




Phytochemistry, pharmacology, and medicinal aspects of *Allium fistulosum* L.: A narrative review

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ABSTRACT

Plants have been employed as traditional remedies for treating several ailments. *Allium fistulosum* L. is an important plant of the family Amaryllidaceae. In this review, its pharmacology, phytochemical, and medicinal aspects have been discussed in detail. It has been reported to be effective against diverse ailments, such as cold, influenza, abdominal pain, cephalgia, arthritis, etc. *Allium fistulosum* medicinal potential is attributed to flavonoids, furostanol saponins, cinnamic acid derivatives, thiolane-type sulfide, and several other bioactive compounds. Subsequently, pharmacological shreds of evidence revealed its anti-obesity, anti-viral, antimicrobial, anti-tumor, anti-oxidant, anti-inflammatory, and immunomodulatory activities. Interestingly, some recent studies also showed the immense potential of *A. fistulosum* to boost immunity against COVID-19. The bioactive composition of this plant should be subjected to clinical trials in the future for paving new aspects to develop a potential plant-based drug to treat human ailments.

INTRODUCTION

Plants have been utilized worldwide to cure several diseases since time immemorial and as per World Health Organization, about 80% of individuals globally still use them (Tugume and Nyakoojo, 2019). The herbal-based medicine could be a novel approach to the replacement of synthetic drugs like aspirin, orlistat, ibuprofen, and others due to their adverse effect of the later on human health (Jagessar, 2020; Maqbool et al., 2019). Plant-based medications are safe, and efficacious owing to the presence of diverse phytoconstituents (Tugume and Nyakoojo, 2019; WHO, 2013). In this context, *Allium fistulosum* L. can be utilized as a useful herbal drug candidate to treat various human diseases. *Allium fistulosum* commonly known as Welsh onion,

is a member of the family Amaryllidaceae. It is grown in Asia, including Korea, Japan, China, and Vietnam (Lee et al., 2018).

Allium fistulosum is a commonly used vegetable crop in various Eastern countries including Japan, Korea, and China (Sung et al., 2018). Western countries have used Welsh onion as traditional medicine against flu, abdominal pain, constipation, headache, arthritis, gastrointestinal disorders, parasitic infestations, cardiac diseases (Sung et al., 2018), colon diseases (Chang et al., 2016), as well as against hypercholesterolemia (Bhat and Nagandram, 2001). In traditional Chinese medicine, Welsh onion is recommended against renal deficiency, dizziness, and cold (Lai et al., 2010), and is also used for the common cold in Japan (Bhat and Nagandram, 2001). Further, plant parts like flowers, leaves, stems, and roots have been used to lower blood pressure, treat cancer, inhibit bacterial strains, and resist viruses, also stem and roots are used as antipyretic and also against the common cold in China (Zhai et al., 2015). The bulbs are used to enhance vision in China (Longe, 2005). Subsequently, the plant is used as an immunity booster in Japan (Ueda et al., 2012). Interestingly, *A. fistulosum* congee (*A. fistulosum* and *Oryza sativa* mixture) was found effective in treating numerous COVID-19 patients at an

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early stage (Hsu *et al.*, 2020). The major bioactive components of the plant include phenolic imidates, cinnamic acid derivatives, phenolic glycoside (Zolfaghari *et al.*, 2021), flavonoids (Choi *et al.*, 2017; Zolfaghari *et al.*, 2021), furostanol saponins (Lai *et al.*, 2010), welsonins A₁ (Nohara *et al.*, 2016), Onionins A1 (Nohara *et al.*, 2017), fructans, polymers of fructose (Lee *et al.*, 2012), and phenylpropenoic acid amides (Park, 2011). Several pharmacological activities have been reported for extracts and isolated compounds of Welsh onion like anti-arthritis, anti-inflammatory, antimicrobial, anti-oxidant, anti-obesity, anti-tumor, anti-viral, and effects on the immune system as proven by animal and cellular models. In this review, we have endeavored to critically assess the scientific information of *A. fistulosum* which includes traditional uses, salient botanical features, bioactive composition, and pharmacological activities which might be used to develop a potential plant-based drug for the management of diverse ailments.

INCLUSION AND EXCLUSION CRITERIA

In light of existing literature, this study was drafted utilizing various online databases, such as PubMed, Google Scholar, Web of Science, and Science Direct. Different keywords used were *A. fistulosum*, Welsh onion, bioactive composition, phytochemistry, ethnomedicine, biological potential, clinical trials, mechanistic insights, mechanism of action, and others. Full-length, peer-reviewed, and English-language papers have been included in this study. The replicated records, conference proceedings, editorials, and also papers not indexed in Scopus and WOS were excluded.

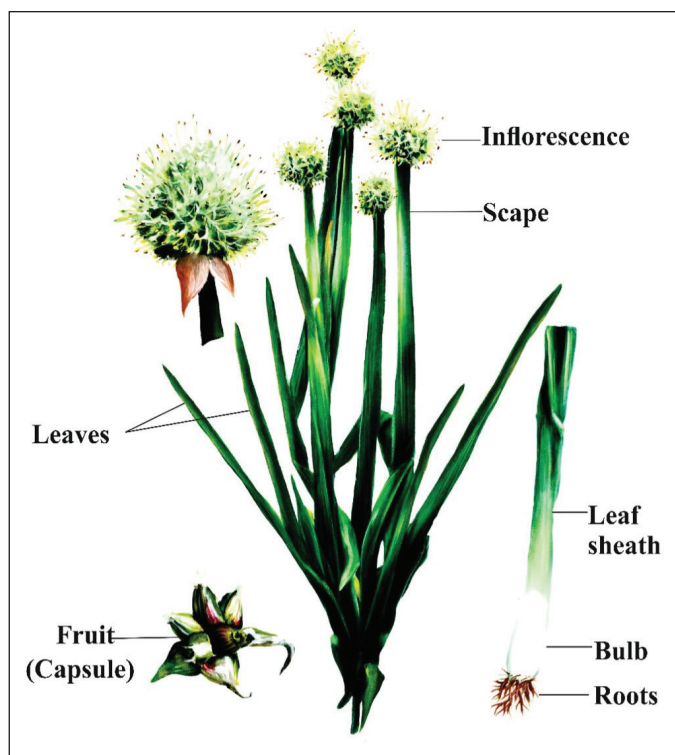


Figure 1. Salient botanical features of *A. fistulosum* (Source: Patanjali Herbal Museum).

