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# Phytochemical and Pharmacological Discoveries of *Eupatorium adenophorum* as a Multi-target Agent Against Diabetic Inflammation and Neuropathy

**Jyoti Srivastava[1], Shilpa Rana[1*], Neha Kukreti[2], Priya[1], Sailo Lalnuntluangi[1] and Lad Neha Manohar Singh[1]**

[1]Pharmacology Department, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun – 248007, Uttarakhand, India; shilparana9994@gmail.com

[2]Amity Institute of Pharmacy, Amity University, Noida – 201303, Uttar Pradesh, India

## Abstract

**Aim:** This review aims to evaluate phytochemical makeup, the taxonomy, botanical features, molecular mechanism and therapeutic rationale to target *Eupatorium adenophorum* (syn. *Argentina adenophora*) as a candidate to cure diabetic inflammation, particularly in diabetic neuropathy. **Methods:** A comprehensive literature search was conducted using databasesincluding Scopus, Web of Science, Science Direct, PubMed, Google Scholar, and Elsevier, for studies published between 2015 and2025. **Result:** Pharmacological studies have shown that extracts and bioactive compounds of *Eupatorium adenophorum* regulate molecular pathways (NF-κB, AMPK, iNOS and pro-inflammatory cytokines) to inhibit oxidative stress and inflammatory responses implicated in insulin resistance and diabetic neuropathy. However, the presence of cytotoxicity and hepatotoxicity, dose-related adverse actions have been noted, and hence, toxicological evaluation and standardisation arenecessary. The future research should focus on bridging the gaps in this current research by bioactive compoundisolation, mechanistic validation, pharmacokinetics, and controlled *in vivo* studies. *Eupatorium adenophorum* has thepossibility of becoming a new phototherapeutic agent in the management of diabetic inflammation and its complications, in particular diabetic neuropathy, with the help of such ethnomedicine and modern pharmacology. **Conclusion:** *Eupatorium adenophorum* has encouraging pharmacological characteristics relevant to neuropathic consequences and inflammation in diabetes. However, to prove its safety and therapeutic effectiveness, more research is needed in the areas of bioactive molecule separation, pharmacokinetic profiling, toxicological standardisation, and carefully planned preclinical and clinical trials.

**Major Findings:** Current evidence shows that Eupatorium adenophorum examines the fundamental metabolic–inflammatory processes linked to diabetic neuropathy by regulating NF-κB, AMPK, oxidative stress, and pro-inflammatory cytokine networks on several targets. Albeit promising neuroprotective, glycaemic, and antioxidant properties, its translational feasibility requires controlled clinical trials, pharmacokinetic profiling, toxicological validation, and strict standardisation.

**Keywords:** Diabetes, Diabetic Neuropathy, *Eupatorium adenophorum*, Inflammation, Inflammatory Cytokine

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## 1. Introduction

Diabetes mellitus, specifically type 2 diabetes mellitus (T2DM), is a chronic metabolic disorder, which is characterisedby continuously elevated levels of glucose in the blood due to insulin resistance and lack of secretion of insulin[1]. In addition to Type 1 and Type 2 diabetes, there are also other types like gestational

*Author for correspondence

diabetes and secondary diabetes caused by drugs and chemicals, as well as monogenic diabetes. When untreated, it may lead to life-threatening complications. Type 1 diabetes mellitus is an autoimmune disease that causes the immune-mediated death of insulin-producing β-cells in the islets of Langerhans, resulting inabsolute insulin deficiency[2,3]. Some risk factors may produce diabetes, including chronological ageing, adiposity, and gestational history[4].

According to the Diabetes Atlas, there were 589 million diabetic adults in 2024. By 2050, 853 million people living in poor nations are predicted to have the disease, demonstrating a fast-growing health burden. Importantly, 81% of these individuals reside in developing countries. This is also concerning in the case of India, where 89.8 million people (10.5%) aged 20 to 79 have diabetes in 2024; this figure will have hit 156.7 million by 2045[5]. As illustrated in Figure 1.

The problem of T2DM is becoming more and more accepted as a disease of glucose homeostasis as well as sustained low-grade inflammation. Metabolic impairment due to chronic hyperglycaemia and dyslipidaemia begins and sustains inflammatory cascades at a cellular and systemic level. Overnutrition results in hypertrophy and hypoxia of adipose tissue and consequently leads to the production of pro-inflammatory adipokines (such as resistin and leptin) and a reduction in anti-inflammatory adiponectin[6]. By attracting macrophages and other immune cells, these signals cause adipose tissue to enter a pro-inflammatory state marked by elevated release of monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α)[7].

The scientific and clinical interest in plant-based therapies for the therapeutic intervention of diabetes and associated inflammatory outcomes has grown exponentially during the last 20 years. Numerous causes are responsible for this tendency[8]. First, people in low- and middle-income nations are disproportionately affected by the worldwide diabetes pandemic, and since they may not have easy access to contemporary medications, herbal therapies provide a sensible and socially acceptable substitute[9]. Second, the drawbacks of traditional medications, such as weight gain with insulin treatment, hypoglycaemia with sulfonylureas, and gastrointestinal discomfort with metformin, have prompted the quest for long-term, safe, and effective supplementary therapies[10,11].

