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# Unlocking the mechanistic potential of *Thuja occidentalis* for managing diabetic neuropathy and nephropathy

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ABSTRACT

Diabetes mellitus and its debilitating microvascular complications, including diabetic neuropathy and nephropathy, represent a growing global health burden. Despite advances in conventional therapies, their suboptimal efficacy and adverse effects necessitate exploring complementary and alternative medicine approaches. *Thuja occidentalis*, a coniferous tree species native to eastern North America, has gained significant attention for its potential therapeutic applications in various disorders, attributed to its rich phytochemical composition. The present comprehensive review evaluates the therapeutic potential of *Thuja occidentalis* in managing diabetic neuropathy and nephropathy, with a particular emphasis on elucidating the underlying cellular and molecular mechanisms. The review delves into the active constituents of *Thuja occidentalis*, such as essential oils, flavonoids, tannins, and proanthocyanidin compounds, which have demonstrated antioxidant, anti-inflammatory, and other beneficial properties in preclinical studies. Importantly, the review provides an in-depth analysis of the intricate signaling pathways modulated by *Thuja occidentalis,* including NF-κB, PI3K-Akt, JAK-STAT, JNK, MAPK/ERK, and Nrf2 cascades. These pathways are intricately linked to oxidative stress, inflammation, and apoptosis processes, which play pivotal roles in the pathogenesis of diabetic neuropathy and nephropathy. Furthermore, the review critically evaluates the evidence-based toxicological data of *Thuja occidentalis* as a more effective and comprehensive therapeutic strategy in diabetes complications. Therefore, the current review aims to provide a comprehensive understanding of the therapeutic potential of *Thuja occidentalis* as an adjunctive treatment strategy for diabetic neuropathy and nephropathy while highlighting the need for further research to optimize its clinical translation.

## 1. Introduction

Diabetes is a metabolic disorder affecting around 382 million people with an increased diabetes complications prevalence of irreversible nephropathy and neuropathy that is considered the reason for mortality with type-2 diabetes.[1,2] Diabetes-induced complications remain challenging in treatment management, with synthetic oral hyperglycemia having many side effects and drug-drug interactions.[1] Synthetic drug treatment problems can be accomplished by integrating multiple phytochemicals with synthetic drugs. Due to their natural origins and traditional use, herbal and nutraceutical therapy is widely practiced as complementary with lesser side effects.[2–4] The various herbal medicinal plants, including *Zingiber officinale, Camellia sinensis leaves, Psidium guajava, Ginkgo biloba, Astragalus membranaceus, Panax ginseng, Lycopus lucidus, Rosmarinus officinalis,* etc., are commonly used in diabetes as a complementary therapy—these medicinal plants comprise active constituents possessing antioxidant and anti-inflammatory properties effective in treating diabetic complications.[5–8] The phytoconstituents of herbal medicinal plants tend to be an effective therapy for diabetes complications by decreasing inflammatory mediators (IL-1, IL-6, and TNF-alpha) and suppressing the nuclear factor kappa beta (NF-κB) mediated renal fibrosis and nerve damage with prolonged diabetes.[8,9] The current review has summarized the beneficial effects of *Thuja Occidentalis* as a rich source of antioxidant and anti-inflammatory constituents preventing diabetic complications through multiple mechanisms by regulating intracellular cascades PI3K-Akt pathway that has a potential role in inflammation-causing the disruption of podocytes cell of epithelium visceral inner layer of Bowman's capsule further contributing the glomerulosclerosis.[9,10] Nephron structural changes in diabetes lead to diabetes nephropathy, i.e., the accumulation of extracellular matrix (ECM) proteins associated with alterations in the

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**Abbreviations**

| | |
|---|---|
| **AGE** | Advanced glycation end products |
| **AMPA** | - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| **AMPK** | Adenosine monophosphate-activated protein kinase |
| **AP-1** | - activator protein 1 |
| **CREB** | - cAMP-response element binding protein |
| **DAG** | Diacylglycerol |
| **DM** | Diabetes mellitus |
| **ERK** | - extracellular signal-regulated kinase |
| **GABA** | - Gamma-aminobutyric acid |
| **ICAM** | Intercellular Adhesion Molecule 1 |
| **JAK-STAT** | Janus kinase/signal transduction and activator of transcription |
| **JNK** | - Jun *N*-terminal kinase |
| **MAPK** | Mitogen-activated protein kinase |
| **NF-κB** | nuclear factor kappa beta |
| **NO** | Nitric oxide |
| **NrF2** | nuclear factor erythroid 2–related factor 2 |
| **NFAT** | - Nuclear Factor of Activated T Cells |
| **NMDA** | - *N*-methyl-D-aspartate |
| **PI3K- AKT** | phosphoinositide 3 kinase/serine-threonine kinase |
| **PKC** | Protein kinase C |
| **RAGE** | Receptor for advanced glycation end products |
| ROS | - Reactive oxygen species |
| **T. *occidentalis*** | *Thuja occidentalis* |
| **TNF alpha** | - tumor necrosis factor |
| **VCAM-1** | Vascular cell adhesion molecule-1 |
| **RAS** | - renin-angiotensin system |
| **IκB** | - inhibitor of NF-κB |
| **IL1** | Interleukin 1 |

glomerular extracellular matrix proteome, including matrix metalloproteinases (MMPs), resulting in renal dysfunction.[11] Therefore, the various inflammatory responses to podocyte apoptosis-like cell adhesion molecules (integrins, cadherins) that get upregulated and growth factors (TGF-β, FGF-R1) contribute to oxidative stress and renal fibrosis.[11,12] The inflammatory and apoptotic molecules like NF-kappa beta (NF-κB), JAK-STAT, JNK, ERK, and Nrf2 signaling pathways are activated, contributing to the development of nephrosclerosis in diabetes and glomerulosclerosis as a secondary complication of diabetes (Fig. 1).[12,13] Also, the chronic hyperglycemia in prolonged diabetes leads to neuropathy complications affecting around 60 % of diabetic patients suffering from neuropathy pain caused due to peripheral nerve damage.[14] Therefore, the oxidative stress-mediated nerve damage and neuroimmune responses contributing to neuroinflammation seem to be etiological factors of peripheral nerve damage.[12] The hyperglycemia-mediated metabolic pathways alterations in the polyol pathway, leading to increased consumption of nicotinic acid adenine dinucleotide phosphate (NADPH), are further involved in mitochondrial oxidative stress-mediated downregulation Nrf2 decreases the production of glutathione (GSH) mediated neuronal damage leading to diabetic neuropathy.[15] The advanced glycation end products (AGE) resulting from hyperglycemia also integrate neuronal disruption like nerve cell metabolism and axon transport-like functioning contributing as pathological factors in diabetic neuropathy.[14] Therefore, the mitochondrial oxidative stress-mediated activation of inflammatory pathways (nuclear factor kappa beta (NF-κB), JAK-STAT, ERK, MAPK) and apoptosis signaling molecules (JNK, P38, JAK-STAT) results in peripheral nerve damage in diabetes (Fig. 1).[14–16] As a result, investigating the repurposing of natural active compounds derived from herbal plants has potent antioxidant and anti-inflammatory properties that show effective alternative and complementary therapy for diabetes and its complications (neuropathy and nephropathy).[6,7] The qualitative phytochemical studies of *Thuja Occidentalis* consequences include bioactive constituents like essential oils, phenolic substances, flavonoids, tannins, polyphenols, and monoterpenes possessing anti-inflammatory and antioxidant properties beneficial for preventing diabetic neuropathy and nephropathy.[17,18] (see Tables 1 and 2, Figs. 1–3)

*Thuja occidentalis* belonging to the Cupressaceae family, often known as white cedar or American herb, is native to eastern North America and grown as a decorative tree in Europe.[17,18] The plant has been widely used as a medicinal plant in treating various diseases as a complementary therapy in India since the 18th century.[18] The plant comprises essential oils and monoterpenes including isothujone, thujone, fenchone, borneol, camphene, fenchone, limonene, myricene, α-Terpine, terpinolene, sabines, α-pinene have been shown to effective in the therapy of anxiety, asthma, bronchitis, cold, acne like health conditions.[17,18] The plant is also a rich source of flavonoids like kaempferol, kaempferol-3-*O*-α-rhamnoside, mearnsitrin, myricetine, myricitrin, quercetin, quercitrin that acts as antioxidant preventing fibrosis.[17,18] The essential oils and monoterpenoids are effective in suppressing the inflammatory mediators (TNF-α and IL-1β), and adhesion molecule-1 (ICAM-1) in inflammatory diseases also prevents the fibroblasts mitosis and metalloproteinases production mediated tissue damages.[37] The other active constituents like tannins (catechine, gallocatechine) and polyphenolic proanthocyanidin compounds (procyanidin B-3, prodelphinidin) contribute to the anti-oxidant and anti-inflammatory activity, which is widely used in *Thuja occidentalis* prevents the oxidative stress-mediated fibrosis in diseases like rheumatoid arthritis, cold, renal dysfunction, and peripheral nerve damage.[17,18] The polyphenolic compound proanthocyanidin has been demonstrated in various *in-vivo* studies as potent antioxidant in scavenging free radical in upregulating nuclear factor erythroid 2-related factor 2 (Nrf2) and attenuating the activation of inflammatory cascades involving (MAPK), nuclear factor-kappa beta (NF-κB), and phosphoinositide-3-kinase (PI3K)/Akt mediated fibrosis.[37] As, the proanthocyanidin tends to suppress the secondary activation of stress-associated signaling pathways of nuclear factor-kappa beta (NF-κB) that transcribes genes of inflammatory mediators (cytokines IL-1, IL-6, TNF-alpha), adhesion molecules (VCAM-1, ICAM-1), pro-oxidant enzymes (COX-2, iNOS) and decreasing the p38, MAPK, ERK-mediated apoptosis have shown to be effective in neurodegenerative, inflammatory disease and metabolic type-2 diabetes disease.[38]

However, various *in-vivo* studies have evaluated the antioxidant and anti-inflammatory properties of herbal medicinal plants used in diabetes, and the quantification analysis of medicinal plants Thuja occidentalis, comprising various bioactive constituents, has confirmed the plant's therapeutic potential.[14–16] However, the evidence of *Thuja occidentalis* medicinal plant-based research lacks the understanding of cellular and molecular mechanisms, and the selection of effective doses with toxic doses still needs to be reported.[14–16] The current review provides molecular mechanisms of medicinal plant *Thuja occidentalis* comprising various phytochemicals modulating intracellular cascades involved in the pathogenesis of diabetes complications (neuropathy and nephropathy) to explain molecular mechanisms better as literature of plant *Thuja occidentalis* in diabetes and its complications.

