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Comprehensive review on the pharmacological potential of *Astilbe rivularis* (Buch.-Ham. ex D. Don) in diabetic complications, evidenced by computational analysis

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Astilbe rivularis is a rare plant with numerous traditional medicinal values, predominantly found in North America and Asia. For centuries, *A. rivularis* has been traditionally employed in regional ethnomedicinal practices to address several health issues. It contains various phytochemicals, such as alkaloids, coumarins, flavonoids, and glycosides, and is recognised for its diverse biological properties, including antimicrobial, anti-inflammatory, antioxidant, and antidiabetic activities. However, research on this plant and its role in diabetic complications remains limited. Moreover, phytoconstituents present in *A. rivularis* might be promising candidates for the treatment of diabetic complications involving oxidative stress, the polyol pathway, the PKC-DAG pathway, the hexosamine pathway, and the formation of advanced glycation end-products (AGEs). Therefore, *in silico* studies were performed targeting RAGE (receptor for AGE), aldose reductase (ALR), and sorbitol dehydrogenase (SDH), which revealed significant interactions with bioactive compounds from *A. rivularis*, emphasising the potential of this plant for the development of therapeutic strategies to manage diabetes-associated complications. This article presents a narrative review supported by *in silico* analyses, primarily focusing on the pharmacognostic, phytochemical, and ethnopharmacological attributes of *A. rivularis*, while further exploring its potential relevance in the context of diabetic complications.

Keywords: *Astilbe rivularis*, Diabetic complications, Ethnomedicine, Phytochemicals

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Introduction

The tenacious importance of herbs in medicine, which dates back thousands of years across varied cultures including Egypt, Greece, China, and India, is reflected in their global resurgence. Even with the significant advancements, the use of herbs for medicinal purposes continues to be relevant today, and a significant proportion of the global population depends on locally accessible herbs, plants, or herbal remedies for the management of diverse ailments[1-3]. Herbal remedies serve as a rich reservoir of phytoconstituents that may be utilised to create drug-like substances, non-pharmacopeials, or synthetic drugs. Plant-based medicines offer accessibility, affordability, safety, and effectiveness, often with minimal adverse effects[4]. The medicinal plants and herbs are taken as a diet in the form of spices, fruits, or vegetables, and are extracted either from different plant organs, like leaves, stems, flowers, seeds, bark, root, etc., or from the whole plant[5]. Herbal medicine is often used alongside conventional medical treatments as complementary or alternative therapies and can provide additional options for patients seeking holistic approaches to health[6,7]. The herbal drugs or products used nowadays are proven to be safe for humans as well as for the environment, as compared to synthetics, and have fewer side effects than synthetic ones[8]. Remarkably, more than 75% of the world's population relies mostly on plant extracts for their health, with about 30% of plants being used as medicines[9,10]. Recently, there has been a growing recognition of medicinal plants as a possible source of pharmaceuticals, and scientific research has improved our understanding and use of therapeutic plants. Detailed research is essential to bridge the gap between evidence-based modern medicine and traditional herbal practices, ensuring the optimal application of phytoconstituents for therapeutic purposes.

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A boon to the phytopharmacological world is the plant *Astilbe rivularis*. It is a plant of the Saxifragaceae family, belonging to the genus *Astilbe*, comprising about 20 genera[11,12]. It thrives well in the rocky mountains and hills and has several traditional medicinal uses[13,14]. According to various studies, *A. rivularis* exhibits some promising and diverse pharmacological properties like anti-inflammatory, antioxidant, antiulcer, antibacterial, antiviral, anticancer, and cytotoxic activities, and even antidiabetic potential[15,16]. Moreover, this plant faces threats, like the *Pucciniostele clarkiana* pathogen, which leads to leaf chlorosis and has contributed to its rare species status. Consequently, it's imperative to intensify efforts to preserve *A. rivularis*[15,17]. Despite its extensive traditional use, scientific evidence regarding its efficacy as a medicinal resource has remained limited until recently. *A. rivularis* has been selected for this review due to its documented use in regional ethnomedicinal practices and its reported richness in bioactive phytoconstituents. This narrative review systematically compiles and critically evaluates the existing preclinical and ethnomedicinal evidence on *A. rivularis*, complemented by supporting *in silico* molecular docking analyses. It aims to highlight its medicinal attributes, explore its potential relevance to diabetic complications, and identify directions for future research.

Description

A. rivularis Buch.-Ham. ex D.Don is a rhizomatous, perennial herb, usually 1-2 m tall, belonging to the family Saxifragaceae, with numerous medicinal properties[12,15]. It is commonly known as '*River Astilbe*', '*Astilbe indica*', or '*Astilbe speciose*'. Its leaves are stalked and pinnately compound with a common hairy petiole and adaxially brown, long, pilose. Leaflets are elliptical to ovate with a cordate or rounded acuminate base and double serrated margin provided with glandular hairs along the veins[15,18]. Flowers bloom from July to October and are yellowish to white, arranged in terminal panicles attached to pale brownish peduncles. Each flower has 2 carpels having a connate base with a sub-superior or semi-inferior ovary and with about 5-10 stamens, and the calyx has 4-5 oval or elliptical to oblong sepals; petals, if present, are obsolete. The fruits are ovoid capsules bearing ellipsoidal seeds tapering towards either end; the stems are long, glandular with brown hairs, that have narrowly racemose branches, and the roots are thick, wiry with erect rhizomes. All the plant parts are mildly aromatic[15,18-20]. Taxonomy and morphology characteristics of this species are represented in Table 1 and Fig. 1(a-d). *Astilbe* is predominantly found on rocky hills at an altitude of 6500-10000 feet[14] and is widely distributed in North America and Asia[11,13]. In India, it is extensively found in the Eastern Himalayan region extending from Kashmir, West Bengal, Sikkim to Assam[19,21,22]. In West Bengal, it is mainly distributed on the roadside of the Darjeeling hills[12].

