zakho, Zakho, 42002, Duhok, Kurdistan Region, Iraq

³ Department of Zoology, Emerson University Multan, Punjab Pakistan

⁴ Department of Zoology, Faculty of Life Sciences, Government College University Faisalabad, Punjab, Pakistan.

⁵ Department of Chemistry, Faculty of Science, Thal University Bhakkar, Punjab, Pakistan

⁶ Department of Zoology, Ghazi University, Dera Ghazi Khan, Punjab, Pakistan.

ARTICLE INFO

Received: 25/10/2024

Accepted: 14/12/2024

Corresponding author:

Rana Mehroz Fazal, Ph. D

E-mail: rfazal@gugdk.edu.pk

Mobile: +923007039111

P-ISSN: 2974-4334

E-ISSN: 2974-4324

DOI:

10.21608/bbj.2024.331198.1047

ABSTRACT

Flavonoids represent a class of plant bioactive compounds renowned for their multifaceted health benefits. Among phytochemicals, polyphenols like Isosaponarin, a well-studied flavonoid, are widely distributed across various herbs and plant families, presenting notable antimicrobial and antioxidant properties. Numerous plant species harbour the Isosaponarin compound, each with distinct clinical and traditional applications. Isosaponarin-rich plants exhibit strong antimicrobial and antioxidant properties alongside noteworthy anti-hyaluronidase activity. This flavone glycoside also upregulates the mRNA gene level of type I collagen production, promoting skin health and wound healing. Studies highlight the significant effect of Isosaponarin on collagen synthesis, particularly notable in its derivation from wasabi rhizome extract and its application as a fragrance ingredient. Moreover, the research underscores its diverse biological activities, encompassing antiplatelet, anti-atopic dermatitis, and anti-tumor effects. This review aims to provide a comprehensive account of the botanical and dietary sources of Isosaponarin while delving into pivotal studies elucidating its antimicrobial and antioxidant prowess, role as an anti-hyaluronidase agent, mitigation of oxidative glutamate toxicity, and facilitation of type I collagen synthesis.

Key words: Antimicrobial, Antioxidant, Anti-hyaluronidase agent Isosaponarin, Multifaceted,.

1. Introduction

Approximately 8,000 flavonoids and their derivatives have been identified in various plant species, establishing flavonoids as one of the most prominent families of metabolites unique to plants. Folate-containing compounds often accumulate in the form of their glycosides.

Glycosylation alters the physical properties of these target compounds, particularly their chemical stability and water solubility, which, in turn, affects their biological characteristics (Bowles et al., 2005). The enzymes that catalyze glycosylation as glycosyl transferases [GT(s)] have been mentioned. One of the main flavonoids in wasabi isosaponarin, a 40-O-

glucosyl-6-C-glucosyl apigenin, is sporadically found in other plant species. It has been documented to stimulate fibroblast cells' synthesis of type-I collagen. Isosaponarin has garnered interest recently due to its ability to stimulate human hair growth (PCT/JP2016-085968). How isosaponarin is biosynthesized in wasabi remains unclear, particularly in the glycosylation stages. Antioxidants have reportedly been found in isosaponarin from wasabi leaves (Nagai et al., 2010). Research was conducted on the antioxidant properties of preparations of gentian tea, which has a high concentration of isosaponarin and some of its representative phytochemicals. The process of 2,2-diphenyl-1-picrylhydrazyl) assay (DPPH), High performance liquid chromatography (HPLC), Ultraviolet (UV) was implemented (Olennikov et al., 2014). Wasabi leaf extract and isosaponarin have the potential to be used as ingredients in a variety of anti-aging cosmetic preparations as well as other medical applications (Han et al., 1999).

This study provides a comprehensive overview of the research conducted to determine the effectiveness of isosaponarin against bacteria, fungi, and protozoa. It also describes the molecular mechanisms of action where appropriate literature data is available. In order to support the significance of the research on isosaponarin on a novel basis, we also elucidate the relative importance of the plant species described. Many of these studies have concentrated on plant extracts that are a part of various region's traditional medical systems. In this review, we also discuss the traditional uses of plants that contain isosaponarin and listed the most notable plant species that contain the compound in terms of availability and biosynthesis.

2. Biosynthesis

The biosynthesis of isosaponarin, or 4-O-glucosyl 6-C-glucosylapigenin, has not been previously clarified, despite reports that wasabi plants collect it in their leaves (Hosoya et al., 2005). First, C-glucoside enzymes would be the same as those that form isovitexin in buckwheat and rice (Nagmoti et al., 2012). In order to create the expressed sequence tags database (EST database), the total RNA extracted from a

number of the wasabi plant's organs, examined their RNA sequences, and created the database. Nevertheless, plausible UGT genes associated with the UGT708 group cannot be detected. In order to verify the build-up of C-glucosyl flavones present in wasabi plants, the phenolic extract using methanol from several wasabi organs were used. Mass spectrometry and HPLC (HPLC/MS) were used. Isoorientin (6-C-glucosyl luteolin), Isosaponarin, and isovitexin (6-C-glucosyl apigenin) were primarily accumulated by wasabi plants in their leaves, especially the cauline leaves and the radical leaf blades, and in their flowers. CGT activity in wasabi plant crude extracts were identified. Two main products were found when apigenin was used as the substrate involving the crude extract of the flowers or leaves. These matched the natural compounds of 7-O-glucosyl apigenin and isovitexin. They indicated that the wasabi plant possesses the O-glucosyl transferase (OGT) activity toward the 7-O-position of apigenin, and the enzyme activity required to make 6-C-glucoside straight from apigenin. The organs with the highest CGT activity were the cauline leaves and flowers.