## 2. Methods

The current review article conducted a comprehensive literature search across multiple databases, including Google Scholar, EMBASE, Science Direct, Scopus, and PubMed, using specific keywords such as "*Thuja occidentalis,*" "Diabetes mellitus," "neuropathy" "nephropathy"

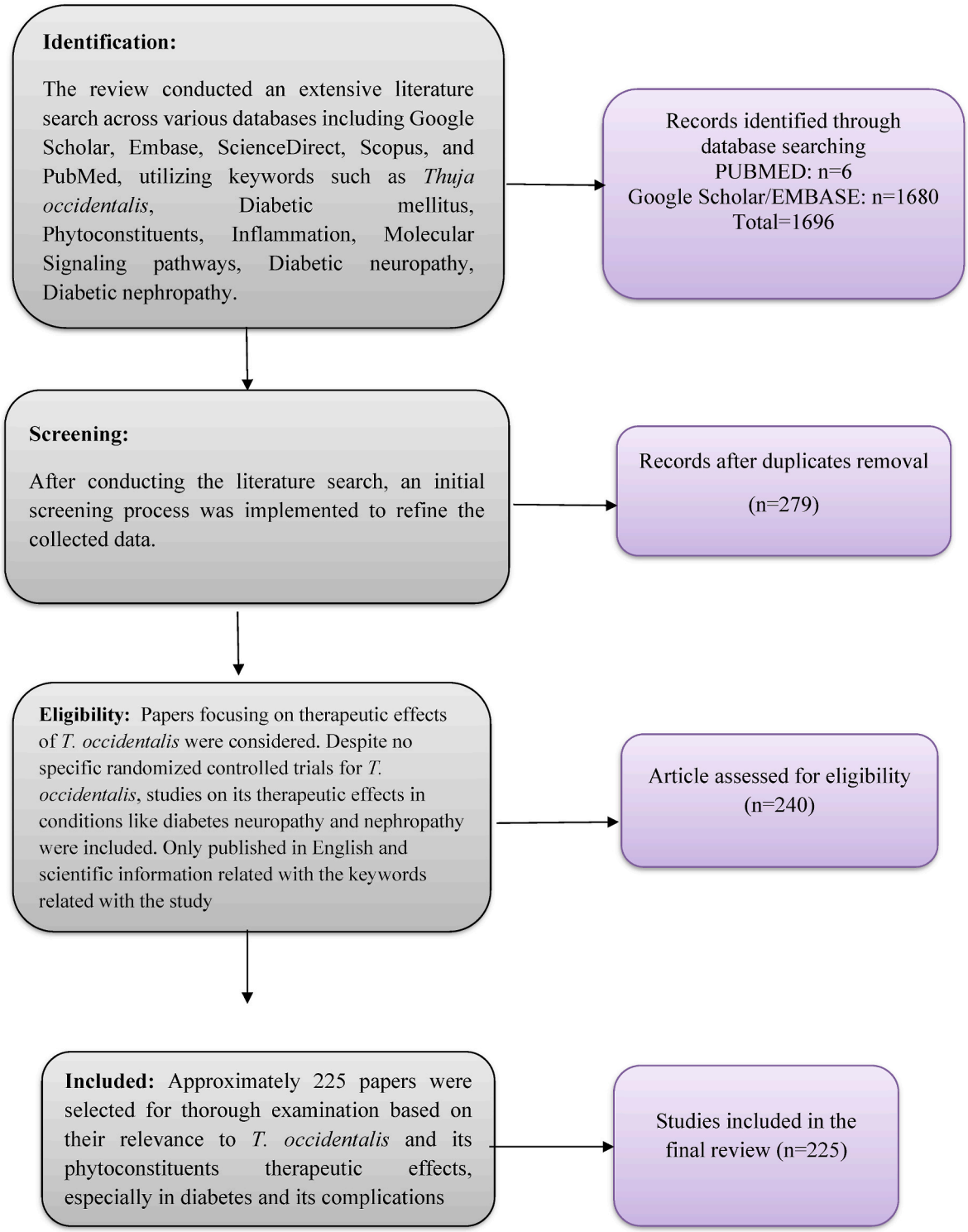


**Fig. 1.** Flow chart methodology.

"Pre-clinical evidence of "*Thuja occidentalis*," "*Thuja occidentalis* and anti-inflammatory pathways," anti-oxidant" "toxicology studies," "Active phytochemicals." The search did not impose any restrictions on the publication date. However, approximately 98 % of the collected data were sourced from articles published between 2000 and 2023. Approximately 199 papers were chosen for in-depth examination following an initial screening process. The authors have reviewed or studied the therapeutic effects of *T. occidentalis,* an herbal extract. There have not been any published randomized controlled trials specifically for *T. occidentalis* or in combination with other herbal medications as a therapeutic effect. The current review summarizes the key findings from this extensive data analysis on *T. occidentalis* in diabetes neuropathy and nephropathy correlated with mechanisms.

## 3. Phytochemistry of active components of *Thuja occidentalis*

Phytochemical screening of *Thuja occidentalis* provides an understanding of active constituents originating in *Thuja occidentalis* dry

**Table 1**
Phytochemical screening of active constituents in *Thuja occidentalis* and biological activities.

| S. No | Group | Compounds | Biological activities | References |
|---|---|---|---|---|
| 1. | Essential oil | Borneol | Antimicrobial, anti-inflammatory properties. | 17 |
| | | Camphene | Anti-Hyperlipidemia, cardioprotective. | 19 |
| | | Fenchone | Antioxidant activity, Antibacterial Activity. | 20 |
| | | Limonene | Anti-inflammatory, antioxidant, anti-stress | 21 |
| | | Myricene | Anxiolytic, antioxidant, anti-aging, anti-inflammatory, and analgesic properties | 22 |
| | | A- Terpine | Antioxidant, anticancer, anticonvulsant, antiulcer, antihypertensive, antinociceptive compound | 18 |
| | | Terpinolene | Acute ulcer, heart pain, skin rashes, used in respiratory condition | 23 |
| | | Thujone (0.76–2.4 % of essential oil, 85 % of α-thujone, 15 % β – Thujone). | Bronchial catarrh, enuresis, cystitis, psoriasis, uterine carcinomas, amenorrhea, and rheumatism. | 24 |
| 2. | Coumarins | *P*-Coumaric acid and Umbelliferone | Antibacterial, antiviral, antifungal, anti-inflammatory, anticancer, anticoagulant, and antihypertensive activities. | 25 |
| 3. | Flavonoids | (+-) – Catechine | Antioxidant enzymes, inhibition of pro-oxidant enzymes | 18 |
| | | (−) – Gallocatechine | Antioxidant, anti-inflammatory, and anticarcinogenic properties | 26,27 |
| | | Kaempherol | Reduces the risk of chronic diseases such as cancer. | 19,28 |
| | | Kaempherol- 3-*O*- α-rhamnoside | Use in cancer and cardiovascular diseases | 18,29 |
| | | Myricitrin | Antioxidant, anticancer, antidiabetic and anti-inflammatory activities | 30,31 |
| | | Myricetine | Antioxidant, anticancer, anti-inflammatory, *anti*-amyloidogenic, antibacterial, and antidiabetic effects. | 18,32 |
| | | Procyanidin B-3 | Antioxidant properties, anticancer, anti-infectious, anti-inflammatory, cardioprotective, antimicrobial, antiviral. | 33,34 |
| | | Prodelphinidin | Antimicrobial, anticancer, anti-nutritional and cardio-protective properties | 19,35 |
| | | Quercetin | Reduces the risk of cardiovascular diseases, metabolic disorders, and certain types of cancer. | 30,36 |
| 4. | Other Tannic acid (~1.3 % of drug) | Thuja polysaccharides & Protiens (~4 % of drug) | Treat liver diseases, bullous bronchitis, psoriasis, enuresis, amenorrhea, cystitis, uterine carcinomas, diarrhea, and rheumatism. | 18 |

leaves comprising essential oils 65 % thujone (85 % α-thujone and 15 % β-thujone), 8 % isothujone, 8 % fenchone, 5 % sabines, 4 % myricene, 2 % α-pinene, those resulted in the concentration of 0.125 mg/ml to 0.5 mg/ml effective as antioxidant property measured in term of percentage inhibition found to be around 50 % at a 0.5 mg/ml concentration of *Thuja occidentalis* methanolic extract.[18,30,71] Other flavonoids (kaempferol, kaempferol-3-*O*-α-rhamnosid, myricetin, myricitrin, quercitrin, quercetin, proanthocyanidins) are also present in the dry *Thuja occidentalis* plant.[17,18]