Chemical constituents

Phytochemical evaluation revealed that *A. rivularis* is rich in alkaloids, polyphenols, flavonoids, tannins, coumarins, glycosides, saponins, terpenoids, and triterpenoids. The major phytoconstituents reported are astilbic acid, astilbin, arbutin, aticoside, bergenin, dimer of bergenin, daucosterol, eucryphin, dimethylaesculetin, palmitine, β-peltoboykinolic acid, acetyl-β peltoboykinolic acid, scopoletin, stilbene, and pentacyclic triterpenoids[12,14,16,25-27]. Other compounds which are found to be present are 11-O-galloylbergenin, (+)-catechin, (−)-catechin, (−)-epiafzelechin, 2-(β-D-glucopyranosyloxy)-4-hydroxyl-benzenacetonitrile, 2-Coumaranone; 2-Buten-1-one, 1-phenyl; undecanoic acid, 2-methyl; 2-Piperidinone, 3,6-bis (1-methyllethenyl)-1-phenyl, trans; crinan 1,2-didehydro; 9-Octadecenoic acid (z)- methyl ester; [1,1-Bicyclopropyl]-2-octanoic acid, 2-hexyl-, methyl ester; 17a-Ethyl-3a1methoxy-17a-aza-D-homoandrost-5-ene-17-one and butanedioicacid, 2,3-bis (8-nonen-1-yl)-, dimethyl ester, 3β-trans-p-coumaroyloxy-olean-12-en-27-oic acid and 6β-hydroxy-3-oxoolean-12-en-27-oic acid, 3β-hydroxyolean-12-en-27-oic acid, 3β,6β, 7α-trihydroxyolean-12-en-27-oic acid, 3β-trans-p-coumaroyloxy-olean-12-en-27-oic acid, stigmasta-5(6), 22(23)-dien-3-beta-yl acetate[16,22,25,28,29]. Furthermore, using GC-MS analysis, we have identified 30 distinct molecules from our earlier

Table 1 — Taxonomical classification of *Astilbe rivularis*[23,24]

Domain	Eukaryota
Kingdom	Plantae
Phylum	Spermatophyta/ Tracheophyta
Subphylum	Angiospermae
Class	Dicotyledonae/ Magnoliopsida
Order	Saxifragales
Family	Saxifragaceae
Genus	Astilbe
Species	*Astilbe rivularis*

Fig. 1 — *Astilbe rivularis* plant images: a) whole plant, b) leaves, c) rhizomes with wiry roots, and d) rhizomes.

research, including several important constituents like beta-sitosterol, hexadecanoic acid, and heptafluorobutyric acid[27]. The structures of a few important constituents have been depicted in Fig. 2.

Therapeutic uses

A. rivularis has been used extensively for ages to treat several diseases and disorders like diarrhoea, dysentery, peptic ulcer, headache, haemorrhages, menstrual disorders, uterine prolapse, infertility, herpes infections, body aches, cough, rheumatoid arthritis, back pain, and muscular swelling, as well as for blood purification and wound healing[14,15,18,26,30,31]. The juice of the plant, as well as the roots and rhizomes, is beneficial in sprains and muscular swellings, body aches, headaches, etc.[12,14,18]. The roots, rhizomes, and even the leaves are remedies for diarrhoea, dysentery, and peptic ulcer, including gastric ulcers and duodenal ulcers. Additionally, they are used for haemorrhage, postpartum bleeding, infertility, and various uterine and menstrual disorders like prolapse of the uterus[14,22,32-35]. The rhizome is traditionally used for quick recovery from bone fractures and joint dislocations[32]. The root has numerous other properties like antipyretic, anthelmintic, orexigenic, aphrodisiac, etc.[20,36,37]. The leaves are considered valuable for blood purification[38]. Various studies suggest that it has anti-inflammatory, antioxidant, astringent, antibacterial, antiviral, anticancer, and cytotoxic activities, especially, the rhizomes have shown promising activities against diabetes and its complications[14-16,25,27,31,39,40]. Traditional uses of *A. rivularis* are summarised in Table 2.

Toxicity

In experiments conducted by Prasenjit *et al.*, the authors found that administration of *A. rivularis* root powder by the oral route did not cause toxic symptoms in mouse models at doses of 100 – 3000 mg/kg. This study also recorded no mortality[47]. In another study, the toxicity of an isolated compound AR-1 did not show any toxic effects at doses of 1-30 mg/kg of body weight of rats throughout the experimental period, including the full survival rate and normal behaviour[26]. However, it is important to keep in mind that herbal extracts usually contain many different active chemicals, which can result in toxicological effects when large doses are used for longer periods. Hence, a strong call for the toxicological evaluation of the plant and its extracts to assess their safety and efficacy is necessary.

Pharmacological activity

Antioxidant activity

Antioxidants play a crucial role in protecting against cell damage triggered by unstable molecules called free radicals. Several plants are recognised for their ability to scavenge free radicals, thereby mitigating oxidative stress[48]. *A. rivularis* extract has demonstrated impressive antioxidant properties, making it a noteworthy candidate in this regard[15]. Mandal *et al.* performed a study to evaluate the radical scavenging activity of the successively extracted, purified solvent fractions, in which they reported that these fractions at a dose of 100 µg/mL exhibited remarkable antioxidant activity, with a 95.23% reduction in free radicals measured by the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical assay, an 80.40% reduction in superoxide scavenging activity, and a 45.83% reduction in lipid peroxidation. The results were comparable to those of reference standards quercetin for the first two and curcumin for the lipid peroxidation assay[18]. Subedi *et al.* further investigated the methanolic extract of the plant, and results revealed that it possessed the potential to reduce free radicals, with EC_{50} 4.05 µg/mL, as determined by the DPPH assay. Furthermore, the total phenolic and flavonoid contents were quantified in the *A. rivularis* extract. The extract was found to contain