The multi-targeted modes of action of phytochemicals produced from therapeutic plants make them very appealing. Plant-derived chemicals can treat hyperglycaemia, oxidative stress, and pro-inflammatory signalling all at once, in contrast to the majority of synthetic medicines that only affect one route[10]. For example, it has been demonstrated that curcumin from *Curcuma longa* suppresses Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) while increasing insulin sensitivity[11], whereas berberine has antioxidant advantages and metformin-like actions through AMP-Activated Protein Kinase (AMPK) activation[12]. In a similar vein, *Momordica charantia* and *Gymnemasylvestre* have shown cytokine modulation, insulin secretagogue, and sensitising properties that reduce blood sugar[13].

## 2. Traditional Role and Interest in *Eupatorium adenophorum*

*Eupatorium adenophorum* Spreng used by various names, such as crofton weed, *banmara*, sticky

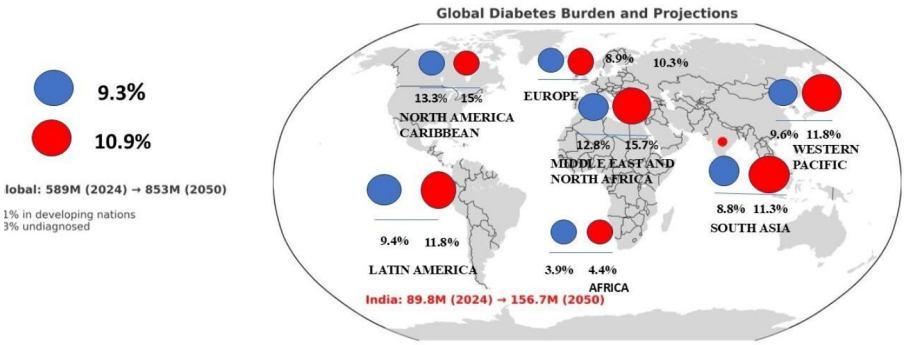



**Figure 1.** Estimated global data of people 20-80 y/o with diabetes by region in 2010 and 2045 (%).

snakeroot, etc. Family: Asteraceae has been consideredone of the forest killer plants. The tribe Eupatorieae, the largest of the 13 tribes in the family Asteraceae, contains the genus *Eupatorium* and has about 1200 species distributed throughout the tropical regions: Asia, Europe, Africa, and America (temperate and subtropical). It has been extensively used in China as traditional Chinese medicine. *E. adenophorum* has long been employed in the treatment of fever, jaundice, inflammation, diabetes, wounds and dysentery. Over the past few years, several studies have been done to explain the pharmacological and chemical properties of *E. adenophorum*. Several phytochemicals have been identified and extracted, such as sesquiterpenoids, triterpenes, flavonoids, phenolics, coumarins, steroids and phenylpropanols. Various pharmacological studies have shown that different biological activitiessuch as anti-oxidant, analgesic, anti-pyretic, anti-cancer activity and anti-inflammatory activity[14].

In many underdeveloped locations, it is used as a blood coagulant, analgesic, antipyretic, cytotoxic agent, antibacterial and antiseptic. The leaves have been used in Nigeria for many years to treat diseases such as fever, inflammation, and diabetes. Root juice has been recommended to cure fever. In order to cure sleep deficit, pure leaf extract is applied tothe eye. Heated liquor of the plant was used to treat jaundice and ulcers. Leaf extract is also used by people of the eastern Himalayan hill stations, including Darjeeling and Sikkim, to treat skin sores, mouth infections, dysentery, and lower body temperature. The Naga people of Manipur traditionally use the fresh leaf juice or powdered leaves 3 times. The juice or herbal tea was traditionally used to treat the stomach, liver, gallbladder, diabetes, cancer, and indisposition[15].

## 3. Current Treatment and Drawbacks

Despite the existence of several high-tech approaches to the treatment of diabetes, the most effective results are achieved through the diagnosis during the early stage and the use of an individual approach to treatment[16]. These results are determined during the first clinical visit, which makes it possible to approach diabetes management individually and specifically[17–19]. The recent advances and management of diabetes are shown in Figure 2.

## 4. Challenges

Diabetes management is still difficult because of many issues with current treatments. The possibility of hypoglycaemia, especially while using insulin and sulfonylureas, is a serious worry since it can result in hazardous and occasionally fatal episodes[20]. Furthermore, thiazolidinediones (TZDs) and insulin are commonly associated with weight gain, which exacerbates metabolic regulation and raises cardiovascular risk[21]. Many medications have negative side effects as well. For example, metformin may induce gastrointestinal distress, TZDs are associated with heart failure, fluid retention, and bone loss, and Glucagon-like peptide-1 (GLP-1) receptor agonists may, in rare instances, cause pancreatitis. Treatment tiredness