BOTANICAL DESCRIPTION OF *A. fistulosum*

The main botanical aspects of *A. fistulosum* are depicted in Figure 1 for correct identification. Bulbs solitary or clustered, cylindrical, 1–2 cm in diameter. Leaves sub-equaling, persistent, 2–6; blade terete, fistulose, 10–40 × 1–2.5 cm. Scape solitary, erect, fistulose, 15–70 × 0.8–2.5 cm. Umbel persistent, erect, compact, 50–100-flowered; spathe bracts persistent, 1–2. Flowers 6–9 mm; tepals erect, yellowish-white; stamens long-exserted; anthers white to yellow; pollen white; ovary crestless; style linear; stigma capitate. Seed coat shining (Eflora-Flora of China, 2023).

ETHNOMEDICINAL IMPORTANCE OF *A. fistulosum*

Ethnomedicines are the traditional heritage used to treat ailments in diverse ethnic cultures. The ethnic group has transferred this knowledge orally over the years to their future generations. *Allium fistulosum* is used by different communities in various countries, such as China, Taiwan, Japan, India, etc. for treating diseases related to the respiratory system, gastrointestinal system, cancer, arthritis, skin disorders, and others (Table 1).

In China, *A. fistulosum* has been extensively employed against various illnesses. In terms of plant parts, whole plant, and roots are recommended for the treatment of the majority of ailments. According to ethnomedicinal records, this plant has been used to treat disorders of the respiratory system, digestive system, arthritis, cephalgia, and other diverse ailments (Table 1).

BIOACTIVE COMPOSITION OF *A. fistulosum*

Plants serve as a reservoir for bioactive compounds, they have a diverse range of chemical structures and are associated with the medicinal potential of plants (Balkrishna *et al.*, 2021; Sharma *et al.*, 2021, 2022; Sonam *et al.*, 2021). The bioactivity, functionality, quantity, and applications of various plant-derived chemical components are affected by a variety of internal and external factors, such as geographical location, altitude, climate change, temperature, seasonal variations, etc. *Allium fistulosum* also have rich bioactive composition, some of which are shown in Figure 2. Several researchers have reported a variety of bioactive compounds from *A. fistulosum*. Vlase *et al.* (2013) reported the flavonoids as isoquercitrin, kaempferol, quercetol, quercitrin; phenolic compounds as ferulic acids, p-coumaric acid; sterols as β -sitosterol, campesterol, stigmasterol and alliin from whole plant. Along with these compounds steroidal saponin, such as yuccagenin (Kim *et al.*, 1991), cinnamic acid amide (Seo *et al.*, 2011), typheramide, alfrutamide (Park, 2011), fistuloimidates (Zolfaghari *et al.*, 2021), and Onionins A1, A2, and A3 (Nohara *et al.*, 2017), were also reported in *A. fistulosum*. Subsequently, Choi *et al.* (2017) documented several flavonoids, such as kaempferol, quercetin, p-coumaric, and ferulic acid, from the aerial parts. Bulbs were found to be rich in welsonins A1 (Nohara *et al.*, 2016), coumaran derivatives, cinnamic acid amides, and hydroxy phenol (Hwang *et al.*, 2020). The leaves contain flavonoids, saponins, steroids (Husori *et al.*, 2016), and β -sitosterol (Liu *et al.*, 2020). Tigu *et al.* (2021) reported that the leaves also contain alliin, alliin, 4-hydroxybenzoic, and p-coumaric acid (Tigu *et al.*, 2021). Terada *et al.* (2006) reported fistulosin from the roots of *A. fistulosum*. Lastly, seeds contain tianshich acid, p-hydroxybenzoic acid, vanillic acid, daucosterol

Table 1. Ethnomedicinal uses of *A. fistulosum* across the globe.

Parts used	Diseases/indications	Country	References
Whole plant	Flu, abdominal pain, headache constipation, Gastrointestinal issue, parasitic infestations, arthritis, and heart disease	South Korea	Sung <i>et al.</i> (2018)
	Digestion, constipation, and colon diseases	Taiwan	Chang <i>et al.</i> (2016)
	Abdominal pain, febrile disease, common cold, and habitual abortion	Korea	Lee <i>et al.</i> (2018); Chen <i>et al.</i> (2011)
	Peripheral vascular disease	Korea	Sung <i>et al.</i> (2015)
	Immunity booster and cold	Japan	Ueda <i>et al.</i> (2012)
	Febrile diseases, headache, abdominal pain, diarrhea, and abortion	China	
	Abdominal pain and phlegmon	East Asia	Lee <i>et al.</i> (2012); Lengbiye <i>et al.</i> (2020)
	Common cold	Japan	
	Renal disorders, dizziness, and cold	China	Lai <i>et al.</i> (2010)
	Heart disease, headache, common cold, and arthritis	Japan	Sung <i>et al.</i> (2014)
Leaves	Blood pressure, heart diseases, common cold, arthritis, and headache	Taiwan	Chen <i>et al.</i> (2000)
	Arthritis, abscesses, catarrh, cardiac diseases, cholera	China	Quattrocchi (2012); Stuart (1911)
	Cold, traumatic injuries	China	Lim (2013)
	Epistaxis, headache, carbuncles, intestinal parasites, and traumatic injuries	India	Longe (2005)
			Longe (2005);
Whole plant and bulbs	Toothache, earache, intestinal infections, mastitis, dysuria, rheumatism, and worm infestation	China	Prajapati and Kumar (2003); Prajapati <i>et al.</i> 2003
Bulbs	Vision impairment, impotence, and dizziness	China	Longe (2005)
Seeds	Carbuncles and sores	China	Longe (2005)
Bulbs and leaves	Febrile diseases, headache, abdominal pain, and diarrhea	China	Sung <i>et al.</i> (2011)
Roots, bulbs, and seeds	Kidney stone	China	Longe (2005)

(Sang *et al.*, 2002), fistulosaponins A–F, and protogracillin (Lai *et al.*, 2010).

PHARMACOLOGICAL PROFILE OF *A. fistulosum*: MECHANISTIC INSIGHTS

In light of existing literature, several studies were found with the pharmacological properties of *A. fistulosum* extracts and compounds. These pharmacological studies provided scientific evidence for some ethnomedicinal uses of this plant. A brief overview of the biological activities of *A. fistulosum* and mechanistic insights into these activities have been depicted in Table 2 and Figure 3, respectively.