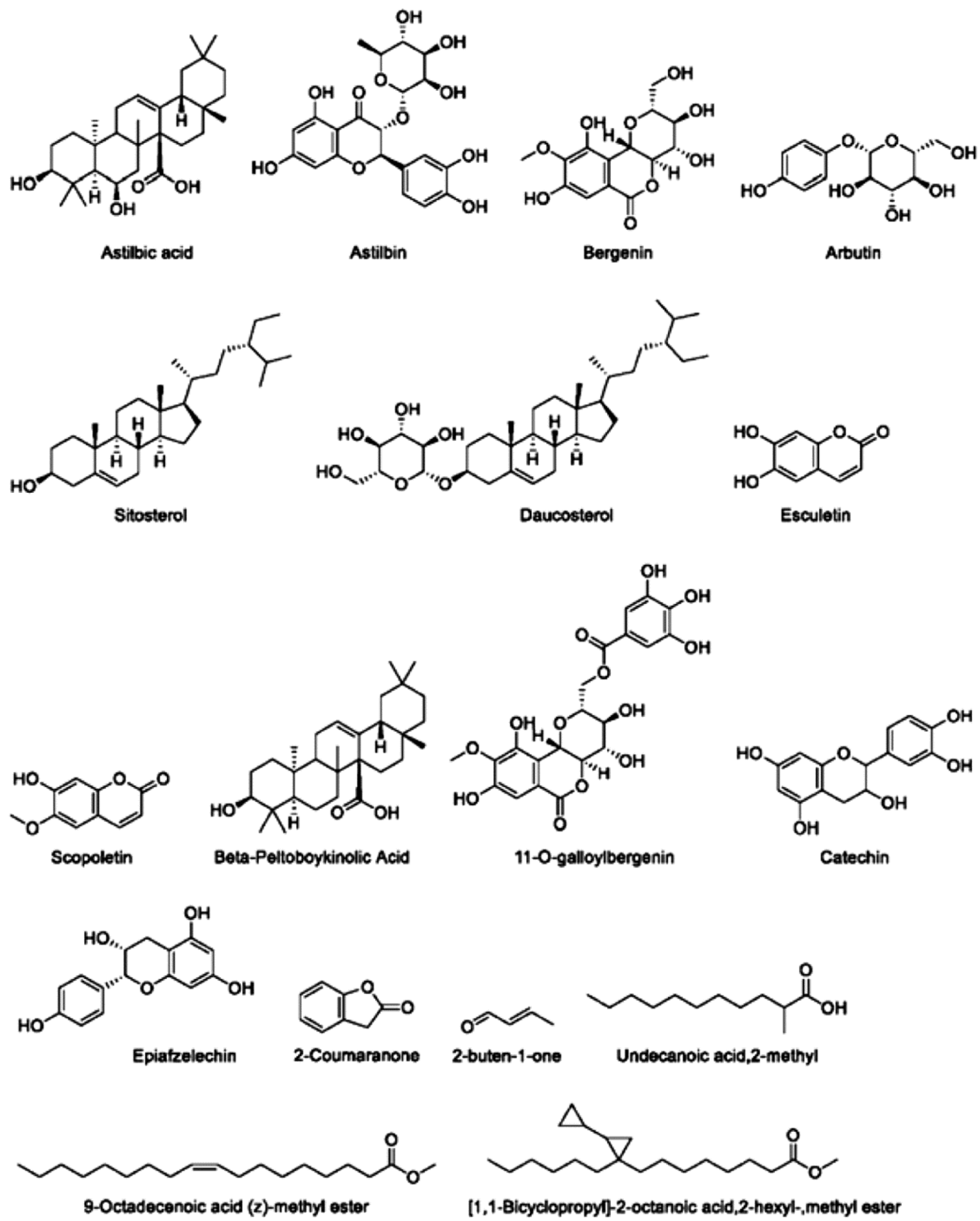

Fig. 2 — Structures of some major chemical constituents of *Astilbe rivularis*.

about 183.11 mg gallic acid equivalent (GAE) per gram of dry weight for total phenolic content and 857.26 mg quercetin equivalent per gram of dry weight for total flavonoid content. Also, the ability of the extract to reduce hexaferricyanide to hexaferrocyanide was evaluated by the Fe^{3+}- Fe^{2+} transformation assay, and a dose-dependent reduction was observed at doses 1-100 µg/mL of extract as compared to the standard ascorbic acid[49]. Similarly, Kaundinnyayana *et. al.* also studied the antioxidant potential of the methanolic extract using the DPPH assay, upon which they discovered that the methanolic extract of *A. rivularis* showed remarkable antioxidant activity with an IC_{50} of 7.88 µg/mL in comparison to that of ascorbic acid (IC_{50} of 5.03 µg/mL)[50]. In another research by Subba and Thapa, the methanolic extract of the plant was assessed for free radical scavenging activity, and the IC_{50} value of ascorbic acid standard was found to be 21.20 µg/mL, while that of *A. rivularis* was observed at 32.05 µg/mL[40]. Next, Hori *et al.* performed the DPPH assay of the methanolic extract of *A. rivularis*