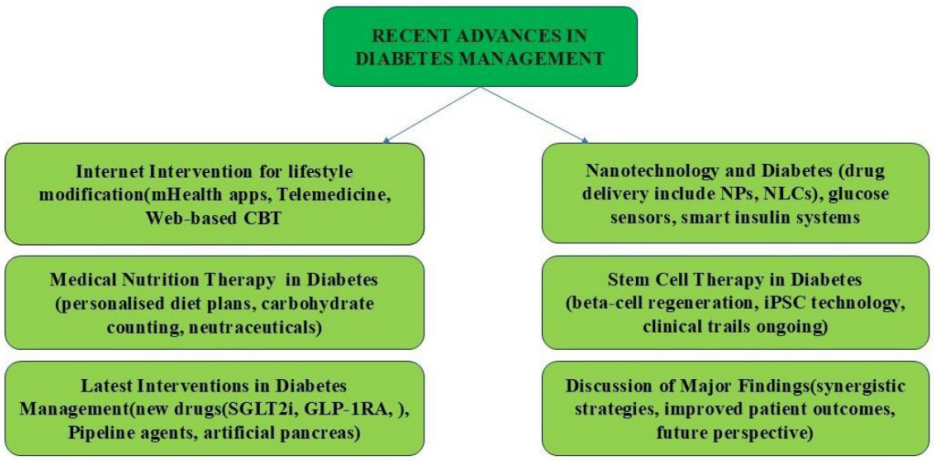



**Figure 2.** Recent advances in diabetes management.

may result from the intricacy of treatment plans, which sometimes call for several daily doses of drugs or injections, close observation, and stringent food restrictions[22]. Additional obstacles include cost and accessibility, because many patients in low- and middle-income areas cannot afford the more sophisticated technologies and newer classes like Sodium Glucose Cotransporter 2 (SGLT) inhibitors and GLP-1 agonists[23]. Furthermore, the efficacy of treatment may be compromised by varying patient reactions brought on by variations in tolerance, resistance, or allergies. Complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease, can still occur even with the best care, especially if glycaemic management is inadequate or persistent hyperglycaemia continues[24]. Last but not least, the lack of a proven treatment or disease-modifying medication emphasises that existing methods primarily control symptoms and blood sugar levels rather than stopping the course of the illness or regaining pancreatic function.

## 5. Taxonomy

Its classifications are the kingdom Plantae, division Magnoliophyta (angiosperms), class Magnoliopsida (eudicots), order Asterales, family Asteraceae and genus *Eupatorium* (the recent changes in phylogenetic definition may now be seen as *Argentina*). Although the older name *Eupatorium adenophorum* is still frequently used in literature[25,26].

### 5.1 Botanical Description

*Eupatorium adenophorum* is a herbaceous shrub growing up to 1-2 m (3.3 or 6.6 ft.) and reaching 3 m occasionally. Numerous erect stems sprout from the plant's woody rootstock. The branches are green, reddish, or purple in hue when they are young, and they are heavily coated with sticky hairs, but as they mature, they become somewhat woody and brown or brownish-green. It has yellowish roots that smell strongly of carrots when they are cut or injured. The inversely shaped, dull green (purple below) leaves have serrated edges and are around 10 cm in length by 6 cm in breadth. The leaves are 3-nerved, glabrous or a little pubescent, and the petiole measures between 4 and 5 cm long. They possess a sharp pointy (pinnacle) and a totally diminished (reduced) base, which has a 2-4 cm narrow stalk. Their stems are often glandular pubescent, and the wide leaf blades are triangular, trowel-shaped, or diamond-shaped (rhomboid), the edges of the blades are blunt or sharp-toothed, and the ends are pointed and mostly glabrous. They bear 50-70 pale white, cylindrical florets (bisexual) in a column of green bracts, male and female (bisexual), which are about 3.5 mm long. This type of floret is clustered into heads and is 5-6 mm wide and organised in level bunches of 10 cm across, which confront the edges of the branches. The seeds are 12 mm long and 0.3 to 0.5 mm wide, slender, reddish-brown to blackish-brown in colour, and slightly curved. Their ribs are four or five small and run lengthwise. They are glabrous and have a ring (pappus) of numerous white hairs (34 mm long) on the top, which they easily part. *E. adenophorum* is a weed throughout the world. It is a roadside, railroad, pasture, and fence line, disturbed, waste and riparian zone weed in the subtropical and warmer temperate countries. It is also mostly common in urban open areas, open woodlands, woodland edges, and forest gaps[27] as shown in Figure 3.

### 5.2 Phytochemistry

Numerous bioactive molecules contain huge potential for evolving curative agents with unique qualities. Flavonoids, coumarins, terpenoids, phenolic acid, alkaloids, glycosides, lignans, tannins, proteins, furocoumarins, resins, steroids, and peptides. Sesquiterpenes, including cadinene derivatives, 9-oxo-10,11-dehydroageraphorone, and euparin, are thought to be the main bioactive components in charge of the anti-inflammatory, antibacterial, and cytotoxic properties[28]. Its ability to scavenge free radicals is further potentiated by phenolic substances like caffeic