## 4. Celluar and molecular mechanisms of diabetic neuropathy

### 4.1. Oxidative stress in diabetic neuropathy

Oxidative stress plays a crucial role in the onset and advancement of diabetic neuropathy, a disabling complication of diabetes mellitus.[72] While the emergence of diabetic neuropathy involves multiple factors, and the exact pathogenic processes remain unclear, several interconnected pathways have been implicated, with oxidative stress playing a central role.[73] Persistent high blood sugar levels, a hallmark of diabetes, sets off a cascade of events contributing to the excessive production of reactive oxygen species (ROS) and subsequent oxidative stress.[74,75] A critical pathway involved is the polyol pathway, activated under hyperglycemic conditions. In this pathway, the aldose reductase reduces glucose to sorbitol, which is then metabolized to fructose by sorbitol dehydrogenase.[76] Increased flux through this polyol pathway leads to sorbitol accumulation inside cells, causing hyperosmolarity and the compensatory efflux of other osmolytes like myoinositol, taurine, and adenosine.[77,78] Myoinositol depletion results in phosphatidylinositol depletion and impaired ATP production. Consequently, Na+/K + -ATPase activity is reduced, impairing axonal transport, structural nerve breakdown, and abnormal action potential propagation.[79,80] Moreover, aldose reductase's reduction of glucose to sorbitol consumes NADPH, which is required for regenerating the crucial antioxidant-reduced glutathione (GSH).[81,82] This NADPH depletion directly contributes to oxidative stress by compromising antioxidant defenses. Additionally, fructose formation from sorbitol promotes advanced glycation end product (AGE) formation, further exacerbating redox imbalance.[83] AGEs themselves play a significant role in diabetic neuropathy's pathogenesis.[84,85] Hyperglycemia accelerates AGE formation through reactive carbohydrate groups attaching to proteins, nucleic acids, or lipids.[86] These modifications can impair protein biological functions, affecting cellular processes and contributing to oxidative stress.[87] Furthermore, extracellular AGEs can bind to their receptor (RAGE), initiating inflammatory responses, activating NADPH oxidases, and generating more ROS. Prolonged inflammation upregulates RAGE expression and stimulates the transcription factor nuclear factor kappa B (NF-κB), perpetuating the cycle of oxidative stress and inflammation.[88,89] The hexosamine pathway is Another pathway implicated in

**Table 2**
Evidence-based studies correlating *Thuja occidentalis* targeting molecular cascades underlying mechanisms of diabetic nephropathy and neuropathy.

| S. No | Active Constituents | Evidenced studies of natural Phytochemicals possessing anti-inflammatory and anti-apoptotic activity | Phytochemistry of *Thuja occidentalis* | Proposed mechanism of *Thuja occidentalis* targeting signaling cascades involved in diabetic nephropathy and neuropathy | References |
|---|---|---|---|---|---|
| 1. | Thujone | The anti-inflammatory effect of thujone has been evaluated in C57BL/6 mice (metastasis model) induced by injecting highly metastatic B16F-10 melanoma cells into mice; the administration of thujone resulted in suppression of the NF-κB pathway and decreased levels of tumor cell proliferation, adhesion, and invasion molecules involving matrix metalloproteinase, extracellular signal-regulated kinase (ERK)-1, ERK-2, MAPK and vascular endothelial growth factor (VEGF) were decreased in metastatic animals. | *Thuja occidentalis* comprises the active ingredient 65 % Thujone (85 % α-thujone and 15 % β-thujone) | Based on the evidence, *Thuja occidentalis's* anti-inflammatory activity is shown by nephropathy by inhibiting the NF-κB and decreasing the levels of down-regulating the expression of matrix metalloproteinase, extracellular signal-regulated kinase (ERK), MAPK pathway and vascular endothelial growth factor (VEGF) and pro-inflammatory mediators causing damage of renal and peripheral nerves. | [18,30,37,38,39,40,41] |
| 2. | Fenchone | IN SILICO studies evaluated the apoptotic activity of fenchone. The interaction of Fenchone with anti-apoptotic proteins Bcl-2 and Bcl-XL showed higher interaction with Bcl2 & BAX than tends to be effective in inhibiting the pro-apoptotic proteins and having anti-apoptotic properties. Furthermore, the antioxidant and anti-inflammatory property of fenchone was also evaluated by using a rat model was induced nephrotoxicity by using doxorubicin (Dox), the administration of limonene showed a preventive effect against Dox-induced renal damage. It decreased the expression of NF-κB, COX-2, iNOS, and nitric oxide. | *Thuja occidentalis* comprises the active ingredient Fenchone in a concentration of 1.4–4 %. | Therefore, the anti-apoptotic activity of *Thuja occidentalis* comprising Fenchone has been proposed for preventing apoptotic cell death in renal damage and peripheral nerve damage by decreasing the levels of pro-apoptotic proteins that provide the correlation of mitochondrial oxidative stress and apoptosis in diabetic nephropathy ad neuropathy. Therefore, the treatment with *Thuja occidentalis* could be an effective strategy in preventing mitochondrial oxidative stress-mediated apoptotic death with decreased levels of pro-apoptotic proteins (Bcl-2 and Bcl-XL). Furthermore, the anti-inflammatory property of the *Thuja occidentalis* mechanism has been showed as beneficial therapy in preventing diabetic neuropathy and nephropathy by inhibiting the NF-κB and decreasing the levels of pro-inflammatory mediators causing damage to renal and peripheral nerves. | [6,42] |
| 3. | Borneol | Borneol active component was evaluated against neuroblastoma cells (SH-SY5Y) and showed neuroprotective by inhibiting the oxidative stress and the up regulation of nrf2. Borneol also showed to be effective in inhibiting the MAPK/p38, PI3L/Akt signaling pathway as evidenced in various studies. | *Thuja occidentalis* comprises the active ingredient borneol in a concentration of 1.4–4 %. | *Thuja occidentalis* tends to be effective in hyperglycemia-induced nephropathy and neuropathy by up-regulating the Nrf2 molecule that transcribes the antioxidant enzymes glutathione (GSH) and superoxide dismutase (SOD) and presents the oxidative stress in diabetes-induced renal and peripheral damage. One of the most likely factors representing oxidative stress in diabetes-induced renal and peripheral damage is the downregulation of Nrf2.<br>Also, the active constituent borneol showed the anti-inflammatory and anti-apoptotic activity by inhibiting the MAPK/p38, PI3L/Akt signaling pathway involved in pathology of neuropathy and nephropathy. | [43–45,46,47–49,42] |
| 4. | Camphene | The apoptotic activity of camphene was evaluated in *t*-BHP-stressed rats induced oxidative stress. The administration of camphene showed anti-oxidative stress by preventing the mitochondrial membrane potential and inhibiting the release of cytochrome *C*-mediated apoptosis. | *Thuja occidentalis* comprises the active ingredient camphene in a concentration of 1.4–4 %. | *Thuja occidentalis* tends to be effective in hyperglycemia-induced nephropathy and neuropathy by preventing mitochondrial oxidative stress and mitochondrial dysfunction is the principal cause of free radicals (ROS/NS) and is associated with apoptosis-mediated renal and peripheral nerves damage in diabetes as a complication that is marked with up-regulation of apoptotic proteins including Bcl2/Bax ratio and caspase-3 levels. Therefore, it may show the beneficial effect of Thuja occidentalis in diabetic neuropathy and nephropathy by preventing mitochondrial oxidative stress and apoptosis along with decreased Bcl2/Bax ratio and caspase-3 levels. | [50–52,53,54] |
| 5. | Limonene | The antioxidant and anti-inflammatory properties of limonene were evaluated using a rat model that induced nephrotoxicity by using doxorubicin (Dox). The administration of limonene showed a preventive effect against Dox-induced renal damage, decreasing the expression of NF-κB, COX-2, iNOS, and nitric oxide. | *Thuja occidentalis* comprises the active ingredient borneol in a concentration of 1.4–4 %. | Therefore, the *Thuja occidentalis* mechanism has been showed as beneficial therapy in preventing diabetic neuropathy and nephropathy by inhibiting the NF-κB and decreasing the levels of pro-inflammatory mediators causing damage to renal and peripheral nerves. | [55–57] |

(*continued on next page*)