Analgesic activity

The ethanol extract (200, 400, and 600 mg/kg) of *A. fistulosum* demonstrated analgesic activity in the hot plate, tail flick, and acetic acid-induced writhing in adult Albino mice. The administration of extract and standard aspirin (300 mg/kg) led to a significant ($p < 0.01$) increase in latency time at 4 hours in both the hot plate and tail flick test as compared to the control. Likewise, the writhing response stimulated by acetic acid was found to be remarkably inhibited by the extract (600 mg/kg) and standard diclofenac sodium (5 mg/kg) with 50% and 46% inhibition, respectively (Nazir *et al.*, 2022).

Anthelmintic activity

The aqueous and ethanolic extracts (50, 100, and 200 mg/ml) of *A. fistulosum* leaves showed dose-dependent and significant anthelmintic effect with decreased paralysis and death time of *Ascaris lumbricoides* when compared with pyrantel pamoate (3 and 6 mg/ml) used as standard drug. It was concluded that both extracts were more efficient than the standard (Husori *et al.*, 2016).

Anti-allergic activity

Allium fistulosum leaves ethanolic extract (200–1,000 µg/ml) exerted anti-allergic activity on calcium ionophore A23187 stimulated mast cell line (RBL-2H3) by notably reducing β-hexosaminidase and indicating a suppressive effect on the degranulation of RBL-2H3 cells (Jippo *et al.*, 2022).

Anti-arthritis activity

The aqueous extract of *A. fistulosum* with rice porridge revealed significant anti-arthritis activity against monoiodoacetate-induced ovariectomized female rats. The extract increased the body weight, bone mineral density, food intake, lean body mass, and fat mass for 11 weeks and also showed enhancement in collagen deposition score and

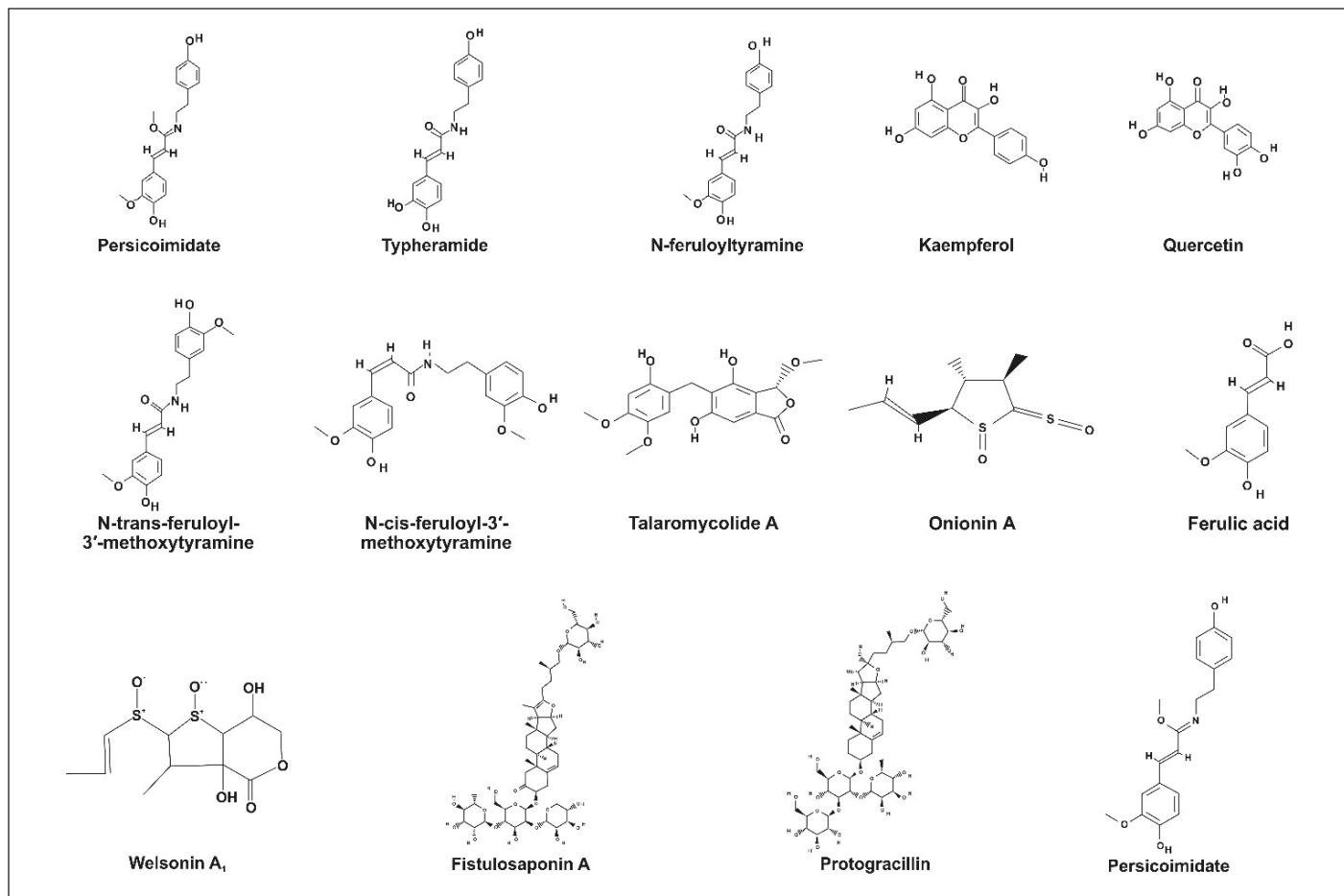


Figure 2. Representative bioactive composition of *A. fistulosum* (Structure source: <https://pubchem.ncbi.nlm.nih.gov>).

knee joint gap. Whereas, the extract showed a reduction in peri-uterine, retroperitoneum, visceral fats, serum alkaline, insulin, glucose, homeostasis model assessment estimate of insulin resistance (HOMA-IR), triglyceride, phosphatase activity, areas under the curves, swelling knee score, leg limping score, right hind paws weight distribution, treadmill running velocity, matrix metalloproteinases (MMP-1 & 13) expressions of messenger ribonucleic acid (mRNA), serum interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) concentrations, as well as tibial surface damage score (Yang *et al.*, 2019). Thus, it was concluded that plant has a healing property to cure women's osteoarthritis.

Anti-glycation activity

Advanced glycation end products (AGEs) are a complex class of substances that can be exogenously or endogenously in nature and have a pathogenic role in the onset and progression of oxidative stress-mediated diseases, such as atherosclerosis, diabetes, and neurological conditions (Vistoli *et al.*, 2013). The ethanolic extract (100 μ l) of Welsh onion exhibited a significant anti-glycation effect by inhibiting the fluorescent AGEs formation with 27.9%,

as compared with positive control; aminoguanidine at 20 mM (75.9%) when monitored after 2 weeks (Ramkissoon *et al.*, 2013). Thus, the Welsh onion can be employed in the management of diverse complications.