**Figure 3.** Flowers and leaves of *Eupatorium adenophorum*.

**Table 1.** List of phytochemicals isolated/identified from the different parts of *Eupatorium adenophorum*

| Sr. No. | Name of Phytochemicals | Compounds | Mechanism of Action | Activity | References |
|---|---|---|---|---|---|
| 1 | Flavanoids | Quercetin<br>Luteolin<br>Kaempferol<br>Eupatilin | Inhibit Cox 2 and 5-Lox enzymes.<br>Scavenge ROS Downregulate NF-KB signalling | Antioxidant, Anti-inflammatory, hepatoprotective | 30,31 |
| 2 | Alkaloids | Eupatorine<br>Pyrrolizidine | Inhibit acetylcholinesterase and cytokine expression | Anti-inflammatory, analgesic,anti-diabetic | 32 |
| 3 | Terpenoids | Adenophorin<br>Sesquiterpenes | Inhibition of the NF-KB pathway suppression of COX-2 and Inos | Cytotoxic, anti-inflammatory, allelopathic. | 33 |
| 4 | Phenolics | Caffeic acid<br>Chlorogenic acid | Antioxidant activity via ROS scavenging<br>Inhibition of the MAPK/NF-KB pathway | Antioxidant, anti-inflammatory, antimicrobial | 34,35 |
| 5 | Coumarins | Lactone-type phenolics | Block the lipoxygenase (LOX) pathway<br>Inhibit platelet aggregation<br>Reduce vascular permeability. | Anticoagulant, Anti-inflammatory | 36 |
| 6 | Essential oils/ volatile oils | p-cymene<br>Cryophyllene<br>Borneol | Inhibit NF-KB translocation<br>Reduce NO and PGE2 levels<br>Interfere with inflammatory mediator release | Antimicrobial, insecticidal, and anti-inflammatory | 37 |
| 7 | Protein and Amino Acids | Proteinaceo uscompounds | Modulate immunity<br>TLR signalling modulation<br>NFKB pathway downregulation.<br>Antioxidant action.<br>Inhibition of NLRP3 inflammasome. | Nutritional | 38 |

acid and chlorogenic acid. Flavonoids, including quercetin, luteolin, and their glycosides, have been found and linked to antioxidant and anti-diabetic potential. Furthermore, monoterpenes (such as α-pinene, β-pinene, and limonene) and sesquiterpenes with antibacterial and insecticidal qualities make up essential oils extracted from the aerial parts. About 96 distinct secondary metabolites have been documented in research publications that isolate and identify pure phytochemicals from *E. adenophorum*[29]. The list of phytochemicals present in the plant extract is shown in Table 1.

## 5.3 Ethnomedical Significance

*Eupatorium* has a long history of being traditionally used in various geographical areas. *E. adenophorum* has been known to have antibacterial, antiseptic, analgesic, antipyretic, blood-coagulating and sedative properties, among its species[39]. Leaf preparations are traditionally applied in wound healing and hemostasis, and decoctions and infusions are applied in the treatment of ulcers, jaundice, gastrointestinal infections, and oral infections. Practices common to the region also encompass the use of this in the treatment of fever, diarrhoea, diabetes, inflammation and skin related disorder[40,41].

## 5.4 Traditional Uses for an Anti-inflammatory and an Anti-diabetic Remedy

Since antiquity, Traditional medical systems like *Ayurveda*, Traditional Chinese Medicine (TCM), Unani, and folk medicine have all made use of medicinal plants to treat both inflammatory disorders and diabetes. Chronic inflammation is deeply linked to the pathogenesis of diabetes, so remedies that targeted "heat", "swelling", or "blood sugar imbalance" were often applied interchangeably[42]. In Ayurveda, for instance, *Curcuma longa*, or turmeric, has been used extensively to treat wounds, inflammation, and metabolic imbalance as well as work as an anti-cancer. Curcumin's

anti-inflammatory and insulin-sensitising properties have since been confirmed[43,44]. *Neem*, or *Azadirachta indica*, is traditionally prescribed as an antipyretic and "blood purifier". In Indian traditional medicine, aqueous extracts of its leaves have been used to treat diabetes's traditional symptoms of excessive thirst and urination. Bitter melon, or *Momordica charantia*, is a well-known traditional antidiabetic vegetable in Asia and Africa that is eaten as food or in decoctions. It is thought to increase pancreatic secretion and lessen sugar cravings. According to *Ayurveda*, *Tinospora cordifolia* (*Guduchi*) is a "*Rasayana*" medication that has antidiabetic and immunomodulatory properties. It is typically prescribed for "*Madhumeha*" (diabetes mellitus). TCM's holistic view of metabolic–inflammatory disease is reflected in the use of plants like *Panax ginseng* and *Scutellariabaicalensis* for both inflammatory conditions and "Xiao Ke" (diabetic wasting syndrome)[45]. Therefore, long before modern science established mechanistic links, traditional medicine continuously acknowledged the dual therapeutic value of botanicals for diabetes and inflammation. Nowadays, a lot of these treatments offer opportunities for the development of phytopharmaceuticals and combination treatments with traditional medications[46,47].