Next, while observing the CGT activity toward apigenin within the wasabi plants' cauline leaves (200 g fresh weight), we tried to purify the CGT from those leaves. The peaks corresponding to CGT and OGT activity were separated by purification with DEAE-Sepharose; the fractions were then collected independently, and the predominant fraction containing CGT activity was designated fraction-A. Then, we examined various dye-ligand resins. Reactive Blue 4 agarose was reported to be able to trap enzyme activity and separate OGT and CGT activities when used for affinity-purification with Cibacron Blue 3GA agarose, Reactive Yellow 3 agarose, Reactive Green 19 agarose, and Reactive Brown 10 agarose. Most of the OGT activity was eliminated from fraction A but not from fraction B following purification with Reactive Blue 4 agarose; we utilized fraction A for additional analysis. After the purification procedure, there was a 1.2% recovery and a partial purification of about 320 times (Sasaki et al., 2015).

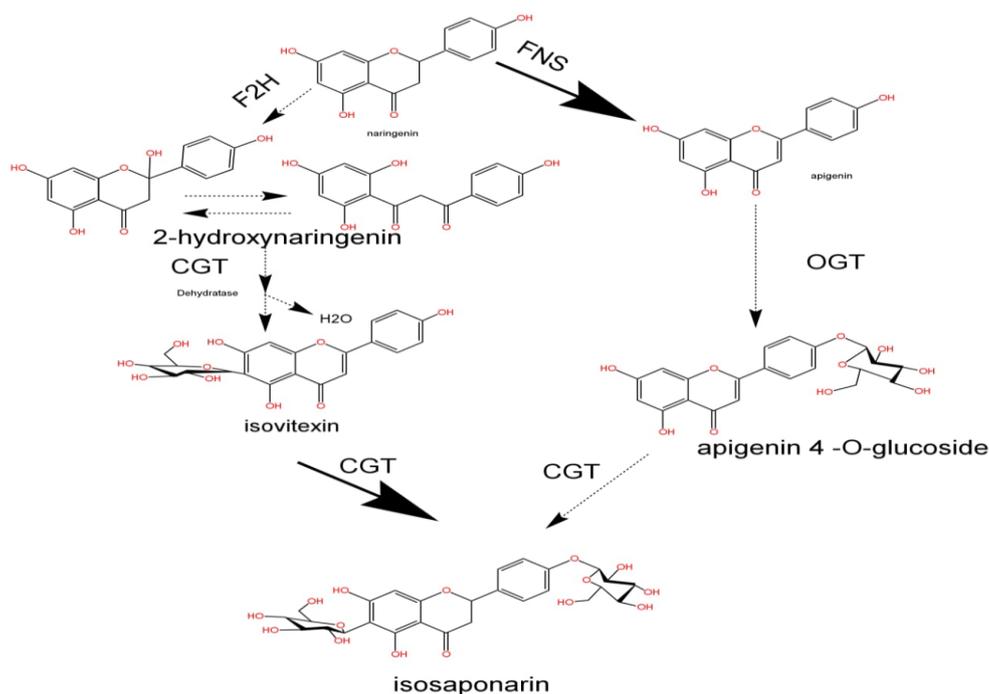


Fig.1. Biosynthetic pathway of isosaponarin, presents a biochemical pathway illustrating the synthesis of 3-deoxyflavonoids. Starting with naringenin as the precursor, the pathway branches into two main routes. These routes involve a series of enzymatic reactions that convert naringenin into various flavonoid compounds, including apigenin and its derivatives.

Chemical Structure of isosaponarin

Isosaponarin belongs to the flavonoid subclass and consists of a flavonoid aglycone (apigenin) attached to sugar moieties. Specifically, its structure is characterized by an apigenin skeleton (5,7-dihydroxyflavone) conjugated to a glucose unit at the C-6 position. This glycosylation enhances its solubility and bioavailability compared to its aglycone counterpart. Isosaponarin is notable for its diverse biological activities, including antioxidant, anti-inflammatory, and potential anti-cancer properties, making it a subject of interest in pharmacological research. Studies have demonstrated its effectiveness in scavenging free radicals and modulating various signaling pathways, contributing to its therapeutic potential (Zhao et al., 2021).

Natural Sources of isosaponarin

medicine and herbal remedies. It is notably found in *Gentiana* species, such as *Gentiana scabra*, and in the leaves of *Perilla frutescens* (perilla leaves) (Shahidi et al., 2017; Rattray et al., 2021). *Pueraria lobata* (kudzu), a vine known for its extensive use in Asian traditional medicine, also contains isosaponarin. Studies have shown the presence of this compound in *Citrus unshiu*, commonly referred to as satsuma mandarin, and in *Glycyrrhiza uralensis* (Chinese licorice) (Zou et al., 2023). Recent research has further explored its occurrence in the *Nelumbo nucifera* (lotus) leaves. Isosaponarin's presence across a broad spectrum of plants suggests its potential pharmacological significance, prompting further exploration into its therapeutic applications, mainly due to its antioxidant,

anti-inflammatory, and hepatoprotective properties (Chang et al., 2022).