**Table 2** (*continued*)

| S. No | Active Constituents | Evidenced studies of natural Phytochemicals possessing anti-inflammatory and anti-apoptotic activity | Phytochemistry of *Thuja occidentalis* | Proposed mechanism of *Thuja occidentalis* targeting signaling cascades involved in diabetic nephropathy and neuropathy | References |
|---|---|---|---|---|---|
| 6. | Myrcene | The antioxidant and anti-inflammatory property of Myrcene was evaluated by using the rat model as the administration of Myrcene inhibits the NF-κB expression and downregulates the pro-inflammatory cytokines (COX-2, iNOS, IL-1β, IL-6, and TNF-α). Additionally, the Myrcene active constituent is evidenced to inhibits the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway and the MAPK/P38 (mitogen-activated protein kinase) pathway. Preventing apoptosis and inflammation | *Thuja occidentalis* comprises the active ingredient Myrcene in a concentration of 1.4–4 %. | Based on the evidence, it has been showed that *Thuja occidentalis* is an effective therapy in preventing diabetic neuropathy and nephropathy with a mechanism of inhibition of NF-κB and decreasing the pro-inflammatory mediators' levels causing renal damage and peripheral nerves. Further, the evidence indicating that Myrcene inhibits the JAK-STAT and MAPK/P38 pathways, thereby preventing apoptosis and inflammation, suggests potential therapeutic benefits in diabetes-related neuropathy and nephropathy. | [58,59] |
| 7. | Terpinolene | The *In Silico* studies evaluated the apoptotic activity of fenchone. The interaction of terpinolene with anti-apoptotic proteins Bcl-2 and Bcl-XL showed higher interaction with Bcl2 & BAX than tends to be effective in inhibiting the pro-apoptotic proteins and having anti-apoptotic properties. | *Thuja occidentalis* comprises the active ingredient borneol in a concentration of 1.4–4 %. | Therefore, the anti-apoptotic activity of *Thuja occidentalis* comprising Fenchone has been proposed for preventing apoptotic cell death in renal damage and peripheral nerve damage by decreasing the levels of pro-apoptotic proteins that provide the correlation of mitochondrial oxidative stress and apoptosis in diabetic nephropathy ad neuropathy. Therefore, the treatment with *Thuja occidentalis* could be an effective strategy in preventing mitochondrial oxidative stress-mediated apoptotic death with decreased levels of pro-apoptotic proteins (Bcl-2 and Bcl-XL). | [42] |
| 8. | kaempferol | The apoptotic activity of kaempferol was evaluated by *IN SILICO* studies. The interaction of terpinolene with anti-apoptotic proteins Bcl-2 and Bcl-XL showed higher interaction with Bcl2 & BAX than tends to be effective in inhibiting the pro-apoptotic proteins and having anti-apoptotic properties. Kaempferol has been evidenced in various studies to inhibit the inflammatory signaling pathway of NF-kB, MAPK/P38 and activates the Nrf2 suggested its anti-inflammatory, anti-oxidant and anti-apoptotic property. | *Thuja occidentalis* comprises the active ingredient kaempferol. | Therefore, the anti-apoptotic activity of *Thuja occidentalis* comprising kaempferol has been proposed to prevenapoptotic cell death in renal damage and peripheral nerve damage by decreasing the pro-apoptotic proteins that provide the correlation of mitochondrial oxidative stress and apoptosis in diabetic nephropathy ad neuropathy. Therefore, the treatment with *Thuja occidentalis* could be an effective strategy in preventing mitochondrial oxidative stress-mediated apoptotic death with decreased levels of pro-apoptotic proteins (Bcl-2 and Bcl-XL). Additionally, the Kaempferol, a flavonoid found in *Thuja occidentalis*, may mitigate diabetes neuropathy and nephropathy by inhibiting NF-kB and MAPK/P38 pathways, reducing inflammation, and activating the Nrf2 pathway to counter oxidative stress and apoptosis. Its multifaceted actions suggest potential therapeutic benefits in alleviating symptoms and halting the progression of these diabetic complications. | [27,60,61,62,63,64,42,54] |
| 9. | Proanthocyanidins | The natural component proanthocyanidins has been evaluated in cell culture studies and provided evidence of reduction of BCL-2 levels and prevented the apoptosis process. Along with it, proanthocyanidins also showed effectiveness in reducing inflammation by inhibiting *c*-Jun *N*-terminal kinase (JNK), p38, extracellular signal-regulated kinase (ERK), PI3K/Akt, nuclear factor-κB (NF-κB) signaling pathways involved in inflammation. | *Thuja occidentalis* comprises the active ingredient kaempferol. | Therefore, the *Thuja occidentalis* as anti-apoptotic resulted by preventing the mitochondrial oxidative stress-mediated apoptotic death with decreased pro-apoptotic proteins (Bcl-2 and Bcl-XL) mediated cell death in renal damage and peripheral nerve damage. Furthermore, the anti-inflammatory property of *Thuja occidentalis* has also been showed by inhibiting the *c*-Jun *N*-terminal kinase (JNK), p38, extracellular signal-regulated kinase (ERK), Akt, nuclear factor-κB (NF-κB) inflammatory signaling pathways involved in renal and peripheral nerve damage. | [65,63,66,67,68,57,59,69,70] |

diabetes-induced oxidative stress and complications.[88] In this pathway, the glycolysis intermediate fructose-6-phosphate is diverted and converted to uridine diphosphate-*N*-acetylglucosamine (UDP-GlcNAc). UDP-GlcNAc can modify transcription factors by attaching to their serine and threonine residues.[89] Under hyperglycemia, increased hexosamine pathway flux activates the transcription factor Sp1, which is implicated in diabetic complications. Sp1 activation results in overexpression of transforming growth factor-β1 (TGF-β1) and plasminogen activator inhibitor-1 (PAI-1), contributing to diabetic neuropathy pathogenesis.[90,91] The protein kinase C (PKC) pathway is another critical player in diabetic neuropathy development.[92,93] Hyperglycemia stimulates diacylglycerol formation, activating PKC, an enzyme involved in various cellular processes, including nerve function and diabetic neuropathy pathogenesis. Activated PKC initiates an intracellular signaling cascade, leading to PAI-1, NF-κB, and TGF-β overexpression.[93] Additionally, PKC increases extracellular matrix component and cytokine production, enhances contractility, permeability, and vascular endothelial cell proliferation, and inhibits Na+/K + -ATPase activity.[94] Furthermore, oxidative stress and free radical generation are significant contributors to diabetic neuropathy

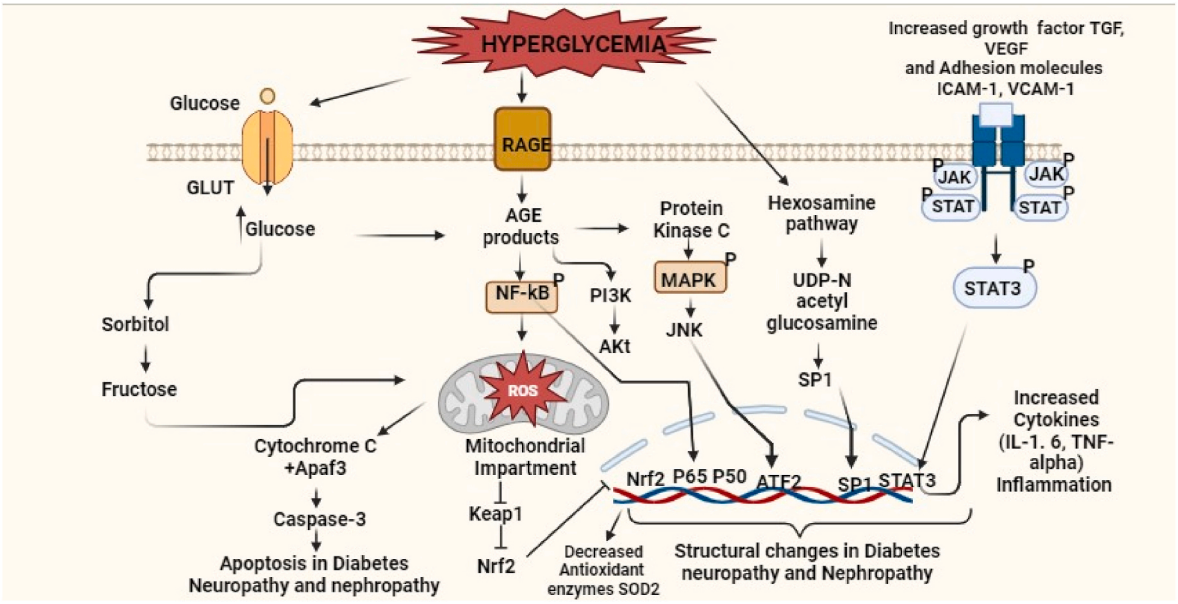


**Fig. 2.** Illustrates oxidative stress and inflammatory molecular mechanisms in diabetic nephropathy and neuropathy.
In diabetic nephropathy and neuropathy, hyperglycemia triggers a cascade of molecular events leading to oxidative stress and inflammation. Elevated glucose levels promote the formation of advanced glycation end products (AGEs), exacerbating reactive oxygen species (ROS) production through impaired mitochondrial function, ultimately inducing apoptosis. Additionally, hyperglycemia activates protein kinase pathways such as NF-κB, JAK, STAT, and PIP3, as well as the MAPK pathway, intensifying inflammatory responses. These pathways collectively contribute to the pathology of neuropathy and nephropathy in diabetes, underscoring the intricate interplay between hyperglycemia-mediated molecular mechanisms, oxidative stress, and inflammation in driving diabetic complications.

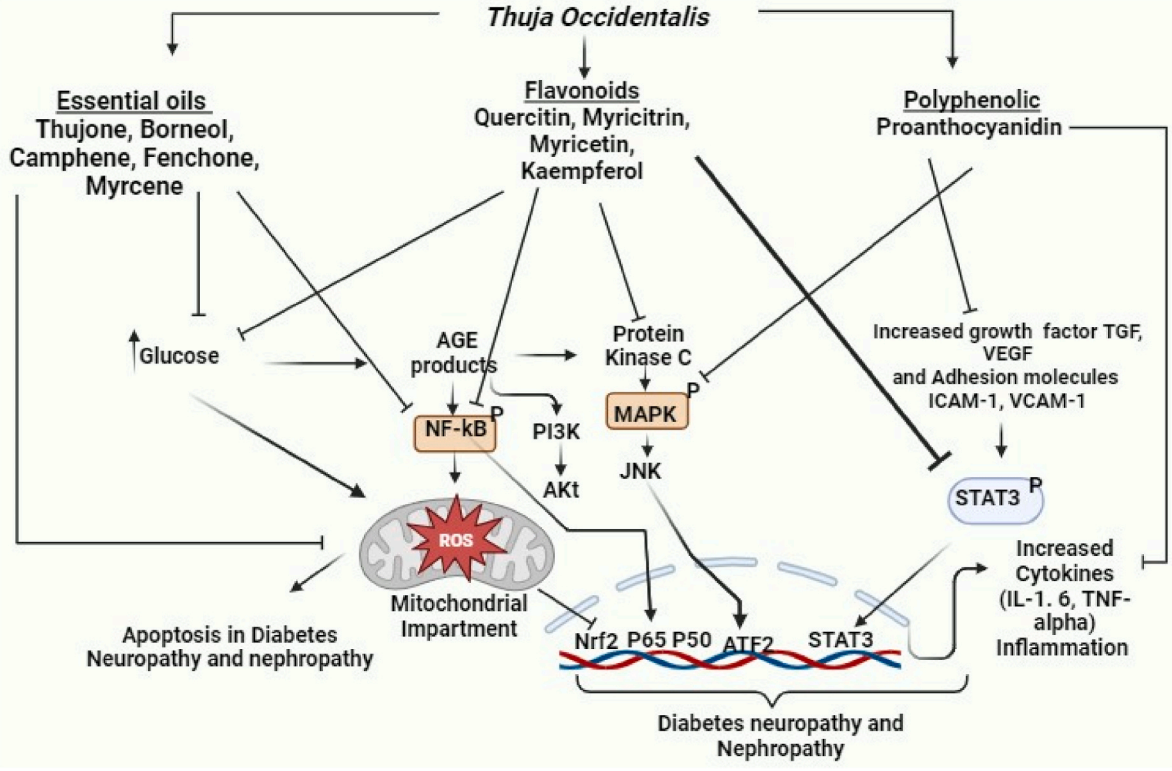


**Fig. 3.** Illustration depicting the multifaceted protective mechanisms of *Thuja occidentalis* against diabetic neuropathy and nephropathy.