Anti-cancer activity

The compounds; N-caffeoyltyramine and isorhamnetin 3-O-galactopyranoside from Welsh onion exhibited an anti-cancer effect on breast cancer (MCF-7) cell line (IC₅₀ 94.4 μ g/ml) whereas, other compounds showed weak effectiveness with >100 μ g/ml (Zolfaghari *et al.*, 2021). Besides, welsonins A₁ (50 μ M) of *A. fistulosum* bulbs significantly attenuated the interleukin-10 (IL-10)-induced cluster of differentiation 163 (CD163) expression in human monocyte-derived macrophages, indicating its potential to suppress tumor-cell proliferation through inhibition of macrophages polarization (Nohara *et al.*, 2016). Furthermore, the ethanolic leaves extract inhibited the cancerous cells (MCF-7, DLD-1, SK-MES-1, and MDA-MB-231) with IC₅₀ values of 2.124%, 2.464%, 3.353%, and 5.819%, respectively (Tigu *et al.*, 2021). The aqueous ethanol extract of Welsh onion stem with varied nitrogen (N) levels (N1 and N2 at 130 and 260 kg/ha) showed anti-cancer activities by significantly decreasing the viability of HepG2

Table 2. Pharmacological profile of *A. fistulosum* extracts and compounds.

Plant parts	Extracts/oil/bioactive compounds	Activity/ pharmacological evidence	Type of study	References
	Ethanol extract	Analgesic	<i>In vivo</i>	Nazir <i>et al.</i> (2022)
	Ethanol extract	Anti-inflammatory	<i>In vivo</i>	Nazir <i>et al.</i> (2022)
	Aqueous and ethanol extracts	Effects on bone growth	<i>In vivo</i>	Ryuk <i>et al.</i> (2021)
	Fistuloimidate A, B, persicoimidate, N-feruloyltyramine, N-caffeoyltyramine, N-coumaroyltyrosine and N-coumaroyltyramine, isorhamnetin 3-O-galactopyranoside, and 1-O-(4-hydroxybenzoyl)- β -D-glucopyranose	Anti-cancer	<i>In vitro</i>	Zolfaghari <i>et al.</i> (2021)
	Ethanol extract	Anti-glycation	<i>In vitro</i>	Ramkissoon <i>et al.</i> (2013)
	Fistuloimidate A, B, persicoimidate, N-feruloyltyramine, N-caffeoyltyramine, N-coumaroyltyrosine and N-coumaroyltyramine, isorhamnetin 3-O-galactopyranoside and 1-O-(4-hydroxybenzoyl)- β -D-glucopyranose	Antimicrobial	<i>In vitro</i>	Zolfaghari <i>et al.</i> (2021)
	Essential oil	Antimicrobial	<i>In vitro</i>	Pyun and Shin. (2006)
	Methanolic extract and isolated compounds such as talaromycolide A-C, cyclo(L-proline-L-leucine), benzoic acid, (Z)-3-phenylpropenal, 2-formyl-3,5-dihydroxy-4-methylbenzoic acid, rubralide C, cyclo(L-proline-L-phenylalanyl)-sclerotinin A, alternariol, penicillide, dicarboxylic acid, radiclonic acid, berkedienolactone, and cyclo(L-tyrosine-L-phenylalanine)	Antimicrobial	<i>In vitro</i>	Zhai <i>et al.</i> (2015)
Whole plant	Furostanol saponins	Antimicrobial	<i>In vitro</i>	Zolfaghari <i>et al.</i> (2016)
	Ethanol extract	Anti-oxidant	<i>In vitro</i>	Ramkissoon <i>et al.</i> (2013)
	Cinnamic acid amides such as N-trans-feruloyl-3'-methoxytyramine, N-trans-p-coumaroyltyramine, and N-cis-feruloyl-3'-methoxytyramine	Anti-oxidant	<i>In vitro</i>	Seo <i>et al.</i> (2011)
	Methanolic extract	Anti-oxidant	<i>In vitro</i>	Obuotor <i>et al.</i> (2018)
	Ethanol and aqueous extract	Anti-obesity	<i>In vivo</i>	Sung <i>et al.</i> (2018)
	Lyophilized aqueous extract	Anti-obesity	<i>In vivo</i>	Sung <i>et al.</i> (2015)
	Ethanol extract	Anti-obesity	<i>In vitro</i>	Sung <i>et al.</i> (2011); Park <i>et al.</i> (2013)
	Raw and boiled extracts	Anti-platelet aggregation	<i>In vitro</i>	Chen <i>et al.</i> (2000)
	Onionins A1	Anti-tumor	<i>In vivo</i>	Nohara <i>et al.</i> (2017)
	Cold, hot aqueous and ethanol extracts	Anti-tumor	<i>In vivo</i>	Arulselvan <i>et al.</i> (2012)
	Aqueous extract	Anti-viral	<i>In vitro</i>	Chen <i>et al.</i> (2011)
	Typheramide and alfrutamide	Anti-inflammatory	<i>In vitro</i>	Park (2011)
	Congee (A mixture of <i>O. sativa</i> + <i>A. fistulosum</i>)	Anti-viral	<i>In vitro</i>	Hsu <i>et al.</i> (2020)
	Methyl alcoholic extract	Anti-viral	<i>In vitro</i>	Seo <i>et al.</i> (2017)
	Ethanol extract	Hepatoprotective	<i>In vitro/In vivo</i>	Hwang <i>et al.</i> (2018)
Aerial parts	Ethanol extract, kaempferol, ferulic acid, quercetin, and coumaric acid	Anti-hyperlipidemic	<i>In vitro</i>	Choi <i>et al.</i> (2017)
Bulbs	Welsonins A ₁	Anti-cancer	<i>In vitro</i>	Nohara <i>et al.</i> (2016)
	Hot aqueous extract and its fructan substance	Anti-viral	<i>In vitro</i>	Lee <i>et al.</i> (2012)
Green leaves	Mucus extract	Effects on immune response	<i>In vitro</i>	Ueda <i>et al.</i> (2012)
Whole plant and roots	Aqueous and ethanol extracts	Anti-inflammatory	<i>In vitro</i>	Park <i>et al.</i> (2011)
Whole plant, leaves, stem, and roots	Alcoholic extract	Antimicrobial	<i>In vitro</i>	Chang <i>et al.</i> (2016)
	Alcoholic extract	Anti-oxidant	<i>In vitro</i>	Chang <i>et al.</i> (2016)