Table 2 — Traditional uses of *A. rivularis*

Traditional use	Part used	Mode of application	Reference
Body ache and headache	Root bark and rhizomes	Juice, Powder	14,41
Toothache	Rhizomes	Infusion/ poultice/ powder	15
Diarrhoea and dysentery	Roots and rhizomes	Juice, Decoction, Paste with honey	42
Peptic ulcer, gastric ulcer and duodenal ulcer	Roots, rhizomes and leaves	Juice	26
Prolapse of the uterus and other uterine disorders	Roots and rhizomes	-	19
Sprains and muscular swellings	Entire plant	Juice	14,40
Blood purifier	Leaves	-	15
Bone fracture and dislocation of joints	Rhizomes	Paste with honey	32
Postpartum bleeding and hemorrhage	Roots and rhizomes	Decoction, Paste with honey	14,43
Infertility and other menstrual disorders	Rhizomes	Decoction, Powder with milk	41,44
Uterine contraction during parturition	Rhizomes	Mixture of ghee with rhizome	38
Jaundice	Root	Powder with curd	45
Appetizer	Root	-	36,46

and stated that the EC_{50} of the extract was found to be 13.0 µg/mL, which was comparable to that of the standard Trolox, whose EC_{50} was 12.2 µg/mL[22]. Gupta *et al.* conducted numerous studies on the antioxidant activity of the plant by performing the DPPH, nitric oxide, and hydrogen peroxide radical scavenging assay, along with total antioxidant capacity, total phenolic content, and reducing power assay, all of which showed significant results[27]. These explicate that *A. rivularis* possesses potent antioxidant potential and could be beneficial in conditions associated with increased oxidative stress, a major culprit in numerous diseases and disorders.

Anti-inflammatory activity

Inflammation is a fundamental defence mechanism of the immune system in response to infections, injuries, or tissue damage. To assess the anti-inflammatory potential of *A. rivularis*, Mandal *et al.* conducted experiments using a carrageenan-induced inflammation model in rats. The results revealed oral administration of *A. rivularis* (200 mg/kg body weight) inhibited carrageenan-induced paw inflammation in albino rats by an impressive 56.20% at 24 hours, which was comparable with the standard non-steroidal anti-inflammatory drug, ibuprofen, administered at a dose of 18 mg/kg body weight with percentage inhibition 48.18%[18]. Based on the pentacyclic triterpenoidal constitution of *A. rivularis*, Jung *et al.* explored the anti-inflammatory potential of 3 pentacyclic triterpenoids obtained from *Astilbe* against vascular inflammatory responses mediated by TGFBIp. The anti-inflammatory activity was evaluated using parameters such as permeability, leukocyte adhesion, and migration, as well as pro-inflammatory protein activation in TGFBIp-activated human HUVECs and mice. The findings showed that compounds effectively suppressed the expression of cell adhesion molecules (CAMs) and the rupture of the TGFBIp (Transforming Growth Factor-Beta-Induced Protein)-induced barrier. Furthermore, each compound demonstrated the ability to suppress leukocyte migration and hyperpermeability induced by TGFBIp in *in vivo* experiments. These results provided strong evidence of the anti-inflammatory properties of compounds contained in *A. rivularis*[51]. Similar anti-inflammatory assessments were performed for two other pentacyclic triterpenoids, using the same parameters, by Kang *et al.* The outcomes, yet again, confirmed the anti-inflammatory potential of *A. rivularis*[52].

Antimicrobial activity

The significance of antimicrobial agents cannot be overstated, particularly in the face of rising drug resistance among microbes[53]. Natural products have emerged as a viable solution, offering the potential to replace expensive drugs while minimising side effects. Within this context, *A. rivularis* and its constituents have shown remarkable efficacy in preventing and treating bacterial and viral diseases.

In the pursuit of understanding the antimicrobial properties of *A. rivularis*, a series of experiments was conducted. One such study includes assessment of antibacterial properties of *A. rivularis* extract against five different bacterial strains, namely *Aeromonas liquefaciens, Bacillus amyloliquefaciens, Bacillus subtilis, Flexibactor sp.,* and *Pseudomonas sp*., using the agar well diffusion method against standard antibiotics like ampicillin (2 µg/mL) and tetracycline

(30 μg/mL). The results demonstrated antibacterial effects against both gram-positive and gram-negative bacteria. At concentrations ranging from 20 to 100 mg/mL, the extract generated a zone of inhibition (ZOI) between 13-24 mm (*p* <0.001). The most significant ZOI of 23 and 24 mm was observed against *A. liquefaciens* and *B. amyloliquefaciens* at concentrations of 100 and 80 mg/mL, respectively[25]. In another test, the antimicrobial activity of the methanolic extract obtained from the dried rhizome of *A. rivularis* was assessed against *Escherichia coli* using the agar disk diffusion method, with Ciprofloxacin (30 mcg) as a standard. The activity was evaluated at different concentrations (0, 3, 6, 12, 100) g/100 mL of the rhizome extract dissolved in a 1% (v/v) solution of DMSO, and the most significant antimicrobial activity was observed at 100 g/100 mL[31]. Rajbhandari *et al.* subjected methanolic extracts of *A. rivularis* to *in vitro* antiviral activity assessments against both HSV-1 and influenza virus A, employing dye uptake assays in the HSV-1/Vero cell system and influenza virus A/MDCK cell system. The extract exhibited potent antiviral activity against both viruses and demonstrated significant IC_{50} values of less than 6.25 μg/mL[30]. In a subsequent study, he isolated 3 compounds from the extract and evaluated their antiviral activity in the same manner, showing strong antiviral potency for 2 of the compounds and justifying the use of *A. rivularis* in ethnomedicine[14].