Table 1. Natural sources of isosaponarin from different parts of plant extraction by different methods strategies.

| No | Plant name | Common name | Parts of the plant used | Methods | Functions | References |
|----|----------------------------------|----------------------|-------------------------|---------------------------|--|--------------------------|
| 1 | <i>Wisteriopsis japonica</i> | Japanese horseradish | Leaves | LC-ESI-MS/MS quantitative | Collagen syntheses in human fibroblasts | (Nagai et al., 2010) |
| 2 | <i>Eupatorium japonicum</i> | Japanese horseradish | Flowers, roots, leaves | HPLC | Antioxidant, anti-collagenase, antibacterial, anti-hyaluronidase. | Hosoya et al., 2005) |
| 3 | <i>Citrullus colocynthis</i> | Bitter apple | Seeds, fruits | UPLC-MS analysis | Antioxidative, hypoglycemic, antibacterial, anti-cancerous, analgesic, pesticidal, antiallergic, antidiabetic, antimicrobial | (Modaressi et al., 2009) |
| 4 | <i>Artemisia anethifolia</i> | Common mugwort | Flowers | HPLC-DAD-EST-TQ-MS | Anti-diabetic potential | (Olennikov et al., 2014) |
| 5 | <i>Gentiana species</i> | Yellow gentian | Leaves | RP-HPLC-UV | They are used for digestion problems such as loss of appetite, bloating, diarrhea, heartburn, wound healing, and cancer. | (Chawech et al., 2015) |
| 6 | <i>Camellia sinensis</i> | Green tea | Leaves | HPLC | Antioxidants, cancer prevention, cardiovascular disorders, and AIDS. | (Han et al., 1999) |
| 7 | <i>Solanum tuberosum</i> | Potato tuber | Tubers | HPLC/ UV analysis | Used for diabetes, heart diseases, and blood pressure (BP) control dyspepsia. | (Nagai et al., 2010) |
| 8 | <i>Lomatogonium corinthiacum</i> | Marsh felwort | Dried leaves | TQ/MS technique | It is used to invigorate the stomach, heal wounds, and control BP and blood sugar. | (Olennikov et al., 2015) |
| 9 | <i>Halenia corniculata</i> | Spurred gentian | Dried leaves | HPLC/ MS | Clearing away heat, eliminating xieris, controlling BP, and | (Olennikov et al., 2015) |

| | | | | | | |
|----|------------------------------|------------------|-----------------------------|------------------|---|--------------------------|
| | | | | | controlling blood sugar and lipid content. | |
| 10 | <i>Vaccaria vegetables</i> | Cow basil | Seeds | HPLC | used to treat sluggish labor, menstruation issues, breast cancer, deficiencies in lactation, and skin issues. | (Chawech et al., 2015) |
| 11 | <i>Spirodela oligorrhiza</i> | Duck weed | Leaves | HPLC/MS | They relieve inflammation, urticaria, and skin symptoms such as eczema and rash. | (Olennikov et al., 2015) |
| 12 | <i>Garcinia macrophylla</i> | Snowball flowers | Leaves, roots, and flowers. | HPLC | Antimalarial, antitussive and diuretic. | (Olennikov et al., 2011) |
| 13 | <i>Dianthus squarrosus</i> | Sweet William | Flowers | HPLC | Fever tonics ease stomach problems and lessen chest congestion. Certain species provide essential oils that are used to treat depression and stress. | (Takasaki et al., 2001) |
| 14 | <i>Stigma maydis</i> | Corn silk | Flowers | HPLC | It can be used as an antioxidant, anti-parasite, hypoglycemic, hypotension, and hypolipidemic compound, as well as to prevent kidney stones. | (Takasaki et al., 2001) |
| 15 | <i>Silene conoidea</i> | Catchfly | Flowers | HPLC-MS analysis | They treat respiratory problems, antioxidants, antidiabetics, and anticancers. | (Asih et al., 2018) |
| 16 | <i>Mentha longifolia</i> | Podina | Flowers, seed | HPLC | They are used to decrease swelling and heal minor skin wounds and sores. They also treat lung infections, headaches, fever, coughing, colds, menstruation disorders, flatulence, indigestion, and urinary tract infections. | (Lu et al., 2022) |

Medicinal plants

There are several medicinal plants that contain Isosaponarin in their various parts including roots, leaves, flower, stem bark. Here is the list of some medicinal plants that are potentially used for the treatment of multiple physiological disorders and contain Isosaponarin. *Asiatica artemisia*: The plant contains diversity of beneficial compounds including Isosaponarin, the effect of the extract prepared by *Asiatica artemisia* was significantly more effective than ranitidine in treating reflux esophagitis (Asker et al., 2010). *Myrtus communis*: Administration of an aqueous extract of *Myrtus communis* fruit significantly reduced dyspeptic and reflux ratings in a randomized controlled experiment (Karamanolis et al., 2006). *Olea Europea*: Giving olive oil for two to six months to post-gastrectomy patients with highly symptomatic duodenal-gastric reflux who did not respond to traditional treatments either eliminated the patients' symptoms or significantly reduced them (Zohalinezhad et al., 2016). *Ydonia oblonga* (quince): When a syrup made from the fruit of this plant was given to kids with gastric disease, their symptoms significantly improved over time (Karamanolis et al., 2006). *Morus alba*: in rats treated with leaf extract from the plant before gastric disease was induced, the amount of mucus on the stomach wall increased.