development through increased glycolytic processes.[95,96] ROS and reactive nitrogen species (RNS) link the physiological mediators and metabolic initiators implicated in progressive nerve fiber damage, dysfunction, and loss in diabetic neuropathy.[97–100] Simultaneously, oxidative stress damages mitochondrial DNA, proteins, and membranes during glycolysis.

### 4.2. Mitochondrial dysfunction in diabetic neuropathy

Mitochondrial dysfunction is a key factor in diabetic neuropathy

pathogenesis. Increased blood glucose levels cause mitochondrial alterations like cytochrome C release, caspase 3 activation, changes in mitochondrial biogenesis and dynamics (fission and fusion), and, ultimately, programmed cell death.[79,80] The rapid glucose influx into mitochondria causes a drop in mitochondrial membrane potential (MMP) and reduced ATP generation, further compromising cellular energy production and function.[81,82] Furthermore, mitochondrial damage reduces neurotrophic support factors like neurotrophin-3 (NT-3) and nerve growth factor (NGF), essential for neuron survival and maintenance.[83] Axons with high mitochondrial concentrations are particularly vulnerable to hyperglycemic injury from mitochondrial dysfunction.[84,85] Oxidative stress and hyperglycemia activate poly ADP-ribose polymerase (PARP), which cleaves nicotinamide adenine dinucleotide (NAD+) into nicotinamide and ADP-ribose residues.[87] This process modifies nuclear proteins, changes gene transcription and expression, depletes NAD+, and diverts glycolytic intermediates to other pathogenic pathways like PKC and AGE, creating a vicious cycle of oxidative stress and cellular damage.[88,89] Vascular factors also play a crucial role in diabetic neuropathy pathogenesis. Nerve blood flow is reduced in diabetic neuropathy, potentially mediated by impaired nitric oxide (NO) bioavailability.[80] Overproduction of superoxide anions by the mitochondrial electron transport chain in diabetic neuropathy leads to the formation of the potent oxidant peroxynitrite by reacting with NO.[79] Peroxynitrite is highly toxic to endothelial cells that produce NO, a potent vasodilator and anti-thrombotic agent. NO also protects against inflammation by regulating Na+/K + -ATPase activity or inhibiting the potent vasoconstrictor peptide endothelin-1 (ET-1) production. Furthermore, hyperhomocysteinemia, characterized by elevated homocysteine levels, is associated with impaired endothelial function and may contribute to diabetic neuropathy development. AGEs and homocysteine synergistically initiate endothelial damage, further exacerbating vascular complications associated with diabetic neuropathy.[88] Therefore, oxidative stress plays a pivotal role in diabetic neuropathy pathogenesis through multiple interconnected pathways, including the polyol pathway, AGE formation, PKC activation, the hexosamine pathway, and mitochondrial dysfunction.[92,93] These pathways generate excessive ROS, overwhelm antioxidant defenses and contribute to oxidative damage to cellular components, inflammation, and apoptosis.[94] Additionally, oxidative stress impairs nerve perfusion, endothelial function, and nitric oxide bioavailability, further compounding vascular complications associated with diabetic neuropathy.[79] The interplay between oxidative stress, inflammation, metabolic abnormalities, and vascular dysfunction creates a self-perpetuating cycle driving nerve fiber damage, dysfunction, and, ultimately, clinical manifestations of diabetic neuropathy.

### 4.3. Inflammation in diabetic neuropathy

Chronic inflammation plays a critical role in the pathogenesis and progression of diabetic neuropathy, a severe complication of diabetes mellitus.[101,102] This complex process is initiated by persistent elevated blood glucose levels, which trigger various inflammatory signaling cascades within the peripheral nerves.[103] At the core of these cascades lies the transcription factor nuclear factor-kappa B (NF-κB), acting as a central orchestrator of inflammatory events that ultimately lead to nerve fiber injury and dysfunction.[104] Under hyperglycemic conditions, NF-κB becomes persistently activated, upregulating numerous pro-inflammatory enzymes and mediators. One such enzyme is cyclooxygenase-2 (COX-2), which is overexpressed in diabetic peripheral nerves due to NF-κB activation.[105] COX-2 catalyzes the production of inflammatory mediators like prostaglandin E2 and reactive oxygen species (ROS).[106] These inflammatory byproducts contribute to nerve injury and create a self-amplifying loop by further activating NF-κB, perpetuating the cycle of inflammation.[107,108] Another critical player in this inflammatory cascade is inducible nitric oxide synthase (iNOS), an enzyme regulated by NF-κB signaling.[109] Like COX-2, iNOS can either activate or be induced by NF-κB, further contributing to the intricate web of inflammatory processes underlying diabetic neuropathy.[110] The inflammatory environment created by the concerted actions of NF-κB, COX-2, iNOS, and various inflammatory mediators attracts and activates immune cells, particularly macrophages, and granulocytes, into the diabetic peripheral nerves.[111] This influx of inflammatory cells is facilitated by the release of cytokines and chemokines from Schwann cells, endothelial cells, and neurons, all influenced by NF-κB signaling.[107] Once recruited, these immune cells release a barrage of damaging agents, including additional cytokines, ROS, and proteases, exacerbating oxidative stress and contributing to myelin breakdown.[109] The excessive accumulation of activated macrophages impedes the regenerative capacity of damaged nerves, further compounding the neuropathic insult.[110] Moreover, the inflammatory processes triggered by hyperglycemia disrupt the delicate balance of neurotrophic factors, such as nerve growth factor (NGF), neurotrophin-3 (NT-3), and insulin-like growth factors (IGFs), which are crucial for neuronal development, maintenance, and survival.[107,108] The intricate interplay between inflammation, oxidative stress, and the disruption of neurotrophic support creates a self-perpetuating cycle that drives the progression of nerve fiber damage and the development of clinical manifestations of diabetic neuropathy.[109] This vicious cycle is fueled by the persistent activation of NF-κB and the subsequent activation of various inflammatory pathways, leading to the recruitment of immune cells and the release of damaging agents.[109,110] Interrupting the inflammatory cascades represents a potential therapeutic avenue for managing diabetic neuropathy.[110] Targeting critical components of the inflammatory signaling pathways, such as NF-κB, COX-2, or iNOS, or modulating the activity of inflammatory mediators and immune cells, may hold promise in mitigating nerve damage and preserving neuronal function in this debilitating complication of diabetes.[110,111]

## 5. Celluar and molecular mechanisms of diabetic nephropathy

### 5.1. Oxidative stress in diabetic nephropathy

Oxidative stress has emerged as a pivotal mediator in the pathogenesis and progression of diabetic nephropathy, a microvascular complication that poses a significant burden on individuals afflicted with diabetes mellitus.[112] This phenomenon is characterized by an excessive accumulation of reactive oxygen species (ROS) and a disruption in the equilibrium between oxidants and antioxidants, initiating a cascade of events that ultimately culminate in renal dysfunction and, if left unabated, end-stage renal disease.[113,114] Diverse sources can be attributed to the augmented generation of ROS in diabetic states, each contributing to the overall oxidative stress burden.[115] A primary contributor is the NADPH oxidase enzyme complex, which catalyzes the production of superoxide anions, a highly reactive form of ROS.[116,117] In diabetic conditions, the activity of NADPH oxidase is upregulated, leading to an increased production of superoxide and the subsequent formation of other ROS species.[118] Furthermore, the formation of advanced glycation end products (AGEs) plays a significant role in exacerbating oxidative stress in diabetic nephropathy.[119,120] These molecules are formed through non-enzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids, and their accumulation is accelerated in persistent hyperglycemic states.[119,120] AGEs can interact with their specific receptors (RAGE) on various cell types, triggering intracellular signaling cascades that ultimately lead to the activation of NADPH oxidase and the subsequent generation of ROS.[121] Additionally, the polyol pathway, an alternative route for glucose metabolism, has been implicated in the development of oxidative stress in diabetic nephropathy. Under hyperglycemic conditions, glucose is shunted into this pathway, leading to the depletion of NADPH, a cofactor essential for regenerating the antioxidant glutathione.[122,123] This depletion compromises the cell's ability to neutralize ROS, contributing to the overall oxidative stress burden. Furthermore,

uncoupled nitric oxide synthase (NOS), an enzyme responsible for producing nitric oxide (NO), can also serve as a source of ROS in diabetic nephropathy.[113,114] When NOS becomes uncoupled due to substrate or cofactor deficiency, it produces superoxide instead of NO, further exacerbating oxidative stress.[113] The deleterious effects of oxidative stress on the renal are multifaceted and contribute to the development and progression of diabetic nephropathy.[112] One primary consequence is the upregulation of genes encoding extracellular matrix (ECM) components, such as collagen and fibronectin.[118] This increased expression leads to the excessive accumulation of ECM proteins, resulting in glomerular and tubulointerstitial fibrosis, a hallmark of progressive renal disease.[113,114] Moreover, oxidative stress can disrupt the glomerular filtration barrier by inducing actin cytoskeleton reorganization in podocytes, specialized cells that play a crucial role in maintaining the selective permeability of the glomerular capillary wall.[114] This disruption leads to proteinuria, a clinical manifestation of diabetic nephropathy and a risk factor for further renal function decline.