Cytotoxic activity and anticancer activity

The cytotoxic assay was performed to determine the LC_{50} using the brine shrimp lethality test. The methanolic extract of *A. rivularis* yielded an LC_{50} value of 92.01 ppm, which is categorised as mildly toxic, but this level of toxicity does not pose a significant risk of acute harm during exposure. As a result, the use of extracts from this plant in traditional medicines is unlikely to cause acute adverse effects on patients, as they do not fall into the highly toxic category[31]. Furthermore, the cytotoxic activity of the *A. rivularis* rhizome extract against both normal (HEK-296 and WRL-68) and cancer (SHSY5Y) cell lines was assessed using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. The plant extract exhibited cytotoxic effects against the neuroblastoma cell line (SHSY5Y) and two normal cell lines, HEK-296 and WRL-68, with IC_{50} values of 83.7, 193.8, and 389.3 μg/mL, respectively. In the results, moderate cytotoxicity was observed against the cancer cell line and a limited effect on the normal cell line, indicating strong inhibition of cancer cell proliferation[25]. Byuna *et al.* studied three isolated compounds from *A. rivularis* , namely, 3β-hydroxyolean-12-en-27-oic acid, 3β,6β,7α-trihydroxyolean-12-en-27-oic acid, and 3β-trans-p-coumaroyloxy-olean-12-en-27-oic acid, and reported that these compounds enhance caspase-8 activation in response to TNF-related apoptosis-inducing ligand (TRAIL). Mechanistically, these compounds increased the expression of the cell-surface receptor DR5 and promoted death-inducing signaling complex (DISC) formation without altering other intracellular apoptosis-related proteins. The elevated DR5 expression was dependent on the activation of a protein called C/EBP homology protein, regulated by the p38 PKC pathway. This effect was independent of p53 and the level of intracellular reactive oxygen species. This novel study identified that these compounds sensitise cancer cells to TRAIL-induced apoptosis by enhancing the assembly of DISC through DR5 upregulation[28]. In another study, a phytosteroid compound, stigmasta-5(6),22(23)-dien-3-beta-yl acetate, was isolated from the rhizome of *A. rivularis*. The compound displayed a remarkable ability to inhibit DNA replication, as demonstrated by its capacity to inhibit the catalytic activity of human dihydrofolate reductase *in vitro*, leading to significant structural changes in the enzyme. Additionally, the compound showed a relatively strong cytotoxic effect on human kidney and liver cancer cells, with less impact on their normal counterparts. The isolated compound induced apoptosis in cancer cells by triggering the production of intracellular ROS and causing genomic DNA fragmentation[29]. These findings underscore the promising potential of *A. rivularis* as an antitumor agent, suggesting its value for further exploration in cancer therapy.

Antiulcer activity

Ulcers are lesions on the mucous lining of the GIT caused by disturbance in the acid-base balance in the GIT. Several medicinal plants have shown favourable effects on ulcers through different mechanisms[54]. Root powder derived from *A. rivularis* demonstrated antipeptic activity against both gastric and duodenal ulcers. Rats pre-treated with this root powder showed protective efficiency levels of approximately 50, 55, 54.79, 61.01, and 56%, respectively, against gastric ulcers induced by ethanol, HCl, indomethacin, swimming stress, or pyloric ligation, as compared to the standard omeprazole, whose protective activity ranged from 60-71%[47]. Beyond the root, *A. rivularis* leaves were also found to have activity against alcohol-induced gastric and cysteamine-induced duodenal ulcers, although this activity displayed seasonal variations[55]. Later, a compound (AR-1) was isolated from leaves of *A. rivularis*, and its antiulcer activity was again assessed. Albino rats were administered leaf powder orally 0.5 hours before the induction of gastric ulcers by ethanol or duodenal ulcers by cysteamine hydrochloride. The antiulcerogenic activity of the collected leaves demonstrated peak efficacy (antigastric ulcer activity - 51.98%, antiduodenal ulcer activity - 47.84%) in May-June and reached its lowest levels in January-February (antigastric ulcer activity - 4.96%, antiduodenal ulcer activity - 3.01%), which was comparable to that of the standard ranitidine[26]. These experimental outcomes confirm the antiulcerogenic activities of *A. rivularis*.

Antidiabetic activity

Over the past few decades, a number of herbal medicines have been used to treat diabetes, i.e., increased blood glucose levels[56]. Han *et al.* in their study revealed two significant compounds isolated from *A. rivularis*, namely, 3β-trans-p-coumaroyloxy-olean-12-en-27-oic acid and 6β-hydroxy-3-oxoolean-12-en-27-oic acid, which are pentacyclic triterpenoids featuring a carboxylic acid group at C-27. They were found to enhance both basal and insulin-stimulated glucose uptake in C2C12 myotubes. Further analysis revealed that these C-27-carboxylated triterpenoids stimulated the phosphorylation of IRS-1, PKB/Akt, and Erk1/2, and activated two critical pathways, namely IRS-1/Akt and Erk1/2, leading to the translocation of glucose transporter 4 (GLUT4) in C2C12 myotubes. Inhibition experiments with triciribine (an Akt inhibitor) and U0126 (an Erk1/2 inhibitor) demonstrated that the ability of these compounds to stimulate GLUT4 translocation and enhance glucose uptake was diminished when the pathways they target were blocked. These findings strongly suggest that the compounds activate the IRS-1/Akt and Erk1/2 pathways, ultimately promoting GLUT4 translocation and enhancing glucose uptake. These observations indicate that C-27-Carboxylated Pentacyclic triterpenoids have the potential to serve as a basis for the development of agents to manage hyperglycemia in diabetes[16]. The *in vitro* antidiabetic activity was further supported by an *in vivo* study by Gupta *et al.*, which showed significant antidiabetic activity in STZ-NAD (Streptozocin-Nicotinamide)-induced diabetes in Wistar rats upon treatment with the hydroalcoholic extract of *A. rivularis*. Additionally, this study depicted the therapeutic effects of the plant extract in diabetic neuropathy upon assessing ALR (aldose reductase) inhibitory activity, sorbitol accumulation inhibitory activity, and antiallodynic and antihyperalgesic activity[27].

***In silico* molecular docking analysis**

To support the literature-based discussion, *in silico* molecular docking was performed by Autodock PyRx (0.8) using a blind docking strategy to explore potential interactions of selected *A. rivularis* phytoconstituents with key targets involved in diabetic complications, including RAGE (receptor for AGE), (ALR) (PDB ID: 3O3U), ALR (aldose reductase) (PDB ID: 4JIR), and SDH (sorbitol dehydrogenase) (PDB ID: 1PL7). FPS-ZM1, epalrestat, and SDI-158 were used as the respective reference standards for RAGE, ALR, and SDH, and the observed docking scores (kcal/mol) have been summarised in Table 3. All docking outcomes were interpreted qualitatively to explore and support mechanistic perspectives rather than to provide confirmatory evidence.