Panax quinquefolium: rats receiving *Panax quinquefolium* first showed a dose-dependent reduction in lipid peroxidation, increased antioxidant status, and a notable decrease in the extent of tissue damage caused by gastric disease (Zohalinezhad et al., 2016).

Salvia miltiorrhiza: By causing rats' lower esophageal sphincters (LES) to contract tonic, *Salvia miltiorrhiza* appears to help treat gastroesophageal reflux disease. It was discovered that the underlying mechanism of

this contractile action is the extracellular Ca^{2+} influx pathway (Karamanolis et al., 2006).

Atropa belladonna: this plant is commonly known as deadly nightshade, contains alkaloid in its leaves and roots responsible for the blockage of muscarinic receptors. In human trials, this anticholinergic herb has been demonstrated to reduce stress and anxiety (Salehi and Karegar-Borzi, 2017).

Brassica oleracea: One of an experimental study demonstrated that administration of *Brassica oleracea* to chronic and severe gastric patients, with better person's work environment, lifestyle, and lower anxiety level, may contribute to varied compositions of acid reflux disease (GERD) (Bhardwaj and Kishore, 2021).

Pharmacological effects of isosaponarin

Isosaponarin as antimicrobial activity

Of all the medicinal properties of plant flavonoids, their antimicrobial and antibacterial properties have drawn the most attention recently, particularly concerning the growing issue of antibiotic resistance. According to Al-Sulivany et al. (2024a), gram-positive bacteria cause food poisoning, endocarditis, toxic shock syndrome, and post-operative wound infections. Infections caused by gram-negative bacteria include meningitis, bloodstream infections, wound or surgical site infections, pneumonia, and infections in hospital settings. These bacteria are resistant to many medications resistant to the majority of drugs already on the market (Brosnahan and Schlievert, 2011). One of the most significant medical discoveries of the 20th century was the discovery of antibiotics, and various antibiotics exert their inhibitory action on various harmful organisms. Antibiotics work through a variety of mechanisms that involve particular target molecules. Most of these mechanisms are linked to inhibiting various processes, including synthesizing cell walls,

proteins, fatty acids, ribonucleic acids, carbohydrates, sterol biosynthesis pathway, and intermediary metabolism. Nonetheless, in recent years, the efficacy of the growing number of microorganisms with multidrug resistance mechanisms and the irresponsible use of commercially available antimicrobial medications pose a continuous threat to the efficacy of antibiotic treatment (Yusuf et al., 2021). Furthermore, bacteria that produce biofilms have a high level of antibiotic tolerance. Prolonged treatment of resistant strains puts patients' health at risk and creates a further environment where bacteria can evolve antibiotic resistance (Yusuf et al., 2021).

Furthermore, some reports state that when used with an antibiotic, flavonoids that do not exhibit significant antimicrobial activity on their own can enhance the antibiotic's effects and, in certain situations, reverse bacterial resistance to the particular antibiotic (Fisher et al., 2017). The most likely cause of their advantageous biological actions is isosaponarin. Of all the tested samples, the extracts from the biennial roots of *E. japonicum* had the most desirable biological properties: they were the most cytotoxic against human colon adenocarcinoma cells, and they also exhibited antibacterial, anti-inflammatory, and mildly probiotic *Lactobacillus* species strains growth-promoting properties (Maisuria et al., 2019). Extracts from *E. japonica* showed antimicrobial properties. The microaerobic strains were the specific focus of this activity. The zones of growth inhibition for *S. sanguinis*, *P. mutans*, *P. acnes* PCM 2400, and *P. acnes* PCM 2334 ranged from 16 to 21 mm. It is possible to target the therapeutic usage of isosaponarin extracts against anaerobic bacteria due to their narrow spectrum of antimicrobial activity (Zheng et al., 2012).

Isosaponarin, 2-O—D-glucopyranosyl-Cucurbitacin I, and 2-O—D-glucopyranosyl-Cucurbitacin L were all present in *C. colocynthis* fruit (O'Neill and Chopra, 2004). The well diffusion method and the disc diffusion method were used to examine the effects of the ethanolic extract of the *C.*

colocynthis fruit, and the findings revealed that it exhibited the usual antibacterial action against both Gram-negative bacteria such as *Klebsiella pneumoniae* and Gram-positive bacteria such as *S. aureus* and *Bacillus subtilis*. However, the pulps ethanolic extract demonstrated more excellent activity against Gram-positive bacteria, whereas the seed extract demonstrated marginally less efficacy against both bacteria (Hussain et al., 2014). Siberian gentian herbs' hydro-ethanolic extracts contained isosaponarin (Chawech et al., 2015). Fifteen microorganisms with minimal inhibition concentration (MIC) values of 120-310 µg/mL were inhibited from growing by extracts of *G. lutea* leaves and flowers that had a high gentiopicroside content (38.85-48.38mg/g). At 50–1600 µg/mL concentrations, *G. asclepiadea* extract was effective against seven different bacteria. Gentiopicroside was discovered to have the broadest range of activity among the gentian phytochemicals (Hameed et al., 2020).