Continued

Plant parts	Extracts/oil/bioactive compounds	Activity/ pharmacological evidence	Type of study	References
Roots	Aqueous extract with rice porridge	Anti-arthritic	<i>In vivo</i>	Yang <i>et al.</i> (2019)
	Aqueous extract	Effects on polycystic ovarian syndrome (PCOS)	<i>In vivo</i>	Lee <i>et al.</i> (2018)
Stem and leaves	Aqueous extract	Effects on bone growth	<i>In vivo</i>	Ko <i>et al.</i> (2019)
	Ethanol extract	Antimicrobial	<i>In vitro</i>	Chang <i>et al.</i> (2013)
	Fistulosaponins A-F, protogracillin, and two others	Anti-ischemia	<i>In vitro</i>	Lai <i>et al.</i> (2010)
Seeds	Aqueous extract	Anti-ischemia	<i>In vivo</i>	Lai <i>et al.</i> (2023)
	Protein extract	Anti-oxidant	<i>In vitro</i>	Zuo <i>et al.</i> (2018)
Fresh bulbs and roots	Cereal bars containing aqueous extract	Anti-obesity	<i>In vivo</i>	Sung <i>et al.</i> (2014)
Roots, stem, and leaves	Ethanol extract	Anti-oxidant	<i>In vitro</i>	Chang <i>et al.</i> (2013)
Leaves	Ethanol extract	Anti-allergic	<i>In vitro</i>	Jippo <i>et al.</i> (2022)

and HeLa cell lines. This activity is attributed to the fact that total phenols and flavonoids are significantly affected by N fertilizers (Zhao *et al.*, 2021). The Onionin A₁ of *A. fistulosum* significantly inhibited the IL-10-induced CD163 expression (M2 macrophage marker), tumor culture supernatant-induced CD163 overexpression, and also, reversed the interleukin-12 (IL-12) downregulation and IL-10 upregulation in ovarian cancer (SKOV3) cell. Moreover, Onionin A₁ inhibited the cell-cell interactions between macrophages and suppressed the protumoral macrophage function. Simultaneously, Onionin A₁ significantly suppressed the tumor weight and lung metastasis in osteosarcoma (LM-8) cell-bearing C3H mice along with suppression in tumor progression of SKOV-3-bearing C57B6 mice (Nohara *et al.*, 2017). Likewise, ethanolic and aqueous extracts (cold and hot) of *A. fistulosum* were investigated for anti-cancer activity against colon carcinoma (CT-26) cells using a mouse model. The hot-aqueous extract significantly inhibited tumor growth and increased the apoptotic index more than other extracts. Moreover, hot-aqueous extract highly suppressed both cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) activities and the levels of IL-6 and TNF- α than other tested extracts. Similarly, hot-aqueous extract displayed a better reduction of cellular markers that were involved in proliferation (cyclin D1 and c-Myc), angiogenesis (vascular endothelial growth factor and hypoxia-inducible factor 1- α), and tumor invasion [MMP-9 and intercellular adhesion molecule (ICAM-1)] (Arulselvan *et al.*, 2012).

Anti-hyperlipidemic activity

The ethanolic extract, p-coumaric acid, quercetin, ferulic acid, and kaempferol from Welsh onion were investigated for anti-hyperlipidemic activity against delipidated serum (DLPS; a mixture of mevalonate and rosuvastatin)-treated HepG2 cells. The extract significantly reduced the low-density lipoprotein receptor (LDLR), pro-protein convertase

subtilisin/kexin type 9 (PCSK9), hepatocyte nuclear factor 1 α , sterol regulatory element-binding protein-2 (SREBP-1c) gene expressions, as well as, LDLR protein expressions without affecting the cell viability. Moreover, the extract protected the lysosomal degradation of LDLR protein in the presence of bafilomycin A1 (lysosomal inhibitor) and blocked the protein synthesis of LDLR. Subsequently, all compounds maintained the LDLR level while quercetin, p-coumaric acid, and kaempferol significantly attenuated the PCSK9 level under conditions of lipid depletion. The tested samples can be effective in lowering hypercholesterolemia in humans (Choi *et al.*, 2017).

Anti-ischemia activity

The fistulosaponins (A–F) and protogracillin (0.5–100 μ M) of *A. fistulosum* seeds displayed an anti-ischemia effect against hypoxia/reoxygenation (H/R)-stimulated injury in human umbilical vein endothelial cell (HUVEC). The tested compounds significantly protected HUVEC from injury and increased the survival of H/R-treated cells, where fistulasaponin A was highly resistant to injury even better than positive control dioscin (Lai *et al.*, 2010). *Allium fistulosum* aqueous seed extract (15, 150, and 300 mg/kg) exerted a protective effect on acute myocardial ischemia in Sprague Dawley rats. Extract and positive control xingling granules (900 mg/kg) significantly decreased serum creatine kinase levels ($p < 0.05$), lactate dehydrogenase levels, and infarcted area ($p < 0.01$) as compared with the saline group (Lai *et al.*, 2023). Thus, the Welsh onion showed a beneficial effect on cardiac function in rat model of acute myocardial ischemia.

Anti-inflammatory activity

The typheramide and alfrutamide compounds of Welsh onion potently inhibited the cyclooxygenases-1 (COX1)