## 6. Diabetic Neuropathy: Pathogenesis and Molecular Mechanism

Chronic hyperglycaemia, metabolic abnormalities, vascular insufficiency, and immune-inflammatory processes all contribute to diabetic neuropathy (DN), a complicated, multifactorial complication of diabetes that damages peripheral nerves. Axonal degeneration is encouraged, nerve conduction is decreased, and neuronal and Schwann cell function is compromised by the convergence of several molecular pathways. The etiopathogenesis of DN is complex and primarily consists of alterations in vascular and metabolic pathways (endothelium damage, polyols, hexosamines, etc.) connected to chronic inflammation and neurodegenerative diseases[48]. According to the pathogenic mechanism, motor neurons in DN are destroyed when neuropathy first develops in the distal terminals of sensory neurons. Numerous factors influence the onset and course of neuropathies, which are followed by Diabetes Mellitus (DM). Although distal symmetric polyneuropathy is the most common type in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), patients with diabetes usually have multiple types of neuropathy. It is crucial to remember that not every patient with diabetes will develop neuropathy. In addition to diabetes, other etiologic factors must be ruled out to diagnose DN. The various forms of DN and the quantity of damaged nerves determine its signs and symptoms. Even though they have few complaints, some DN patients may have mild to moderately significant sensory loss on physical examination. On the other hand, people may suffer from a severe neuropathic impairment without exhibiting any symptoms. The most frequent symptoms are numbness, excruciating pain, which makes patients stay awake at night, and paresthesia, which is a pins-and-needles sensation. Such pain can be dull or achy, searing or stinging. A cohort study of the prevalence of neuropathy in DM found that 59% of the respondents had T1DM and 66% had T2DM. Approximately 10 per cent of patients had DN at the time of diabetes diagnosis. Regrettably, one out of five patients will develop DN within a decade of the progression of the diabetes. The problem is that ulcers may lead to diabetic foot, which is one of the vascular complications associated with DN, and amputation in the end, unless an individual receives proper care. Moreover, neuropathy has been detected in 18.8 to 61.9 of the T2DM patients in India. Peripheral neuropathy is one of the types of neuropathy experienced by more than 50 percent of diabetics across the world[49].

Diabetic peripheral neuropathy (DPN) is the most common microvascular complication of type I and type II diabetes mellitus, and is clinically characterised by painful neuropathy in 30 percent of patients[50]. Diabetic peripheral neuropathy implies the occurrence of symptoms and/or signs of damage toperipheral nerves, which happen to individuals with diabetes, without any other triggers of neuropathy. The neuropathies occur in approximately 5-10% of patients in the early years of diabetes, and after 20 years, it is believed that approximately 60-70 % of patients have at least some form of diabetic peripheral neuropathy. Diabetic sensory neuropathy puts at risk 25% of the chances of foot ulcers and amputation of limbs. Individuals who have diabetic neuropathy experience approximately a 20-year lower survival rate compared to those with diabetes mellitus and without peripheral neuropathy in 3 years[51,52].

Numerous neuropathic symptoms can occur in diabetic patients, and hyperglycemia is a significant contributing factor in some etiologies. The pathologic process of DN is intricate, and its precise molecular mechanism remains unidentified[53]. The molecular mechanism and pathways are shown in Table 2 and Figure 4.

## 7. Evidence of Anti-inflammatory and Antidiabetic Activity of *Eupatorium adenophorum*

Anti-inflammatory and antioxidant effects on the cellular level: Aqueous leaf extract (EASL-AE) dramatically decreased intracellular ROS and DNA oxidation indicators in human Caco-2 intestinal cells subjected to oxidative stress. It also inhibited pro-inflammatory cytokines TNF-α and IL-1β and NF-κB signalling. Additionally, the extract included powerful antioxidants detected by LC-MS/MS (e.g., gentianic acid, L-tyrosine) and showed high free-radical scavenging[71].

Isolated Cryptochlorogenic Acid (ccga) on the inflammatory reactions that lipopolysaccharide (lps) provoked in RAW264.7 cells: RAW264.7 cells were pretreated with 200, 100 and 50 μg/mL of CCGA and incubated with 10 mg/ml of LPS in the presence of the treatment. Cytotoxicity of CCGA was tested using Cell Counting Kit (CCK8). The mechanism of action of CCGA in the reduction of inflammation was also established using Western blot, quantitative reverse transcription-polymerase chain reaction, and enzyme-linked immunosorbent assay (ELISA). CCGA of **A. adenophora** significantly reduces NO, iNOS, pro-inflammatory cytokines (TNF-8), IL-18, IL-6, IL-8), and COX-2 in LPS-stimulated RAW264.7 cells. It is safe up to 200 mg/mL. Its anti-inflammatory potential is further evidenced by the fact that it prevents IKK/IKB phosphorylation, which prevents NF-kB activation[72].

Anti-diabetic effect in *in vivo* rodent model: Standardised hydroalcoholic leaf extract (AAHY) at 200–400 mg/kg enhanced oral glucose tolerance and

**Table 2.** Molecular mechanism underlying the pathogenesis of diabetic neuropathy

| Mechanisms | Pathways | Effect | References |
|---|---|---|---|
| Metabolic mechanism | Polyol Pathway | Under hyperglycemic conditions, the polyol pathway converts excess glucose to sorbitol and fructose, causing oxidative stress, NADPH depletion, redox imbalance, and osmotic stress in nerve cells. The impairment of sodium/ potassium ATPase disrupts signalling, triggers inflammation and causesapoptosis, contributing to diabetic neuropathy and microvascular disease. | 54 |
| | PKC Pathway | Increased diacylglycerol in diabetes causes oxidative stress, NF-κB translocation, and ROS production, which in turn promotes inflammation and apoptosis in diabetic neuropathy. Additionally, it causes microvascular damage, ischemia, and neuronal injury by interfering with the synthesis of NO and increasing VEGF, TGF-β, type IV collagen, and fibronectin. | 55,56 |
| | Hexosamine Pathway | By converting fructose-6-phosphate into UDP-GlcNAc through GFAT, the hexosamine pathway aids in diabetic neuropathy and promotes the expression of VEGF, TGF-α/β, and PAI-1. Hyperglycemia elevates GFAT and UDP-GlcNAc activity, connecting it to insulin resistance in muscle and adipose tissues. This pathway can be modulated to enhance insulin sensitivity and reduce the progression of DN. | 57,58 |
| | AGE | Chronic hyperglycemia activates the AGE pathway, which causes non-enzymatic protein glycation to form AGE, which binds toproteins and initiates RAGE signalling. Diabetic neuropathy is exacerbated by the AGE–RAGE interaction, which stimulates NF-κB and promotes inflammation, vascular dysfunction, and damage to neurons. The seriousness and consequences of DN are correlated with increased RAGE expression in Schwann cells and microvessels. | 59 |
| | Oxidative Stress | Diabetic neuropathy is caused by oxidative stress, which raises ROS, which inhibits Bcl-2 and causes apoptosis through JNK, PARP, and BAX. Nerve degeneration is made worse by decreased endoneurial blood flow and microvascular degeneration. | 60 |