Isosaponarin as an antioxidant agent

Antioxidants can prevent or lessen the harm of oxidative reactions or oxidants in the body. There are two types of antioxidants: endogenous antioxidants, which are found in the form of enzymes and are also referred to as intracellular antioxidants and vitamins C and E. Superoxide dismutase, catalase, glutathione peroxidase, copper, zinc, and manganese superoxide dismutase are examples of antioxidant enzymes found in cells. In addition to vitamins A, C, and E, flavonoid compounds are secondary antioxidants (Hameed et al., 2020). Many researchers are interested in tamarillo fruit because of its flavonoid glycosides and isosaponarin, which have the potential to act as antioxidants in the body. Plant antioxidants encompass a diverse group of natural compounds renowned for their capacity to neutralize or scavenge free radicals. Their strong preventive and therapeutic effects have garnered considerable attention from scientists, pharmacologists, and medical professionals (Bhardwaj and Kishore, 2021). The locally grown *C. colony* of this fruit was used to extract isosaponarin. Due to the significant role of reactive oxygen species in

inflammation, cancer, tissue damage, and other diseases, the flavonoids were demonstrated to have strong antioxidant effects. This makes them an important therapeutic target (Modaressi et al., 2009). Among other things, isosaponarin demonstrated anti-tumor solid activity, antibacterial and probiotic activity, and good radical scavenging activity against superoxide anion radicals (O₂) using ESR9. Antioxidants have reportedly been found in isosaponarin found in wasabi leaves (Nagai et al., 2010). Research was done on the antioxidant properties of preparations of gentian tea, which has a high concentration of Isosaponarin and some of its representative phytochemicals. The study was conducted by HPLC-UV based analysis of compounds and DPPH free radical scavenging assay-based assessment of antioxidant potential. (Olennikov et al., 2014). The method used to evaluate the DPPH– radical scavenging activity (DPPH) was described by Asker and Shawky (Asker et al., 2010). The method of (Asayama et al., 1996). was used to measure the ABTS free radical scavenging activity (ABTS, SA); the method of Ding et al. (2010) was used to determine the superoxide anion scavenging activity (O₂, SA) in phenazine metho-sulphate-nicotinamide adenine dinucleotide-nitroblue tetrazolium systems; the β -carotene bleaching assay (CBA) was carried out in β -carotene-oleic acid-DMSO-H₂O₂-system. Results demonstrated the potential of antioxidant property present in the plant (Olennikov et al., 2011).

Isosaponarin as anti-hyaluronidase agent

In young skin, hyaluronic acid is found on the margins of the elastin fibers and collagen; aging skin vanishes. Shrinking turgidity, wrinkles, and elasticity are some effects of aging skin that can arise from decreases in hyaluronic acid levels brought on by an upsurge in hyaluronidase levels. Because they have anti-aging properties for the skin, hyaluronidase inhibitors are beneficial ingredients (Ozen et al., 2011; Baumann, 2007). The effect of isosaponarin, extracted from *W. japonica* leaves, on human fibroblast collagen synthesis was examined. According to Nagai et al., (2010) flavone glycoside

enhanced the mRNA gene level of type I collagen production. When wasabi leaf extract and Isosaponarin were applied to human fibroblasts, type I collagen production increased. Isosaponarin demonstrated similar inducible activity to that of the wasabi leaf extract. Additionally, Isosaponarin elevated the mRNA expression levels of type I collagen. Typically, TGF- β signaling stimulates the transcription of procollagen α 1 (I) in fibroblasts. Nonetheless, isosaponarin treatment did not increase TGF-b1 production. Both the TbR-II protein and its mRNA significantly increased. Consequently, increased TbR-II may upregulate collagen synthesis, and not by TGF-b1 during isosaponarin therapy. Collagen acquires its stable triple-helical structure through folding and post-translational modification. P4Hs catalyze the formation of 4-hydroxyproline residues, which are necessary for synthesizing triple-helical collagen molecules. Isosaponarin treatment increased the P4Ha (I) protein and its mRNA level. Procollagen folding requires HSP47 for it to happen (Baumann, 2007). HSP47-knockout mice could not survive, and there were either few or no collagen fibers in the extracellular matrix. There was no effect of isosaponarin treatment on HSP47. Isosaponarin triggered the modification provided by P4H but did not affect how the procollagen supplied by HSP47 folded. These results suggest increased isosaponarin production of type I collagen depended on TbR-II and P4H rather than up-regulated cell viability and TGF-b1 (Kivirikko et al., 1998). Investigations into its molecular target and signaling pathways are required in the collagen production process that isosaponarin stimulates. Wasabi leaf extract and isosaponarin have the potential to be used as ingredients in a variety of anti-aging cosmetic preparations as well as other medical applications (Baumann, 2007).

Isosaponarin as an anti-oxidative glutamate toxicity agent

The central nervous system (CNS) primarily uses glutamate as an excitatory neurotransmitter. However, excessive glutamate levels can lead to severe oxidative

glutamate toxicity and damage to nerve cells, which are closely linked to the etiology of numerous CNS disorders, including epilepsy, ischemic stroke, and neurodegenerative diseases (Nagai and Okunishi, 2009).