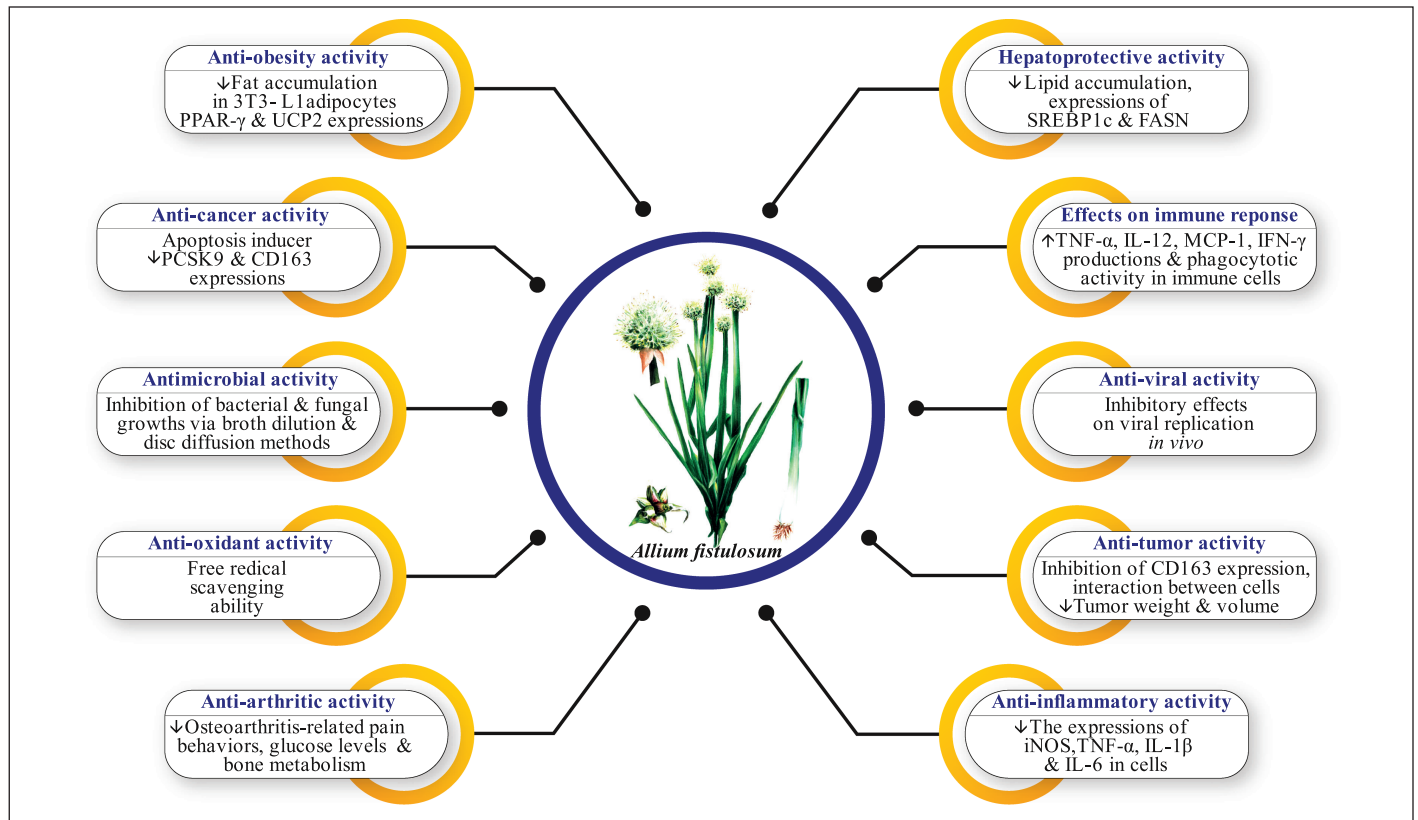


Figure 3. Mechanistic insights into the biological potential of *A. fistulosum*. ↑- Increased ↓- Decreased. PPAR- γ : Peroxisome proliferator-activated receptor gamma; CD163: Cluster of differentiation 163; UCP-2: Uncoupling protein-2; ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); IL-1 β : Interleukin-1 β ; DPPH: 2,2-diphenyl-1-picrylhydrazyl; IL-6: Interleukin-6; IL-10: Interleukin-10; TNF- α : Tumor necrosis factor- α ; IL-12: Interleukin-12; SREBP-1c: Sterol regulatory element-binding protein-2; FASN: fatty acid synthase; MCP-1: Monocyte chemoattractant protein-1; IFN- γ : Interferon- γ ; CD163: Cluster of differentiation 163; iNOS: Inducible nitric oxide synthase.

enzyme even greater than aspirin (COX1 inhibitor), while also inhibiting the lipoxygenases-15 and COX 2 enzymes. However, typheramide is slightly more potent than COX 2-specific inhibitor named NS-398 (Park, 2011). On the other hand, *A. fistulosum* roots aqueous and whole plant ethanolic extracts lowered the mRNA and protein expressions of iNOS, generation of COX-2, and nitric oxide along with, mRNA levels of IL-1 β , TNF- α , & IL-6 in lipopolysaccharide (LPS)-stimulated BV2 microglia cells without affecting the cell viability (Park *et al.*, 2011). Subsequently, *A. fistulosum* ethanolic extract displayed anti-inflammatory properties toward carrageenan-stimulated edema in adult Albino mice. Oral administration with extract (600 mg/kg) and standard ibuprofen significantly reduced edema with 70.27% and 58.10% inhibition, respectively (Nazir *et al.*, 2022). These findings suggested that the plant has the potential to be used for inflammatory disease.

Antimicrobial activity

The N-coumaroyltyramine from the subterranean part of the Welsh onion showed the highest anti-bacterial effect against *Staphylococcus aureus* and *Escherichia coli*. Subsequently, N-feruloyltyramine and N-coumaroyltyrosine attained effectiveness only against *S. aureus* while, 1-O-(4-hydroxybenzoyl)- β -D-glucopyranose and isorhamnetin

3-O-galactopyranoside were active toward *E. coli* (Zolfaghari *et al.*, 2021). Similarly, fistulosaponin G-J of *A. fistulosum* displayed anti-bacterial activity against *E. coli* and *Enterococcus faecalis* (Zolfaghari *et al.*, 2016). The methanolic extract along with sclerotinin A, cyclo (L-proline-L-phenylalanine, talaromycolide A-C, cyclo (L-proline-L-leucine), dicarboxylic acid, benzoic acid, 2-formyl-3,5-dihydroxy-4-methylbenzoic acid, (Z)-3-phenylpropenal rubralide C, alternariol, penicillide, radiclonic acid, berkedienolactone, and cyclo (L-tyrosine-L-phenylalanine) of *A. fistulosum* exhibited anti-bacterial effect against *Bacillus megaterium*, *Bacillus subtilis*, *Clostridium perfringens*, *Micrococcus tetragenus* and *E. coli* (Zhai *et al.*, 2015). Likewise, the alcoholic extracts from different parts (root stem and leaf) of *A. fistulosum* prepared from rice wine (Michiu Tou; 34% and Michiu; 19.5% alcohol) showed antimicrobial ability toward *B. subtilis*, *Pseudomonas aeruginosa*, *E. coli*, and *S. aureus* where highest potential found with Michiu Tou comparatively Michiu extract (Chang *et al.*, 2016). Also, essential oil from the whole plant exhibited an anti-fungal effect on *Trichophyton soudanense*, *Trichophyton erinacei*, and *Trichophyton rubrum* (Pyun and Shin, 2006). Lastly, the stem and leaves ethanolic extract attained effectiveness toward *P. aeruginosa*, *B. subtilis*, *E. coli*, and *S. aureus* (Pyun and Shin, 2006).