**Table 2.** Continued...

| Mechanisms | Pathways | Effect | References |
|---|---|---|---|
| Signal Transduction Pathways / Enzymes/ processes | MAPK signalling pathway | JNK, p38, and ERK are among the MAPKs that control neuronal survival and apoptosis; ERK supports proliferation but also plays a role in neurological pain, while JNK and p38 encourage cell death. Overactivation of JNK and p38 in DRG and sural nerves is associated with aberrant neurofilament phosphorylation and the advancement of neuropathy in diabetic patients as well as models. | 61 |
| | Impaired insulin signalling | Diabetes-related impaired insulin signalling lowers neurotrophic support, mitochondrial function, neuropeptide regulation, and glucose metabolism, all of which lead to PNS dysfunction. Lack of insulin exacerbates neuropathic damage by interfering with Schwann cell myelination and lipid metabolism through the PI3K/AKT/mTOR pathway. | 62 |
| | NF-κB | In diabetic nerves, Schwann cells, and vascular tissues, NF-κB, a crucial transcription factor in inflammation and apoptosis, is elevated. Diabetic neuropathy and inflammatory demyelination are caused by the upregulation of inflammatory genes (COX-2, iNOS, endothelin-1) and adhesion molecules due to hyperglycemia and oxidative stress-induced NF-κB stimulation. | 63 |
| | COX-LOX | Because they mediate inflammatory responses, the COX and LOX enzymes are important in diabetic neuropathy. While 12/15-LOX activation in neurons and glial cells increases NF-κB, MAPK signalling, and pro-inflammatory responses, which contribute to nerve damage, hyperglycemia and oxidative stress, cause COX-2 overexpression, which hinders prostaglandin function and nerve signalling. | 64,65 |
| | Interleukins | In diabetic neuropathy, interleukins (ILs) control inflammatory actions; IL-1, IL-6, and IL-8 are pro-inflammatory, while IL-4 and IL-10 are anti-inflammatory. Elevated IL-1 and IL-6 in the spinal cord and serum worsen inflammation and neuropathic degeneration, while hyperglycemia raises IL-6, IL-17, and IL-13 in nerves and DRG, which correlate with metabolic abnormalities. | 66 |
| | Neurotropic and cellular signalling | Via Trk and p75NTR receptors, neurotrophins control neuronal survival, growth, plasticity, and signalling, impacting the MAPK, PI3K, and JNK pathways. Diabetic neuropathy is caused by deficiencies in neurotrophins, such as NGF, but treatments like gene or cell-based delivery of trophic factors, such as bone-marrow-derived endothelial progenitor cells, have the potential to restore nerve function and neurovascular health. | 67 |
| | TNF-α | Diabetic neuropathy is associated with elevated levels of TNF-α, a pro-inflammatory cytokine released by monocytes and macrophages that causes necrosis, apoptosis, and immune activation. Deficits in nerve conduction are associated with elevated levels of TNF-α and iNOS, whereas high glucose further increases MCP-1 and TNF-α in microglia,intensifying neuroinflammation. | 68 |
| | Autophagy | By removing damaged organelles and protein aggregates, autophagy shields neurons. However, hyperglycemia in type 2 diabetes hinders this process by causing NO-mediated S-nitrosation of ATG4B, which increases neurotoxicity and sural nerve pathology. Restoring autophagy and mitochondrial biogenesis through SirT1 activation, such as that caused by isoliquiritigenin, suggests a possible treatment approach for diabetic neuropathy. | 69,70 |
| | Malabsorption and DN | Diabetes can cause exocrine pancreatic insufficiency (EPI) in type 2 diabetes (T2DM), which can result in weight loss, fat malabsorption, steatorrhea, and gastrointestinal distress because it affects both endocrine and exocrine pancreatic functions. | |