As a result, the nervous system must maintain the glutamate level strictly, and drugs that control its release may be used as treatments (Beal, 1992). Isosaponarin impeded the 4-Glutamate released from synaptosomes triggered by AP. Glutamate transporters reverse the glutamate that 4AP causes to be released from neurons, using vesicular exocytosis, which depends on Ca^{2+} . This result validates the hypothesis that isosaponarin prevents synaptosomes-mediated 4-AP-evoked Ca^{2+} -dependent vesicular glutamate release. Furthermore, efficient vesicular neurotransmitter release depends on an intracellular Ca^{2+} increase in nerve terminals, primarily mediated by N- and P/Q-type Ca^{2+} channels (Lazarevic et al., 2018). Here, we discovered that isosaponarin decreased an increase in (Ca^{2+}) brought on by terminal nerve depolarization with 4AP. Additionally, even though isosaponarin-induced control of glutamate release continued following a single blockade of the P/Q or N-type Ca^{2+} channels, the effect of isosaponarin was inhibited when both channel types were blocked simultaneously. These findings imply that the influence of isosaponarin released from nerve terminals on vesicular glutamate may be explained by the combined inhibition of N and P/Q type Ca^{2+} channel activities. Moreover, Ca^{2+} influx can be changed to control the release of neurotransmitters by adjusting the plasma membrane potential (Catterall and Few, 2008).

Traditional and clinical uses of isosaponarin

Isosaponarin compound has no currently reported uses. Numerous studies are being conducted to look into its traditional and therapeutic applications. Isosaponarin is a flavone glycoside extracted in significant quantities from wasabi leaves. A perennial herb of the Brassicaceae family, wasabi (*Wasabia japonica*) is grown in Japan. Wasabi rhizome extract and fragrance ingredients have been shown to exhibit a range of biological

activities, such as antiplatelet, anti-atopic dermatitis, and anti-tumor effects (Wu and Saggau, 1997). Additionally, isosaponarin, also known as apagenin-6-C-glucosyl-4'-O-glucoside, was produced from Wasabi leaves to encourage human fibroblasts to produce type I collagen, a substance that is now included in makeup (Nagai et al., 2010). The inhibitory effect of isosaponarin on glutamate release in rat synaptosomes was reported by Asih et al., (2018). These reports on benefits indicate that isosaponarin may also be used as a functional food ingredient. The most likely cause of their advantageous biological actions is isosaponarin. Since *E. japonicum* was the most cytotoxic and antibacterial agent against human colon adenocarcinoma cells, it had the most desirable biological characteristics and anti-inflammatory properties, combined with a mild stimulation of the growth of probiotic *Lactobacillus* spp. Strains, which are known to be beneficial (Cazarolli et al., 2009).

Moreover, dietary isosaponarin may aid in managing and preventing diabetes (Morimitsu et al., 2000). Wasabi leaf extract and isosaponarin have the potential to be used in a variety of anti-aging and cosmetic preparations, as well as other medicinal applications (Nagai et al., 2010). It has been demonstrated that isosaponarin, extracted from the fruits of *C. colonynthis*, has significant antioxidant effects. This is important for treating various disorders because reactive oxygen species are crucial in tissue damage, inflammation, cancer, and other disorders (Modaressi et al., 2009). The most likely cause of their advantageous biological actions is isosaponarin. *E. japonicum* had the most favourable biological characteristics because it was the most cytotoxic against human colon adenocarcinoma cells and possessed antibacterial, anti-inflammatory, and mildly probiotic *Lactobacillus* species strains beneficial to the colon (Al-Sulivany et al., 2024). Harnessing compounds with antioxidant and antimicrobial properties represents a key objective for future research aimed at advancing food additives and the pharmaceutical industry.

conclusion

In conclusion, integrating photochemistry and ethnopharmacology

has significantly advanced the development of novel medications derived from plant substances, particularly by investigating compounds like isosaponarin. This paper has demonstrated that plants containing isosaponarin exhibit promising antioxidant, antibacterial, antifungal, and anti-hyaluronidase properties, reinforcing their potential for drug design. The increasing prevalence of antimicrobial resistance highlights the urgency of exploring natural compounds with diverse biological effects, such as isosaponarin, which may offer multi-target therapeutic solutions. Future research should focus on in vitro testing of isosaponarin-containing plant mixtures to determine their relative efficacy and potential synergistic interactions with other compounds. Including isosaponarin in traditional medicine systems further supports its therapeutic potential and underscores the need for continued exploration into its applications. Given the promising initial findings, continued investigation into isosaponarin and related compounds could lead to innovative treatments addressing microbial pathogens and related conditions.

Conflict of Interests:

The authors have no conflict of interest.

Funding: The authors have not declared it.