Discussion and future directions

Across many cultures and civilisations, using plants as traditional medicine has long been a practice. For an extensive period, traditional healers

Table 3 — Binding affinities of chosen compounds from *Astilbe rivularis*

Ligands	Binding Affinity (kcal/mol)		
	RAGE (3O3U)	ALR (4JIR)	SDH (1PL7)
11-O-galloylbergenin	**-9.6**	**-8.8**	**-8.2**
Arbutin	-7.6	-7.6	-6.8
Bergenine	-8.0	-7.0	-7.0
Catechin	-9.0	**-10.1**	-7.2
Daucosterol	**-9.3**	**-9.0**	**-9.2**
Epiafzelechin	-8.6	**-9.4**	-7.0
Scopoletin	-7.2	**-8.2**	-6.3
β-Sitosterol	**-9.9**	**-8.4**	**-8.6**
2-Coumaranone	-6.4	-6.7	-5.1
2-Buten-1-one	-7.0	**-7.6**	-5.7
Undecanoic acid, 2-methyl	-5.9	-6.9	-4.7
Crinan 1,2-didehydro	-8.1	-7.9	-7.4
9-Octadecenoic acid (z)- methyl ester	-6.6	-7.0	-5.3
[1,1-Bicyclopropyl]-2-octanoic acid, 2-hexyl-, methyl ester	-7.2	--	--
Esculetin	-7.0	**-7.8**	-6.1
Standard	**-9.1**[p]	**-7.4**[q]	**-7.9**[r]

[p]FPS-ZM1; [q]Epalrestat; [r]SDI-158

and diverse societies have relied on the medicinal properties of plants to address a range of ailments[57]. This traditional knowledge frequently includes treatment using particular plant components, such as leaves, roots, or bark[58]. The scientific underpinnings of traditional plant treatments are often investigated by researchers, despite the notable progress gained in contemporary medicine, to identify and comprehend the bioactive substances in these plants to develop herbal remedies supported by data[57,59]. Rich sources of bioactive chemicals found in plants might be used as molecular targets for many pharmacological applications and drug development. This possibility creates opportunities for affordable substitutes for modern medications[60,61]. Still, there is a lack of approved herbal formulations, so it is essential to carefully identify and evaluate plants that are of pharmacological importance.

A. rivularis is a remarkable medicinal plant with a long history of traditional use as a folk remedy[12,14]. Its varied phytoconstituents, including steroids, reducing sugar, tannins, phenols, flavonoids, coumarins, alkaloids, saponins, terpenoids, and glycosides, are responsible for its therapeutic effectiveness, along with anti-inflammatory, antibacterial, antioxidant, antidiarrhoeal, and antipeptic ulcer effects, and various other activities[15,25]. Numerous *in vivo* and *in vitro* data support these activities, further emphasising its significance as a gift from nature with a wide range of potential benefits for mankind. However, this plant is facing relentless extinction, driven by the persistent forces of deforestation and urbanisation[15,17]. *A. rivularis* presents itself as a promising candidate in the exploration of plant-based therapeutic potentials and emerges as a potential molecular target for drug development and pharmacological applications. Beyond its medicinal potential, utilising plant-based remedies like *A. rivularis* offers a more economical alternative to contemporary pharmaceuticals[61,62]. However, it is essential to address the challenge that only a limited number of herbal formulations have undergone rigorous experimental validation and scientific approval[63]. Consequently, there is a pressing need to systematically screen plants like *A. rivularis*, assessing their pharmacological significance and substantiating their therapeutic efficacy through scientific validation.

Oxidative stress, characterised by an imbalance between ROS production and our body's ability to detoxify them, plays a vital role in the progression of various diseases, particularly diabetes complications[64,65]. In diabetes, chronic hyperglycemia contributes to increased ROS production through multiple pathways, including the polyol pathway, AGEs formation, and mitochondrial dysfunction. These elevated ROS levels contribute to the development and exacerbation of diabetes-related complications, like nephropathy, retinopathy, and neuropathy[66]. Oxidative stress also extends its influence beyond diabetes, being implicated in the pathophysiology of cardiovascular diseases, neurodegenerative disorders, and inflammatory conditions[67]. Understanding the complex interplay between oxidative stress and disease progression is crucial for developing targeted therapeutic strategies to mitigate their impact on health. Moreover, the polyol pathway, also known as the sorbitol-aldose reductase pathway, is a critical biochemical route implicated in the development of diabetic complications. This pathway becomes particularly active under hyperglycemic conditions, a hallmark of DM[68,69]. The polyol pathway involves two key enzymes: ALR and SDH. ALR, the first enzyme in this pathway, reduces glucose to sorbitol using NADPH as a cofactor. Sorbitol is then oxidised to fructose by SDH, with NAD+ serving as a cofactor. Under normal physiological conditions, the polyol pathway processes only a small fraction of glucose. However, in the context of chronic hyperglycemia, as seen in diabetes, the flux of glucose through this pathway significantly increases. This hyperactivity of the polyol pathway has several deleterious effects. Firstly, increased consumption of NADPH by aldose reductase reduces its availability for other critical cellular processes, such as the regeneration of GSH[70]. Reduced glutathione is a vital antioxidant that protects cells from oxidative stress. Consequently, diminished GSH levels lead to increased cellular vulnerability to oxidative damage. Consequently, the accumulation of sorbitol within cells poses another significant problem. Sorbitol, being a polyol, does not easily diffuse across cell membranes, leading to its intracellular accumulation. This results in osmotic stress, which can cause cellular swelling and dysfunction. In tissues such as the retina, kidney, and peripheral nerves, this osmotic stress contributes to the pathogenesis of diabetic complications like retinopathy, nephropathy, and neuropathy, respectively[71]. Eventually, the conversion of sorbitol to fructose by SDH increases intracellular levels of fructose and its metabolites. Fructose metabolism further exacerbates oxidative stress by increasing the formation of AGEs and ROS, ultimately contributing to vascular and tissue damage commonly seen in diabetes[72,73]. Scientific literature indicates that *A. rivularis* exhibits potent antidiabetic activity[16]. However, it is noteworthy that despite this recognised potential, the exploration of this plant in the context of diabetic complications remains limited. Therefore, our investigation has identified several phytoconstituents, including β-sitosterol, 11-O-galloylbergenin, catechin, Esculetin, and Daucosterol, as highly promising candidates derived *from A. rivularis* in targeting the RAGE, ALR, and SDH receptor, a crucial target for oxidation and inflammation regarding diabetic complexities (Table 3 and Fig. 3-5). Here, docking scores for