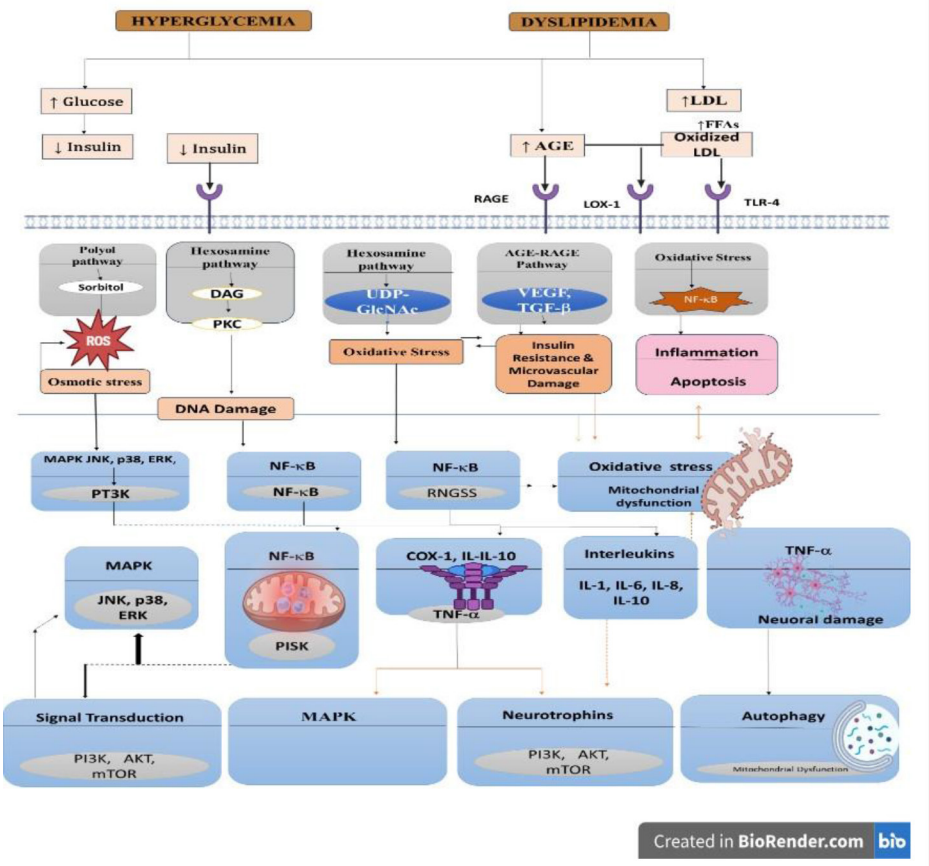



**Figure 4.** Molecular mechanisms and pathogenesis of diabetic neuropathy.

fasting blood glucose in STZ-nicotinamide-induced T2D rats. It also dramatically decreased HbA1c, which was equivalent to metformin (150 mg/kg).Additionally, the extract normalised blood biochemical indicators (SGPT, SGOT, urea, creatinine), decreased oxidative stress marker (MDA), and restored antioxidant markers (SOD, GSH), indicating protective effects on the kidneys and liver.Regeneration of pancreatic β-cells and islet structure was demonstrated by histology, and the lipid profile improved (↓ TG, ↓ TC, ↑ HDL)[73].

## 7.1 Action on Molecular Targets of *Eupatorium adenophorum*

### 7.1.1 For Anti-Inflammatory Activity

The stages of inflammation are redness, swelling, heat, and pain, which the body uses against the harmful external bacteria and germs. The inflammatory properties of *E.adenophorum* ethanolic leaf extract are probably due to the reduction of IL-1β and COX2, as well as the quenching of hydroxyl radicals (reactive oxygen species, ROS). It promotes TGF-β which plays an important role in tissue repairment, raises splenic CD4±T cellsand serumTNFα, and suppresses proinflammatory mediators like COX2 and IL1β, which control prostaglandin metabolism. Additionally, the extract lowers the effects of oxidative stress by scavenging hydroxyl radicals. It successfully reduces DNFB-induced foot paw inflammation in DTH mouse models, applying it topically shows more effect as compared to intravenous administration, resulting to more rapid reduction of swelling. These results show how effective this treatment is[74].

### 7.1.2 For Anti Diabetic Activity

Through the measurement of glucose uptake in a cell-based bioassay. Liang *et al.,* conducted an experiment to assess the anti-diabetic efficacy of different materials extracted from*E. adenophorum*. According to the results, the compounds Eupatorinone A, Eupatorinone C, and Muurol-4-en-3,8-dione increased the uptake of glucose in L6 cells. Compared to the control, Eupatorione A, C and

Muurol-4-en-3,8-dione infused to L6 cells enhanced their uptake of glucose by 1.42, 1.21 and 1.60- fold respectively[75].

### 7.2 Toxicological and ParadoxicalPotential of *Eupatorium adenophorum*

Exposure to *E. adenophorum* increases ROS (NO, superoxide, and hydroxyl radicals), which causes apoptosis, DNA/protein damage, and changes in cell architecture. Its toxicity is caused by mitochondrial dysfunction, which includes cytosolic release, decreased membrane potential, and ROS generation mediated by complex I. Oxidative stress and mitochondrial damage are highlighted as important toxicity mechanisms as a result of this disruption of the Bax/Bcl-2 balance, activation of caspases, and DNA fragmentation[76].

By lowering antioxidants like GSH and NADPH and upsetting the thiol-protein redox balance, *E. Adenophorum*causes mitochondrial dysfunction. The conformation of the mitochondrial permeability transition pore is changed by this oxidation, which encourages its opening and sets off necrosis and apoptosis, which ultimately results in necrotic cell death and multi-organ failure.

By increasing ROS, which sets off pro-inflammatory factors, *E.adenophorum*causes severe inflammatory reactions. It causes pyroptosis in the mouse spleen at concentrations above 10% that is characterised by caspase-1 activation and IL-1 release mediated by inflammasome complexes. However, the precise mechanisms behind this process remain unknown, but pyroptosis is an immune effector mechanism that induces the secretion of cytokines in response to diverse pathological stimuli[77].