5. References

- Al-Sulivany BSA, Ahmed DY, Naif RO, Omer EA, Saleem PM, 2024. Pathology and Medicinal Plant Treatment of Gastroesophageal Reflux Disease. *Afr. J. Gastroenterol. Hepatol.* 7(1): 256–271.
- Al-Sulivany BSA, Ahmed DY, Naif RO, Omer EA, Saleem PM, 2024a. Phytochemical Profile of *Eruca sativa* and Its Therapeutic Potential in Disease Prevention and Treatment. *Glob. Acad. J. Agric. Biol.* 6(3): 57–64.
- Asker MMS, Shawky BT, 2010. Structural characterization and antioxidant activity of an extracellular polysaccharide isolated from *Brevibacterium otitidis* BTS 44. *Food Chem.* 123: 315-320.
- Asayama K, Dobashi K, Kawada Y, Nakane T, Kawaoui A, Nakazawa S, 1996. Immunohistochemical localization and quantitative analysis of cellular glutathione peroxidase in fetal and neonatal rat tissues: fluorescence microscopy image analysis. *Histol. J.* 28: 63-71.
- Asih IAR, Manuaba IBP, Berata K, Satriyasa BK, 2018. The flavonoid glycosides are antioxidants from terong Belanda (*Solanum betaceum*). *Biom. Pharma J.* 11(4): 2135-2141.
- Baumann L, 2007. Skin ageing and its treatment. *J Pathol.* 211(2): 241-251.
- Beal MF, 1992. Mechanisms of excitotoxicity in neurologic diseases. *FASEB J.* 6(15): 3338-3344.
- Bhardwaj K, Kishore L, 2021. Natural remedies: For gastroesophageal reflux. *J. Med. Plants.* 9(4): 114–118.
- Brosnahan AJ, Schlievert PM, 2011. Gram-positive bacterial superantigen outside-in signaling causes toxic shock syndrome. *FEBS J.* 278(23): 4649-4667.
- Bowles D, Isayenkova J, Lim EK, Poppenberger B, 2005. Glycosyltransferases: managers of small molecules. *Curr. Opin. Plant Biol.* 8(3): 254-263.
- Catterall WA, Few AP, 2008. Calcium channel regulation and presynaptic plasticity. *Neuron.* 59(6): 882-901.
- Cazarolli LH, Folador P, Moresco HH, Brighente IMC, Pizzolatti MG, Silva FRMB. 2009. Stimulatory effect of apigenin-6-C-β-L-fucopyranoside on insulin secretion and glycogen synthesis. *Eur. J. Med. Chem.* 44(11): 4668-4673.
- Chawech R, Jarraya R, Girardi C, Vansteelandt M, Marti G, Nasri I, Fabre N. 2015. Cucurbitacins from the leaves of *Citrullus colocynthis* (L.) Schrad. *Molecules.* 20(10): 18001-18015.
- Chang YB, Ahn Y, Suh HJ, Jo K, 2022. Yeast hydrolysate ameliorates dexamethasone-induced muscle atrophy by suppressing MuRF-1 expression in C2C12 cells and C57BL/6 mice. *J Funct. Foods.* 90: 104985.
- Ding HY, Chou TH, Liang CH, 2010. Antioxidant and antimelanogenic properties of rosmarinic acid methyl ester from *Origanum vulgare*. *Food Chem.* 123(2): 254-262.
- Fisher RA, Gollan B, Helaine S, 2017. Persistent bacterial infections and persister cells. *Nat. Rev. Microbiol.* 15(8): 453-464.
- Hameed B, Ali Q, Hafeez MM, Malik A, 2020. Antibacterial and antifungal activity of fruit, seed