### 5.2. Mitochondrial dysfunction in diabetic nephropathy

Mitochondrial dysfunction, a hallmark of diabetic nephropathy, also plays a significant role in the generation of ROS.[119] In diabetic conditions, oxidative phosphorylation in the mitochondrial respiratory chain becomes impaired, leading to the leakage of electrons and the subsequent formation of superoxide and other ROS species.[119,120] This mitochondrial impairment not only exacerbates oxidative stress but also contributes to the overall renal injury and dysfunction observed in diabetic nephropathy.[115] ROS can also activate various signaling pathways that contribute to the pathogenesis of diabetic nephropathy.[118] For instance, the AGE-RAGE pathway, when activated by AGEs, triggers downstream signaling cascades that further promote oxidative stress, inflammation, and the production of pro-fibrotic factors.[119,120] Similarly, when ROS is stimulated, the protein kinase C (PKC) pathway can activate NADPH oxidase, perpetuating the cycle of oxidative stress.[118] While moderate levels of ROS are essential for maintaining various cellular functions, such as gene expression, molecular transcription, and signaling transduction, excessive and uncontrolled ROS production can overwhelm the body's antioxidant defense mechanisms.[119,120] The antioxidant defense system, comprising enzymes like superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), glutathione reductase (GR), and paraoxonase, plays a crucial role in neutralizing ROS and maintaining redox homeostasis.[121] However, in diabetic conditions, the excessive production of ROS can deplete these antioxidant reserves, leading to oxidative damage to cellular components, including lipids, proteins, and nucleic acids.[120,122,123] Therefore, oxidative stress acts as a central mediator in the development and progression of diabetic nephropathy, operating through various mechanisms, including the generation of ROS from diverse sources, the activation of signaling pathways, the disruption of the glomerular filtration barrier, the promotion of extracellular matrix accumulation and fibrosis, and the contribution to mitochondrial dysfunction.[122–124]

### 5.3. Inflammation in the pathogenesis of diabetic nephropathy

Inflammation plays a critical role in the development and progression of diabetic nephropathy, a severe microvascular complication associated with diabetes mellitus.[125,126] Chronic hyperglycemic conditions trigger various inflammatory signaling pathways contributing to extracellular matrix accumulation, cellular hypertrophy, inflammatory responses, prothrombotic states, and accelerated apoptosis. Several transcription factors, such as NF-κB, AP-1, CREB, and NFAT, are critical regulators of the genes involved in these processes.[127] Notably, NF-κB initiates inflammatory and immune responses and apoptosis, particularly in persistent high blood sugar levels. Activating NF-κB leads to increased expression of pro-inflammatory genes, including MCP-1, TNF-α, IL-6, and IL-8.[127–129] These inflammatory mediators further exacerbate the inflammatory processes within the kidneys, leading to the recruitment of inflammatory cells and the subsequent release of additional cytokines and chemokines, creating a self-sustaining cycle of inflammation. In addition to NF-κB, the AP-1 transcription factor also plays a pivotal role in diabetic nephropathy, as it is sensitive to changes in redox balance and influences cellular processes such as proliferation, hypertrophy, and differentiation.[129,130] The persistent activation of AP-1 upregulates various genes involved in extracellular matrix accumulation, cellular growth, and inflammatory responses, contributing to the pathogenesis of diabetic nephropathy.[131,132] The mitogen-activated protein kinases (MAPKs), a group of serine/threonine kinases, are also key players in regulating cellular processes like proliferation, differentiation, motility, apoptosis, and survival.[131–138,139] Diverse stimuli, including oxidative stress and cytokines, can activate these kinases. Members such as p38 MAPK and JNK (*c*-Jun NH2-terminal kinase) have been implicated in the pathogenic processes associated with diabetic nephropathy.[140–142,143] The persistent activation of p38 MAPK is linked to the recruitment of inflammatory cells, increased extracellular matrix production, and cellular proliferation, contributing to the inflammatory processes and oxidative stress involved in the development and progression of diabetic nephropathy.[140,141,144] The inflammatory cascades in diabetic nephropathy produce various chemokines and cytokines, such as MCP-1 (monocyte chemoattractant protein-1) and TNF-α (tumor necrosis factor-alpha).[142,145] MCP-1 is crucial in recruiting monocytes/macrophages to the inflammation site, while TNF-α amplifies the inflammatory response and promotes apoptosis.[145] These inflammatory mediators further exacerbate renal injury by promoting glomerular and tubulointerstitial inflammation, leading to the accumulation of extracellular matrix proteins and the subsequent development of fibrosis.

Other pathways involved in the inflammatory mechanisms of diabetic nephropathy include the renin-angiotensin-aldosterone system (RAAS) and the endothelin system. Angiotensin II, a key component of the RAAS, induces the production of inflammatory cytokines and activates NF-κB, further contributing to the inflammatory processes within the kidneys.[124,125] Similarly, endothelin-1, a potent vasoconstrictor peptide, can stimulate the production of inflammatory mediators and promote the activation of NF-κB, exacerbating the inflammatory response in diabetic nephropathy.[142,145] The interplay between inflammation, oxidative stress, and the activation of various signaling pathways creates a self-perpetuating cycle that drives the progression of diabetic nephropathy. Inflammatory mediators can generate reactive oxygen species (ROS), activating transcription factors like NF-κB and AP-1, leading to the upregulation of inflammatory genes and amplifying the inflammatory response.[142,145] Conversely, oxidative stress can also trigger inflammatory signaling cascades, further exacerbating the inflammatory processes within the renal milieu.[50–52,143,146–148] Consequently, the intricate interplay between inflammation, oxidative stress, and various signaling pathways creates a self-sustaining cycle that drives the progression of renal injury and the development of fibrosis, ultimately leading to the deterioration of renal function in diabetic nephropathy.[148,149] Targeting the inflammatory cascade through therapeutic interventions, such as administering herbal plants with anti-inflammatory properties and bioactive compounds, might serve as complementary therapies in managing diabetic nephropathy by reducing inflammation and oxidative stress.[147,60,149,150]

## 6. Molecular mechanisms of *thuja occidentalis* in diabetic nephropathy and neuropathy

### 6.1. Thuja occidentalis as preventing strategy in mitochondrial oxidative stress-related mechanisms in diabetic complications

Mitochondrial oxidative stress is a common risk factor in the pathogenesis of diabetic neuropathy and nephropathy.[50] Oxidative stress has also been associated with necrosis via induction of mitochondrial permeability transition.[50,51] This review highlights the importance of

mitochondria in regulating redox balance, modulating cellular responses to oxidative stress, and influencing cell death pathways in diabetic renal and peripheral diseases.[52] ROS/NS-mediated cellular dysfunction corresponds with progressive disease in diabetic nephropathy and neuropathy disease.[51,52,146] Mitochondria are the principal cause of free radicals (ROS/NS), and their impacts on cellular pathways are associated with apoptosis-mediated renal damage in diabetes.[51] As evidenced, the study suggested that *Thuja occidentalis* extract, particularly its bioactive derivative thujone, holds promise in mitigating oxidative stress and preventing mitochondrial impairment.[146] While direct evidence of *Thuja occidentalis* extract's efficacy in reducing or preventing mitochondrial-generated oxidative stress may not be explicitly provided in the given context, speculation based on the mechanisms elucidated in the study is feasible.[147] Specifically, the study indicates that thuja induces a biphasic generation of reactive oxygen species (ROS) in functional p53-expressing mammary epithelial carcinoma cells.[148] This biphasic ROS generation appears pivotal for activating the p53 signaling pathway and initiating apoptosis. Notably, the activation of p53 leads to a secondary phase of mitochondrial ROS generation, forming a positive feedback loop that amplifies the thuja signal and prompts mitochondrial changes, ultimately culminating in cytochrome *c* release and caspase-driven apoptosis.[147,60] This intricate molecular crosstalk suggests that *Thuja occidentalis* targets mitochondrial apoptosis effectively, highlighting its potential as a therapeutic agent for combating oxidative stress and preserving mitochondrial function.[147] In hyperglycemia, the excessive accumulation of ROS represents the mitochondrial-generated oxidative stress mechanisms causing the increased intracellular $Ca^{2+}$ concentration glomerular podocyte apoptotic damage in diabetes nephropathy.[51,148] Similarly, mitochondrial oxidative stress significantly contributes to neurodegeneration in peripheral neuropathy, which is viewed as increased mitochondrial calcium overload, which aggravates mitochondrial fragmentation and bioenergetics-mediated neuronal injury.[60] The phytochemical estimation confirms flavonoids like flavonols, kaempferol, kaempferol-3-*O*-α-rhamnoside, mearnsitrin, myricetine, myricitrin, quercetin, quercitrin in *Thuja occidentalis* having antioxidant effect preventing the mitochondrial oxidative stress. *Thuja occidentalis* extract prevents the up-regulation of apoptotic proteins, including Bcl2/Bax ratio and caspase-3 levels, which are evidence for mitochondrial oxidative stress-mediated cell apoptosis.[149] Further, the upregulated PI3K and Akt are modulated by flavonols, confirming ROS production reduction and preventing the mitochondrial oxidative stress with decreased expression of caspase-3 mediated apoptosis.[148] Flavonoids are a class of natural chemicals identified in *Thuja occidentalis* with anti-diabetic pharmacological properties. The active constituent proanthocyanidins in *Thuja occidentalis* showed an anti-apoptotic effect by reducing the Bcl-XL. Also, the other active constituents including quercetin, borneol, beta myrcene, kaempferol present in *Thuja occidentalis* inhibit the p38 mediated apoptosis[128, 129.130] Therefore, suggesting that *Thuja occidentalis* possesses the anti-apoptotic effect and can be a potential treatment approach in preventing diabetes nephropathy and neuropathy by regulating mitochondrial oxidative stress-mediated renal tissue apoptosis and preventing neurodegeneration in peripheral neuropathy.