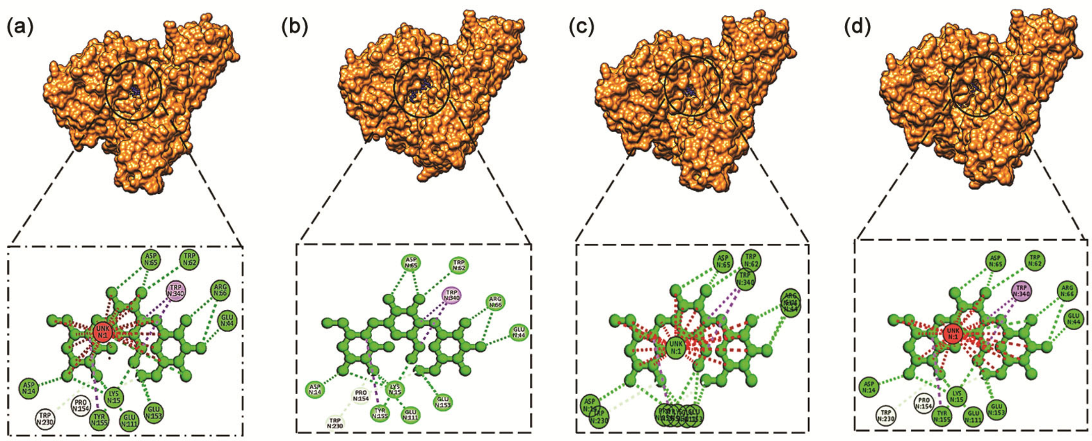

Fig. 3 — Possible binding interactions of best ligands against 3O3U. a) 11-O-galloylbergenin, b) Daucosterol, c) β-sitosterol, and d) FPS-ZM1.

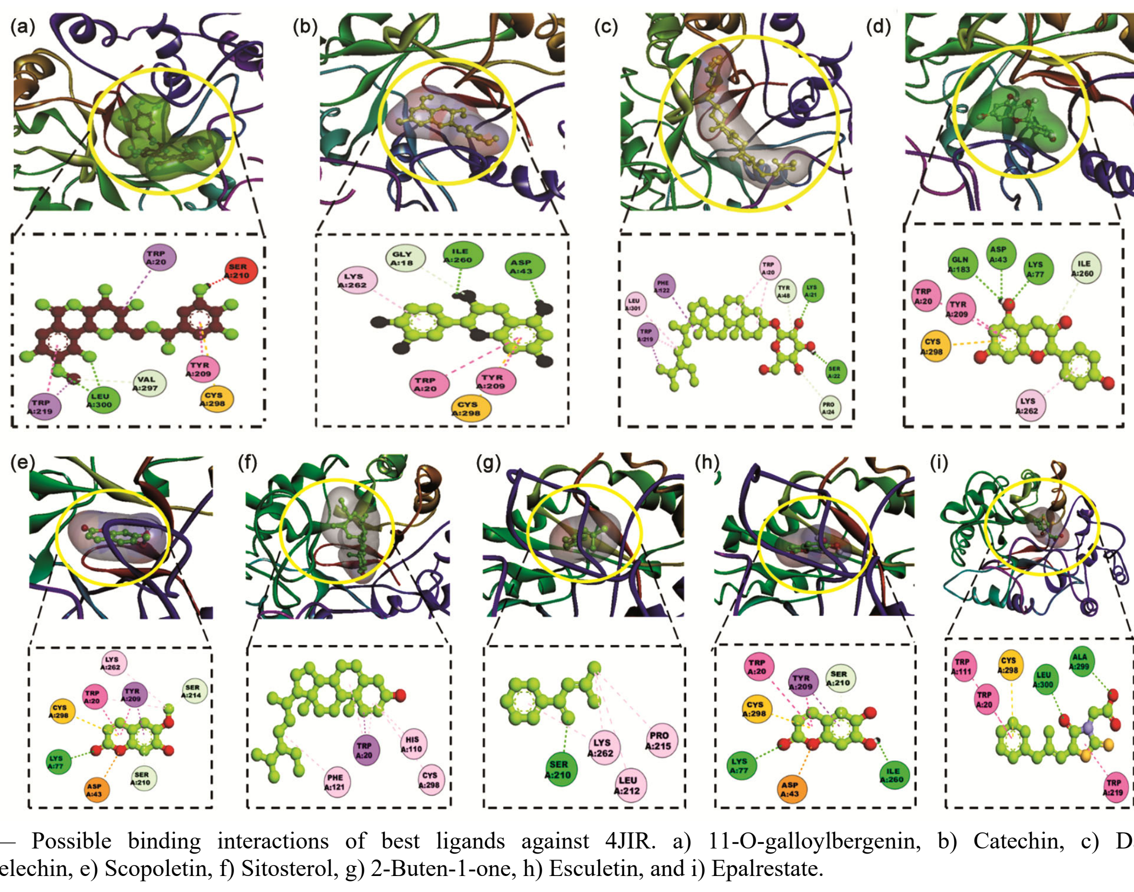

Fig. 4 — Possible binding interactions of best ligands against 4JIR. a) 11-O-galloylbergenin, b) Catechin, c) Daucosterol, d) Epiafzelechin, e) Scopoletin, f) Sitosterol, g) 2-Buten-1-one, h) Esculetin, and i) Epalrestate.