- and root extracts of *Citrullus colocynthis* plant. *Biol. Clin. Sci. Res J.* 2020(1).
- Han XY, Wang W, Myllylä R, Virtanen P, Karpakka J, Takala TE, 1999. mRNA levels for α -subunit of prolyl 4-hydroxylase and fibrillar collagens in immobilized rat skeletal muscle. *J. Appl. Physiol.* 87(1): 90-96.
- Hosoya T, Yun YS, Kunugi A, 2005. Five novel flavonoids from *Wasabia japonica*. *Tetrahedron.* 61(29): 7037-7044.
- Hussain AI, Rathore HA, Sattar MZ, Chatha SA, Sarker SD, Gilani AH, 2014. *Citrullus colocynthis* (L.) Schrad (bitter apple fruit): A review of its phytochemistry, pharmacology, traditional uses and nutritional potential. *J. Ethnopharmacol.* 155(1): 54-66.
- Karamanolis G, Polymeros D, Triantafyllou K, Tzathas C, Ladas S, 2006. Olive oil for symptomatic relief of duodeno-gastroesophageal reflux after gastrectomy. *Eur. J. Gastroenterol. Hepatol.* 18(11): 1239.
- Kivirikko KI, Myllyharju J, 1998. Prolyl 4-hydroxylases and their protein disulfide isomerase subunit. *Matrix Biol.* 16(7): 357-368.
- Lazarevic V, Yang Y, Ivanova D, Fejtova A, Svenningsson P, 2018. Riluzole attenuates the efficacy of glutamatergic transmission by interfering with the size of the readily releasable neurotransmitter pool. *Neuropharmacol.* 143: 38-48.
- Lu CW, Yeh KC, Chiu KM, Lee MY, Lin TY, Wang SJ, 2022. The effect of Isosaponarin derived from Wasabi leaves on glutamate release in rat synaptosomes and its underlying mechanism. *Int. J. Mol. Sci.* 23(15): 8752.
- Maisuria VB, Okshevsky M, Déziel E, Tufenkji N, 2019. Proanthocyanidin interferes with intrinsic antibiotic resistance mechanisms of gram-negative bacteria. *Adv. Sci.* 6(15): 1802333.
- Morimitsu Y, Hayashi K, Nakagawa Y, Fujii H, Horio F, Uchida K, Osawa T, 2000. Antiplatelet and anticancer isothiocyanates in Japanese domestic horseradish, wasabi. *Mech. Ageing Dev.* 116(2-3): 125-134.
- Modaressi M, Delazar A, Nazemiyeh H, Fathi-Azad F, Smith E, Rahman MM, Sarker SD, 2009. Antibacterial iridoid glucosides from *Eremostachys laciniata*. *Phytotherapy Research.* 23(1): 99-103.
- Nagai M, Akita K, Yamada K, Okunishi I, 2010. The effect of isosaponarin isolated from wasabi leaf on collagen synthesis in human fibroblasts and its underlying mechanism. *J. Nat. Med.* 64(3): 305-312.
- Nagai M, Okunishi I, 2009. The effect of wasabi rhizome extract on atopic dermatitis-like symptoms in HR-1 hairless mice. *J. Nutr. Sci. Vitaminol.* 55(2): 195-200.
- Nagmoti DM, Khatri DK, Juvekar PR, Juvekar AR, 2012. Antioxidant activity free radical-scavenging potential of *Pithecellobium dulce* Benth seed extracts. *Free Radic Antioxid.* 2(2): 37-43.
- O'Neill AJ, Chopra I, 2004. Preclinical evaluation of novel antibacterial agents by microbiological and molecular techniques. *Expert. Opin. Investig. Drugs.* 13(8): 1045-1063.
- Olennikov DN, Kashchenko NI, Chirikova NK, 2014. A novel HPLC-assisted method for investigation of the Fe²⁺-chelating activity of flavonoids and plant extracts. *Molecules.* 19(11): 18296-18316.
- Olennikov DN, Kashchenko NI, Chirikova NK, Tankhaeva LM, 2015. Iridoids and flavonoids of four Siberian gentians: Chemical profile and gastric stimulatory effect. *Molecules.* 20(10): 19172-19188.
- Olennikov DN, Tankhaeva LM, Agafonova SV, 2011. Antioxidant components of *Laetiporus sulphureus* (Bull.: Fr.) Murr. fruit bodies. *Appl. Biochem. Microbiol.* 47: 419-425.
- Ozen T, Demirtas I, Aksit H, 2011. Determination of antioxidant activities of various extracts and essential oil compositions of *Thymus praecox* subsp. *skorpilii* var. *skorpilii*. *Food Chem.* 124(1): 58-64.
- Rattray RD, Van Wyk BE, 2021. The botanical, chemical and ethnobotanical diversity of southern African Lamiaceae. *Molecules.* 26(12): 3712.
- Salehi M, Karegar-Borzi H, Karimi M, Rahimi R, 2017. Medicinal plants for management of gastroesophageal reflux disease: a review of animal and human studies. *J Altern Complement Med.* 23(2): 82-95.
- Sasaki N, Nishizaki Y, Yamada E, Tatsuzawa F, Nakatsuka T, Takahashi H, Nishihara M, 2015. Identification of the glucosyltransferase that mediates direct flavone C-glucosylation in *Gentiana triflora*. *FEBS Lett.* 589(1): 182-187.
- Shahidi F, Ambigaipalan P, Chandrasekara A, 2017. Recent advances in phytochemicals in fruits and vegetables. *Fruit and Vegetable Phytochemicals: Chem and Human Heal*, 2nd Edition, 1323-1356.
- Takasaki M, Konoshima T, Kuroki S, Tokuda H, Nishino H, 2001. Cancer chemopreventive

activity of phenylpropanoid esters of sucrose, vanicoside B and lapathoside A, from *Polygonum lapathifolium*. *Cancer Lett.* 173(2): 133-138.

- Wu LG, Saggau P, 1997. Presynaptic inhibition of elicited neurotransmitter release. *Trends Neurosci.* 20(5): 204-212.
- Yusuf E, Bax HI, Verkaik NJ, van Westreenen M, 2021. An update on eight “new” antibiotics against multidrug-resistant gram-negative bacteria. *J Clin Med.* 10(5): 1068.
- Zohalinezhad ME, Hosseini-Asl MK, Akrami R, Nimrouzi M, Salehi A, Zarshenas MM, 2016. *Myrtus communis* L. freeze-dried aqueous extract versus omeprazole in gastrointestinal reflux disease: a double-blind randomized controlled clinical trial. *J Evid Based Complement Altern Med.* 21(1): 23–29.
- Zou X, Wang X, Zhang M, Peng P, Ma Q, Hu X, 2023. Pre-baking-steaming of oat induces stronger macromolecular interactions and more resistant starch in oat-buckwheat noodle. *Food Chem.* 400: 134045.
- Zhao Y, Chen L, Wang S, 2021. Flavonoids in herbal medicine: Biological functions and mechanisms of action. *Phytomedicine.* pp. 87, 153–161.
- Zheng C, Hu C, Ma X, Peng C, Zhang H, Qin L, 2012. Cytotoxic phenylpropanoid glycosides from *Fagopyrum tataricum* (L.) Gaertn. *Food Chem.* 132(1): 433–438.