### 6.2. *Thuja occidentalis and Nrf2 mediated mechanisms in diabetic neuropathy and nephropathy*

One of the most likely factors representing oxidative stress in diabetes-induced renal and peripheral damage is the downregulation of Nrf2 signaling, associated with reduced antioxidants (glutathione and superoxide dismutase).[18,43,44] Hyperglycemia produces free radicals, but it also impairs the endogenous antioxidant defense enzymes in diabetic patients indicating the alterations in the Nrf2 expression that further transcribes antioxidant enzymes.[43–45] The decreased levels of antioxidant enzymes are the biomarkers for increased ROS production indicating the impairment in mitochondrial functioning due to elevated glucose concentration in diabetes which has been reported by *in-vivo* studies.[45] These findings contribute to the beneficial usage of natural active compounds in the herbal medicinal plant *Thuja occidentalis* comprising bioactive compounds like polyphenolic flavonoids (Quercetin and proanthocyanidin) with antioxidant properties.[18] Various studies have suggested the usefulness of polyphenolic flavonoids like (Quercetin) in preventing oxidative stress-mediated renal fibrosis and peripheral neuronal damage like complications of diabetes with increased activity of Nrf2 that gets implicated as a defense mechanism in oxidative stress.[18,151,152] The other bioactive polyphenolic compound, proanthocyanidin, has effectively reduced oxidative stress by modifying the Nrf2 signaling pathway, thus indicating the antioxidant mechanism of proanthocyanidins.[60,65,152,153] As a result, it has been showing, based on the evidence, the beneficial effect of *Thuja occidentalis* preventing renal fibrosis and peripheral nerve damage induced by activating the Nrf2 up-regulating antioxidant enzymes reducing the increased production of ROS-mediated damages in diabetic complications.

### 6.3. *Thuja occidentalis regulating NF-κB resulted in inflammation-mediated renal fibrosis and peripheral nerve damage*

Inflammation in diabetes is the hallmark of diabetic nephropathy and neuropathy.[65] The accumulation of infiltrating macrophages, and T-lymphocytes in the interstitial are responsible for causing the damage in the glomeruli associated with renal injury in nephropathy. The transcriptional factor nuclear factor kappa beta seems to be a significant factor in triggering pathogenesis by transcribing pro-inflammatory mediators (TNF- alpha, IL-6, IL-18, COX-2, and iNOS and nitric oxide) & apoptotic proteins (Bcl2, BAX) mediated renal cells damage induced by hyperglycemia.[154,155] The increased cytokine urine concentration expresses renal hypertrophy due to the alterations in glomerular endothelium's permeability, mesangium's swelling, and elevated fibronectin level associated with cell adhesion in the extracellular matrix of renal tissue damage. There are also increased glomerular membrane thickness-like changes in the renal due to the activation of intracellular NF-κB cascade-mediated inflammation expressing high levels of cytokines levels (TNF- alpha, IL-6, IL-18), further eliciting increased oxidative stress-mediated apoptosis.[18–38,43–45,50–52,60,65,71–164] At the same time, the hyperglycemia results in the formation of harmful advanced glycation end products (AGEs) that bind to the receptor for advanced glycation end products (RAGE) induced oxidative stress activating transcriptional factor NF-κB increasing the expression of pro-inflammatory mediators contributing to the pathogenesis of diabetic neuropathy and nephropathy.[18,165–167] The increased NF-κB expressions enhance neurological dysfunction, including axonal atrophy mediated and forming glycated proteins of extracellular matrix (laminin) & fibronectin producing free radicals mediated neuropathic pain.[167] The phytochemical screening of *Thuja occidentalis* provided evidence of the presence of active compounds like essential oils (thujone, borneol, camphene) used as an anti-inflammatory in various diseases that tend to be effective in inhibiting NF-κB and decreasing the pro-inflammatory mediators (interleukin-6 and tumor necrosis factor-α).[8,9,39] As evidenced by various studies, the essential oils thujone, fenchone, α-pinene camphor, and borneol active components identified in *Thuja occidentalis* have shown anti-inflammatory biological activity.[17,18,61] The main component thujone obtained from *Thuja occidentalis* has been marked to be a curable approach in inhibiting the NF-κB expression, further reducing the inflammatory mediators (IL-6 and IL-8) causing damage contributing to anti-inflammatory properties.[165,166,40,58,61–63,168,169] Additionally, the active constituent beta myrcene, quercetin, and kaempferol present in Thuja occidentalis has anti-inflammatory properties by inhibiting the NF-kB signaling pathway involved in the pathogenesis of neuropathy and nephropathy. Therefore, it can be suggested that *Thuja occidentalis* is beneficial in preventing diabetic neuropathy and nephropathy by inhibiting the NF-κB.

### 6.4. *Thuja occidentalis preventing mechanism in growth factors and adhesion molecules representing glomerulosclerosis and peripheral nerve damage*

Recently, many growth factors have been identified as the origin of the pathogenesis of diabetes-induced neuropathy, causing structural changes in the nephron and contributing to glomerulosclerosis and glomerulonephritis.[170] The various growth factors like TGF-beta, CTGF, and VEGF are mainly responsible for causing the alterations in renal tissue, including cellular hypertrophy of tubular epithelial cells, glomerular mesangial cells, and progression of interstitial fibrosis.[171] This further causes the accumulation of extracellular matrix production mediated thickness of glomerular membrane-like alterations seen in diabetic nephropathy, increasing the risk of urinary albumin excretion in patients.[172] The other diabetes-induced peripheral neuropathy complication is also associated with elevated levels of cytokines growth factors mediated oxidative stress causing dorsal root ganglion (DRG) neurons indicating neuroinflammation mediated apoptotic neuronal death.[173] Therefore, the anti-inflammatory natural active constituents tend to be a preventive strategy in reducing cytokines and chemokines (TGF- beta, CTGF, and VEGF) that get elevated as the immune system responds against oxidative stress under pathological conditions. Elevated levels of growth factors like TGF-alpha, IL-1 beta, CTGF, and VEGF as noxious stimuli that directly activate downstream inflammatory (NF-κB, p38 MAPK/ERK) and apoptotic cascades (JNK, JAK-STAT, p38 MAPK/ERK) regulates inflammation and apoptosis.[18,174–176] Therefore, the active constituents like flavonoids (proanthocyanidins, myricetin, and quercetin) and essential oils (thujone, fenchone, α-pinene camphor, and borneol) present in *Thuja occidentalis* possesses anti-inflammatory property used in various diseases preventing inflammation-induced apoptosis.[8,9,58,61,62,168,169,63] The bioactive component proanthocyanidins are effective in preventing oxidative stress by regulating and decreasing the growth factors and cytokines, further activating inflammatory (NF-κB, p38 MAPK/ERK) and apoptotic signaling cascades (JNK, JAK-STAT, p38 MAPK/ERK) in inflammatory and autoimmune diseases.[18,53] Furthermore, the natural active constituents kaempferol, myricetin, and quercetin also suppress the cytokines and growth factor-mediated signaling of inflammation and apoptosis.[177,178] *Thuja occidentalis,* as a rich source of essential oils (thujone) has proven to effectively suppress transforming growth factors mediated activation of inflammation-mediated apoptotic pathways in various diseases.[179,180] Therefore, the *Thuja occidentalis* possesses active constituents that reduce transforming growth factors and regulate the phosphorylation of downstream inflammatory (NF-κB, p38 MAPK/ERK) along with apoptotic signaling cascades (JNK, JAK-STAT, p38 MAPK/ERK) that is involved in causing diabetes nephropathy and neuropathy.[53] Based on such evidence, *Thuja occidentalis* is a beneficial therapeutic approach in diabetes complications of neuropathy and nephropathy by modulating the transforming growth factors and cytokines-mediated inflammatory and apoptosis cascade signaling involved in the pathology of neuropathy and nephropathy.