Anti-obesity activity

Obesity, a metabolic disorder is characterized by an excess accumulation of fats in the body. In this context, several reports revealed the anti-obesity potential of *A. fistulosum*. The aqueous and ethanolic extracts significantly decreased the lipid accumulation, final body weight, serum level of leptin, weight of adipose tissues, triacylglycerol, alanine transaminase (ALT) levels, and adipocyte area whereas, enhanced the adiponectin level, high-density lipoprotein (HDL)-cholesterol level, adenosine monophosphate-activated protein kinase- α 1 and 2 mRNA expressions in liver tissue of high-fat diet (HFD) obese mice. Moreover, ethanolic extract lowered the aspartate transaminase (AST) level, low-density lipoprotein (LDL)-cholesterol, food efficiency ratio, total cholesterol, and peroxisome proliferator-activated receptor gamma (PPAR- γ) mRNA expression, whereas, enhanced uncoupling protein 2 mRNA expression. Thus, extracts can be an ingredient of functional food to control obesity in people (Sung *et al.*, 2018). Similarly, lyophilized whole plant extract (aqueous) significantly reduced the body, liver weight, food efficiency, serum triglyceride, leptin, glucose, total and LDL cholesterol, AST, ALT, creatinine, mRNA uncoupling protein-2 (UCP-2) and adiponectin levels, adipocyte size and fat accumulation while, enhanced the HDL-cholesterol, mRNA PPAR- γ , and leptin levels in HFD obese mice (Sung *et al.*, 2015). Likewise, cereal bars containing *A. fistulosum* fresh bulbs and roots aqueous extract significantly attenuated the body weight gain, food efficiency ratio, subcutaneous and visceral fats, liver, adipocytes area, and other lipid parameters whereas, increased the β 3-adrenoreceptors, UCP-2, and PPAR- γ mRNA expressions in HFD obese mice (Sung *et al.*, 2014). Whole plant ethanolic extract significantly attenuated weight gain, triglycerides, total cholesterol, leptin, adiponectin, white adipose tissue area, mRNA expression of SREBP1c, PPAR γ and FAS, LDL-cholesterol, and white adipose tissue weight in HFD mice (Sung *et al.*, 2011). In the *in vitro* study, the extract reduced the intracellular lipid accumulation and free glycerol release by 36.7% and 84%, respectively in 3T3-L1 adipocytes (Park *et al.*, 2013). As a result, the plant might be useful in treating metabolic disorders linked to obesity, such as hyperlipidemia and insulin resistance.

Anti-oxidant activity

Allium fistulosum was reported to be a strong anti-oxidant evident by various studies. The extracts from different parts (root, stem, and leaf) were prepared in rice wine (Michiu Tou; 34% alcohol and Michiu; 19.5% alcohol) and exhibited an anti-oxidant effect with 6.2–15.5 mmol TE/g in Trolox equivalent antioxidant capacity. Further, extracts showed a scavenging effect with IC₅₀ ranging between 14.6 and 26 μ g/ml in 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. The effect of alcohol concentrations on the anti-oxidant profile needs further validation (Chang *et al.*, 2016). The ethanolic extract of *A. fistulosum* showed an anti-oxidant effect with 1.220 and 0.812 mg ascorbic acid/ml using ferric reducing antioxidant power (FRAP) and DPPH assays, respectively (Ramkissoon *et al.*, 2013). Similarly, protein extract from the seeds of this

species showed anti-oxidant potential with IC₅₀ of 1.43, 1.37, 2.17, and 0.006 mg/ml in DPPH, hydroxyl, superoxide radical and chelating assays, respectively as well as, this extract increased the reducing power at 700 nm (Zuo *et al.*, 2018). Additionally, ethanolic extract of the whole plant exhibited an anti-oxidant effect with IC₅₀ of 0.58 and 0.24 mg/ml in DPPH and metal chelating assays. Whereas, absorbance with 3.38 and 6.35 mg equivalent of ascorbic acid/g at 563 nm was observed during FRAP and total phosphomolybdate assays, respectively (Obuotor *et al.*, 2018). Some compounds N-trans-feruloyl-3'-methoxytyramine and N-cis-feruloyl-3'-methoxytyramine from the whole plant showed potent DPPH scavenging activity as compared with N-trans-p-coumaroyltyramine (Seo *et al.*, 2011). The ethanolic extracts of *A. fistulosum* stem and leaves displayed higher DPPH and 2,2-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid (ABTS) scavenging effects than that of root extract (Chang *et al.*, 2013). Besides, the aqueous ethanol extract of Welsh onion stems with different nitrogen levels (N1 and N2: 0130 and 260 kg/ha) as urea fertilizer showed DPPH and ABTS scavenging effects (Zhao *et al.*, 2021). Thus, *A. fistulosum* can be used to develop antioxidant-rich food products that will help in the fight against oxidative stress-mediated disorders.

Anti-platelet aggregation activity

The raw and boiled *A. fistulosum* green leaf and white sheath extracts were evaluated against adenosine diphosphate (ADP)-stimulated platelet aggregation where green extracts significantly and potently suppressed the platelet aggregation and adhesion more than white extracts. In addition, green extracts significantly affected the thromboxane release from platelets and also stimulated the cyclic adenosine monophosphate (cAMP) level. Moreover, ADP stimulation of platelets caused their [Ca²⁺] elevation, which was suppressed by the green extract (raw) while increased by green extract (boiled). Furthermore, the raw extract also stimulated cAMP levels (Chen *et al.*, 2000). Thus, results revealed that raw extracts inhibited platelet function while boiled extracts activate platelets.

Anti-viral activity

Welsh onion was reported to be broad spectrum anti-viral agent. For instance, *A. fistulosum* congee (40–80 g with 50 g rice/400 ml water) was evaluated against SARS-COV-2. Administration with congee on day 1 in male patient resulted in sweating, phlegm release, and a decrease from 38.5°C to 37.3°C in body temperature after 2–3 hours. Subsequently next day, more phlegm was discharged and the temperature declined to 36.7°C. Interestingly, only one patient completely recovered in 11 days, while other patients were recovered usually within 3–4 days after consuming congee (Hsu *et al.*, 2020). The hot aqueous extract along with its compound, fructan from leaves showed an effect on influenza A virus (IFV-As)-infected mice, with a significant decrease in virus replication (titer) in bronchoalveolar lavage fluid (BALF) and lung, followed by increased production of neutralizing antibodies in BALFs. Whereas, only fructan enhanced neutralizing antibodies production in sera of mice. Additionally, from day 3 to day 7, extract and compound both showed a consistent drop in body weight which was recovered after day 9 (Lee *et al.*, 2012).