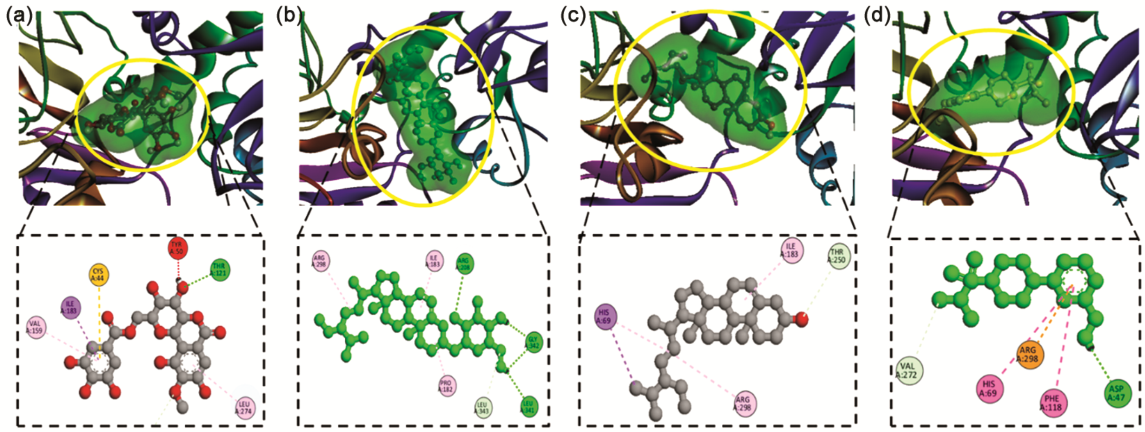

Fig. 5 — Possible binding interactions of best ligands against 1PL7. a) 11-O-galloylbergenin, b) Daucosterol, c) β-Sitosterol, and d) SDI-158.

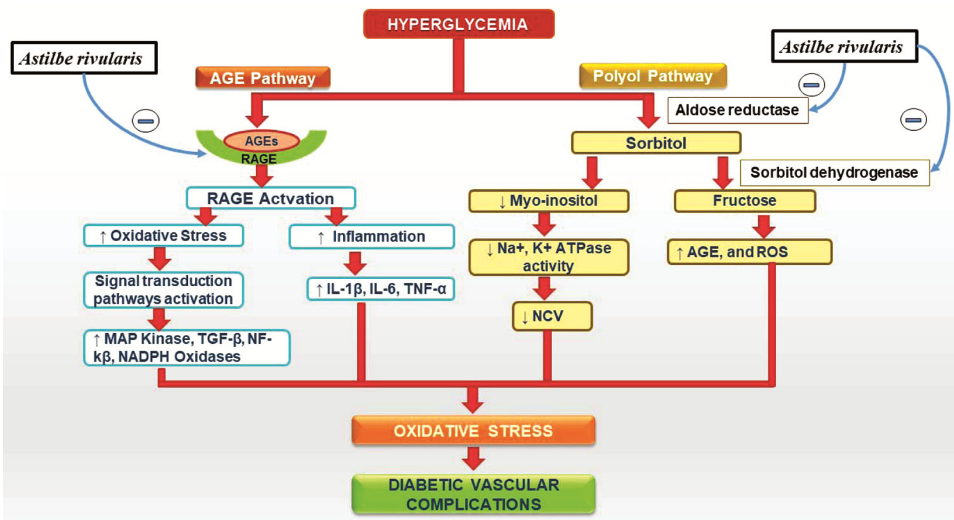

Fig. 6 — Hypothesised Mechanism of *Astilbe rivularis* on diabetic complications induced by AGEs and the Polyol Pathway.

RAGE, ALR, and SDH range from -5.9 to -9.9 kcal/mol, -6.7 to -10.1 kcal/mol, and -4.7 to -9.2 kcal/mol, respectively. Out of them, 11-O-galloylbergenin, Daucosterol, and β-Sitosterol showed comparatively higher docking scores than their respective standards. However, these three compounds exhibited acceptable H-bonding activity against these receptors. Hereafter, it can be concluded that phytocompounds derived from *A. rivularis* are effective in combating diabetic complications. Based on these circumstances, the figure that formed part of our hypothesised model is provided in Fig. 6.

Conclusion

The regional folk medicine literature has documented the beneficial effects of *A. rivularis* in the treatment of several diseases. Despite these traditional claims, the existing body of research on its potential effects remains insufficient, confining its status primarily to ethnomedicine. Consequently, there is a prominent gap in our understanding of the medicinal properties of the plant. To bridge this knowledge gap, further studies are needed, particularly to isolate and assess the potential bioactive compounds in *A. rivularis*. Such investigations are crucial for validating and elucidating the therapeutic values attributed to this plant in ethnomedicinal practices, potentially unlocking new avenues for its application in modern medicine. Moreover, incorporating molecular docking studies targeting the RAGE, ALR, and SDH receptors reveals favourable interactions with bioactive compounds from *A. rivularis*, strengthening the case for considering this plant in innovative antidiabetic interventions. This supports the development of potential pharmaceutical strategies for managing diabetic complications. Still, further research is essential to confirm the efficacy of these compounds.

Conflict of interest

No potential conflict of interest was reported by the author(s).

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