The potential therapeutic interventions against its toxicity- Strong antifungal and pesticidal properties are exhibited by secondary metabolites, especially sesquiterpenes. While leaf extracts containing 10Hβ/10Hα-9-oxo-agerophorone and euptox A suppressed Pythium myriotylum at 100 µg/mL, crude extracts (ethanol, acetone, and ether) completely inhibited *Fusarium graminicarum* and *Colletotrichum glycines* at 100 mg/mL.*Bipolaris* and *Fusarium* species were among the fungi whose growth and spore production were further suppressed by*Euptox.*According to recent research, cadinan-3-ene-2,7-dione (CED) and euptox A are antifungal agents that cause cell death by interfering with fungal membranes and ergosterol synthesis. *Phytophthora capsici* growth was also inhibited by oil extracts. *E.adenophrum* showed toxicity against aphids (*Aphis gossypii*, *Brevicorynebrassicae*), *Radish aphids*, and *Mythimna separata*, demonstrating its broad bioactive potential in addition to its antifungal activity.

Recent researches have indicated that *E.adenophorum*is antitumour and anticancer. As an example, a study found that euptox A, an isolated natural product, had enormous potential in cancer prevention by modulating cellular characteristics. Likewise, the antitumor activity of euptox A was isolated *in vitro* against three cell lines using the 4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT) assay. The results revealed that the euptox A had a dose-dependent, pronounced antitumor effect on the three tumour cell lines *in vitro*. Even though the 50 percent inhibitory concentration (IC50) of euptox A against the three tumour cell lines was 369 ug/mL, 401 ug/mL, and 427 ug/mL, the percent inhibition of euptox A against human lung cancer A549 cells, Helacells, and Hep-2 cells were 76.42, 68.30, and 79.05, respectively, at the concentration of 500 ug/mL. A different study found that the essential oil induced apoptosis in HCC (hepatocellular carcinoma) by inhibiting the activity of AKT (protein kinase B) and STAT3 (signal transducer and activator of transcription 3) and turning on the mitochondrial and endoplasmic reticulum apoptotic signalling pathways[78–80].

Aqueous extracts (300–400 mg/kg) significantly decreased fever. While ethanolic gel formulations improved wound healing by speeding contraction, decreasing epithelialisation time, and increasing tensile strength. These results imply that bioactive compounds derived from *E.adenophorum*have potential as drugs or feed additives to combat health issues, especially those associated with inflammation and oxidative stress brought on by its toxicity[81].

## 8. Future Perspective and Research Gaps

*Eupatorium adenophorum* holds significant potential for managing diabetic neuropathy due to its neuroprotective, anti-inflammatory, and antioxidant properties. Future research should focus on elucidating

its precise molecular mechanisms, including effects on oxidative stress, inflammatory cytokines, AGE-RAGE signalling, and neuronal regeneration. Comprehensive phytochemical profiling and advanced omics approaches - such as proteomics, metabolomics, and transcriptomics - are essential to identify the bioactive compounds and their specific molecular targets[82].

The development of standardised extracts and optimised formulations will improve reproducibility, bioavailability, and therapeutic efficacy. Dose optimisation, pharmacokinetic studies, and long-term safety evaluations are crucial to establish safe and effective therapeutic windows. Furthermore, translational and clinical research areneeded to validate preclinical findings, assess clinical efficacy, and explore combination therapies with current interventions. Addressing these research gaps will facilitate the development of safe, targeted, and integrative treatments for diabetic neuropathy and its associated complications[83,84].

## 9. Limitations

Even though *E.adenophorum*showed promising preclinical data; its clinical translation is constrained by a number of factors. To start with, it lacks clinical trials that limit the efficacy and safety validation in humans. Second, plant extracts are extremely variable in composition and thus reproducible, and difficult to standardise. Lastly, regulatory obstacles associated with herbal products, which include quality checks, safety evaluation and approval procedures, also hinder the introduction of *E.adenophorum*-derived therapeutics. It is important to eliminate these restrictions so as to proceed with its safe and effective application in clinical settings**.**

## 10. Conclusion

The phytoconstituents of *E. adenophorum,* besides being antidiabetic and anti-inflammatory, possess strong restorative potential. The various molecular mechanisms of action of alkaloids, flavonoids, phenolics, terpenoids and essential oils include cytokine modulation, pro-inflammatory signalling pathways, and antioxidant defensive stimulation. Such multitarget interventions can be used to dampen the development of diabetic neuropathy by enhancing glycaemic regulation, systemic inflammation and neural integrity via regulation of NF-κB and AMPK signalling. Together, all these features confirm the prospect of *E. adenophorum* as a new candidate producer of integrative therapeutic interventions on diabetes and its chronic neurological outcomes. It is crucial to stress, though, that the majority of the evidence currently available comes from *in vitro* and experimental animal research. Although, these results highlight *E.adenophorum's* therapeutic potential as an integrative intervention for diabetes and its long-term neurological complications. Clinical validation through carefully planned human studies is necessary to determine its efficacy, safety, dosage parameters, and translational relevance.

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## Author Contribution

Jyoti Srivastava: Manuscript preparation and collection of data; Shilpa Rana: Guidancethroughout the preparation of the manuscript; Neha Kukreti, Lad Neha Manohar, and Priyahelped in preparation of the graphical abstract and compiling the data; Sailo helped with the referencing part of the manuscript. All authors have read and agreed to the published version of the manuscript.