Whole plant aqueous extract attained an effective response on adenovirus (ADV41 and ADV3)-infected human lung carcinoma (A549) cells that exhibited an anti-viral effect closer to its cytotoxic concentration at EC₅₀ value >960 µg/ml (Chen *et al.*, 2011). In contrast, whole plant methyl alcoholic extract significantly reduced the hepatitis A virus titer by 2.07 log after co-treatment at 50 µg/ml (Seo *et al.*, 2017).

Effects on bone growth

The Welsh onion roots aqueous extract increased the longitudinal bone growth by promoting insulin-like growth factor-1 and transforming growth factor signaling, with a significant decrease in body weight gain, retroperitoneal, visceral fat, serum osteocalcin, and total area under the curve, along with a notable increase in fasting serum glucose, insulin, HOMA-IR, serum ALP, femur, tibia bones length, and hypertrophic growth in weanling rats. In addition, the extract markedly improved the survival, alkaline phosphatase (ALP) activity, and mRNA gene expressions of bone morphogenetic protein-2 and Smad4 while, decreased the dickkopf-related protein-1, phosphorylation of insulin receptor substrate-2 and Akt in MG-63 osteoblast cell (Ko *et al.*, 2019). Hence, the longitudinal bone growth of children and adolescents can be achieved by utilizing Welsh onion. *Allium fistulosum* extracts (aqueous and 30% ethanolic) demonstrated facilitation of bone growth in vitamin D and calcium deficient C57BL/6 mice. Both extracts (150 and 450 mg/kg) significantly increased bone mineral density (BMD), bone mineral content, and growth in a way that encouraged the development of the osteogenic markers (calcium, collagen type 1, ALP, and osteocalcin) in the bone. Additionally, both extracts also displayed significant alkaline phosphate activities. Thus, *A. fistulosum* can be used to develop functional foods that will promote bone formation and raise BMD (Ryuk *et al.*, 2021).

Effects on immune response enhancement

The mucus extract from green leaves of *A. fistulosum* showed significant enhancement of TNF- α and monocyte chemotactic protein-1 (MCP-1) in leukemic monocytes (RAW 264) and IL-12 in macrophage-like J774.1 cells *in vitro* and also increased the TNF- α , IL-12 and phagocytotic activity in peritoneal cells, LPS-interferon- γ (IFN- γ) production in spleen cells and the activity of natural killer cells of mice *in vivo* (Ueda *et al.*, 2012). These findings revealed that *A. fistulosum* can enhance natural immunity and can be used as a major defense against various diseases.

Effects on polycystic ovary syndrome (PCOS)

Allium fistulosum's roots extract (aqueous) significantly decreased the blood triacylglycerol, luteinizing hormone, number of follicular cysts, and relative mRNA expressions of luteinizing hormone receptor whereas, increased the blood glucose, relative mRNA expressions of Kitl, bone morphogenetic protein, progesterone receptor, estrogen receptor 1, Cyp19a1, restoration of estrogen and plasma testosterone levels in letrozole-induced PCOS female Sprague Dawley rats. Additionally, the extract normalized the estrus cycle as indicated by the presence of epithelial nucleated and cornified

cells in rats (Lee *et al.*, 2018). Thus, the extensive property of this plant is mediated by normalizing hormonal levels that were altered by PCOS.

Hepatoprotective activity

The ethanolic extract of *A. fistulosum* significantly reduced the lipid accumulation, mRNA expression of SREBP1c, and fatty acid synthase (FASN) in oleic acid (OA)-induced non-alcoholic fatty liver disease model using HepG2 cells, without affecting the cell viability. Moreover, the extract significantly attenuated body, liver, and epididymal fat weight, food efficiency ratio, and plasma levels of ALP, ALT, and AST in the western diet-fed obese mice (Hwang *et al.*, 2018).

Vasorelaxant activity

The raw and boiled *A. fistulosum* green leaf and white sheath extracts-induced vasodilatation in norepinephrine (NE)-precontracted aortae of rats, where green extract (<5 $\times 10^{-4}$ g/ml) stimulated vasorelaxation that was completely inhibited in the presence of indomethacin (inhibitor of prostanoid synthesis). Moreover, boiled green and white extracts evoked the vasocontractile responses in NE-precontracted or resting vessel rings, which was abolished by thromboxane A₂ (TXA₂)-receptor antagonist, SQ29548 as well as, the release of endothelium-derived contracting factor, TXA₂ was also stimulated by white extract (Chen *et al.*, 1999).

CLINICAL EVIDENCE OF *A. fistulosum*'s BIOLOGICAL POTENTIAL

Welsh onion has been proclaimed to have health benefits, several formulations reported the efficacy of its formulations against different diseases but effective targeted constituents have not been focused on a large scale. In this context, some studies highlighted the medicinal efficacy of individual or herbal formulations containing *A. fistulosum* has been included here. A 29-year-old male patient was diagnosed with wind-cold joined by dampness, characterized by an impaired flow of Lung-Qi. He was given a detoxifying powder formulation (Jing Fang Bai Du San) consisting of *A. fistulosum* (three pieces), *Citrus tangerina* (6 g), *Schizonepeta* (5 g) along with other ingredients. It was observed that after one dose, the patient sweated and recovered from cold and fever with improvement in headache and body pain along with pulse stabilization (Li, 2006). The children (3rd and 25th percentiles in height, aged between 5 and 12 years) had significant enhancement in height after treatment with *A. fistulosum* root extract (5 g) in a double-blind and placebo-controlled trial (Shim *et al.*, 2021). The clinical studies of the bioactive components of the plant should be futuristic work for researchers to develop novel efficacious remedies which are safe and cost-effective.

CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, the information about medicinal uses, chemical constituents, and pharmacological profile of *A. fistulosum* is documented in this study. Traditionally, this plant has been used for treating cold, influenza, abdominal pain, cephalgia, ulcers, parasitic infestations, arthritis, and cardiac disorders in several countries. Fistuloimides, onionins A1,

cinnamic acid amides, flavonoids, and fistulosaponins constitute the bioactive composition of *A. fistulosum* which are reported to be anti-obesity, anti-cancer, anti-oxidant, antimicrobial as well as anti-viral agents. Several pharmacological actions were reported using different plant parts but the active phytochemicals and their mechanistic insights are still obscure. A few clinical trials of *A. fistulosum* were reported with the plant alone or as an ingredient of herbal formulations. *Allium fistulosum* as well as its bioactive composition could be developed as a drug-developing candidate after detailed follow-up studies.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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