### 6.5. *Thuja occidentalis modulating PI3K/Akt pathway-mediated glomerulosclerosis and peripheral nerve damage*

Renal fibrosis is the final common manifestation of diabetes-induced nephropathy characterized by cell proliferation and progressive deposition of extracellular matrix (ECM) in the glomeruli (glomerulosclerosis) and interstitial space (tubulointerstitial fibrosis), resulting in a progressive decline in renal function.[11] The intracellular transforming growth factor-1 (TGF-1) signaling of PI3K-Akt has seemed to be involved in glomerulosclerosis and tubulointerstitial fibrosis.[181] Therefore, the inhibition of PI3K-Akt activation was reported to be a potential target in preventing the ECM deposition in the interstitial of renal damage in nephropathy. Further, the evidence reported the neuroprotective effect of PI3K/Akt pathway in diabetic peripheral neuropathy.[10] As observed, the decrease in the activity of PI3K in peripheral nerves enhances diabetes-induced neuropathic pain by degeneration of nerve fibers.[181] The reactivation of the PI3K/Akt pathway seems to prevent the mitochondrial neuronal damage induced by diabetes and enhance nerve fiber regeneration, decreasing neuropathy pain. PI3K/Akt signaling also regulates cell survival pathways by preventing the activation of pro-apoptotic proteins caspase 9, Bad/Bax that is involved in apoptotic cell death.[181] Therefore, the various studies evaluated the phytochemicals interaction with PI3K/Akt signaling and provided a better understanding of the mechanism of action of such active constituents derived from *Thuja occidentalis* herbal medicinal plant comprising α-thujone and flavonoids (proanthocyanidins, myricetin, and quercetin) possessing antioxidant, anti-apoptotic, anti-inflammatory properties.[10,17,61,46,66,67,181,182] The active component thujone effectively prevents apoptotic neuronal death in neurodegenerative diseases. Treatment with thujone has shown a protective effect in neurodegenerative disease by inhibiting the phosphorylation of PI3K/Akt pathway-mediated apoptosis.[183] Like wisely, the natural active constituents, including proanthocyanidins, myricetin, and quercetin, suppress the PI3K/Akt pathway-mediated apoptosis.[51,60,149,64,183–188] Therefore, the *Thuja occidentalis* could be an effective therapy in preventing diabetic neuropathy and nephropathy by inhibiting the PI3K/Akt pathway as it comprises these active constituents that seem to prevent apoptosis which is one of the requirements of preventing renal fibrosis caused by the deposition of ECM in glomeruli and interstitial space in diabetes nephropathy.[11,185,186] Along with it, the increased glucose-mediated peripheral nerve damage and central neuron damage involving the mitochondrial oxidative stress could be decreased with *Thuja occidentalis* comprising such active components preventing the phosphorylation of PI3K/Akt signaling pathway mediated apoptosis.[18,60,148,149]

### 6.6. *Thuja occidentalis and JAK-STAT in diabetic neuropathy and nephropathy*

Enhanced expression of JAK and STAT proteins has been observed in diabetes-induced nephropathy, indicating the significant involvement of activated JAK-STAT signaling in causing glomerulosclerosis and tubulointerstitial fibrosis.[189] Hyperglycemia in diabetes induces inflammatory processes, and oxidative stress-mediated glomerulosclerosis characterizes renal damage and tubulointerstitial fibrosis through activation of Janus kinase/signal transducer, further increasing the expression of TGF-β1 that gets an accumulation of extracellular matrix (ECM).[18,190] In diabetes neuropathy, the nerve injuries are the consequences of neuronal damage in the central and peripheral nervous system underlies the particular mechanism of involvement of the neuroimmune system by activation of glial cells (astrocytes) further carries the neuroinflammation signaling by the activation of JAK-STAT pathway mediated increased levels of inflammatory mediators producing hyperexcitability of dorsal horn neurons involved in the pathological process of diabetes neuropathy.[191,192] The naturally occurring active constituents like (kaempferol, proanthocyanidins, myricetin, kaempferol, and quercetin) showed a potent therapeutic effect in preventing the neuroinflammation-mediated apoptotic cell death by inhibiting the activation of the JAK-STAT pathway that gets activated by noxious stimuli of growth factors, cytokines, and transcribes inflammatory and apoptotic proteins[27,68,193] *Thuja occidentalis* comprises such active constituents as flavonoids (proanthocyanidins, kaempferol, myricetin, and quercetin) and essential oil (thujone, isothujone, fenchone, α-pinene, camphor, and borneol) retains anti-inflammatory and anti-apoptotic properties.[18,22,193–195] These essential oils have been evaluated in various studies to inhibit the activation of JAK-STAT signaling.[193] Based on such evidence, the current review discusses the potential role of *Thuja occidentalis* in diabetic neuropathy and nephropathy with a mechanism of inhibition of JAK-STAT and preventing nerve damage and renal fibrosis.

### 6.7. *Thuja occidentalis* and JNK in diabetic neuropathy and nephropathy

The increased implication of *c*-Jun amino-terminal kinase (JNK) signaling pathway is a diverse cellular stress response initiating tubular damage in diabetes nephropathy caused via the mechanism of enhanced formation of advanced glycation end products (AGEs) as a result of hyperglycemia.[196,197] AGEs are considered to play a critical role in the pathogenesis of diabetic nephropathy that accumulate in glomerular endothelial cells and podocytes that participate in evoking ROS generation with significant overproduction of growth factors and cytokines as a factor of promoting activation of *c*-Jun amino-terminal kinase (JNK) signaling causing renal fibrosis underlying destructive mechanism of tubular damage secondary to glomerular injury.[197,198] Consequently, the activation of *c*-Jun amino-terminal kinase (JNK) in astrocytes of the spinal cord is also involved in diabetes-induced peripheral neuropathy characterized by nerve damage i.e., dorsal root ganglion (DRG) neuron apoptosis with elevated levels of pro-inflammatory mediators and cytokines representing oxidative stress.[18,174] As a result, the high glucose promotes the DRG neuronal death by activation of a JNK signaling pathway, further stimulating the apoptotic pathway and causing the release of mitochondrial cytochrome C into the cytosol, activating caspase-3 mediated apoptotic neuronal death measured with elevated expression of Bim/Bax proteins.[18,199] Therefore, indicating the significant role of activation of JNK signaling in mitochondrial oxidative stress-inducing apoptotic DRG neuronal death.[200] Blockage of the JNK pathway tends to be a promising therapeutic strategy in preventing diabetic neuropathy and nephropathy.[201–203] Findings of various studies provided evidence that natural active components like flavonoid (kaempferol) tend to be effective in preventing the activation of JNK signaling mediated apoptosis marked by decreased expression of pro-apoptotic proteins and caspase-3, suggesting the herbal medicinal plants comprising kaempferol possesses beneficial protective effect against oxidative stress, inflammation, and apoptosis in diseases.[18,40,204,205] Other plant-derived flavonoids like proanthocyanidins, myricetin, and quercetin prevent oxidative stress and apoptosis by inhibiting the JNK signaling pathway involved in mitochondrial oxidative stress.[10,18,40,205–207] As a result, the flavonoids (proanthocyanidins, myricetin, and quercetin) suppress the release of cytochrome *C*-induced apoptosis marked with decreased levels of pro-apoptotic proteins (Bax, active caspase-9, and caspase 3).[10,106,40,206,207] *Thuja occidentalis* seems to be a rich source of various active components possessing anti-apoptotic, antioxidant properties that could be beneficial for the treatment of diabetes complications (neuropathy and nephropathy) by inhibiting the JNK signaling.[18,38] The JNK signaling is involved in causing mitochondrial oxidative stress-mediated renal fibrosis underlying apoptotic destructive mechanism of tubular damage secondary to glomerular injury in diabetic nephropathy that could be a preventive strategy for dorsal root ganglion (DRG) neuron apoptosis in diabetes neuropathy.[18,173,174,208] Therefore, *Thuja occidentalis* has been proposed to be an effective therapy for diabetic nephropathy and neuropathy by inhibiting the JNK pathway.

### 6.8. *Thuja occidentalis* and p38/MAPK, ERK in diabetic neuropathy and nephropathy

p38MAPK, ERK pathways regulate apoptosis and stress responses under pathological conditions; the activation of mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK) further phosphorylates downstream proteins from extracellular stimuli responsible for causing inflammation, oxidative stress, and apoptotic cell death in various diseases.[18,209] In diabetes, the hyperglycemia-mediated renal damage, and peripheral nerve damage involve the multifaceted mechanisms related to the polyol pathway, oxidative stress, and enhanced formation of advanced glycation end products (AGEs) through activation of p38MAPK, ERK signaling, further promoting diabetes-induced inflammation and apoptosis in neuropathy and nephropathy.[18,209–211] p38MAPK and ERK signaling activation causes glomerular and tubulointerstitial damage in diabetic nephropathy.[212,213] Hyperglycemia-induced nephropathy results in damage to peripheral nerves and central sensitization.[209] The central sensitization involves enhanced activity of AMPA and NMDA excitatory synaptic neurotransmission current along with decreased GABA inhibitory synaptic neurotransmission current contributing to neuropathic pain due to central sensitization after nerve injury and increasing the neuroimmune response of glial cell migration activating p38MAPK, ERK signaling increasing inflammatory mediators promoting neuropathic pain.[46,209,214] The Peripheral neuropathy involves the dorsal region ganglion neurons damage responsible for neuropathy pain stimulated by enhanced expression of glial cells with activated purinergic (P2X4) and chemokine receptors on glial cells attributing to increased intracellular calcium ion.[209,214] Further, the enhanced intracellular calcium ion concentration causes oxidative stress mediated by the activation of p38MAPK, ERK signaling induces the release of PGE2 and IL1β or through phosphorylation of transcription factor NF-κB, ATF2 transcribing genes of pro-inflammatory mediators (IL-1 beta, TNF-alpha, COX, prostaglandin (PGE2, BDNF) leading to persistent neuropathic pain hyper sensitization.[18,46,183] However, the phytochemical ingredients (kaempferol, proanthocyanidins, myricetin, quercetin, α-thujone) have been evaluated as potent antioxidants and anti-apoptotic and anti-inflammatory properties that inhibit the activation of downstream p38MAPK, ERK pathway mediated inflammation, and apoptotic oxidative stress.[181,46,64,47–49,215–217] The phytochemical screening of *Thuja occidentalis* resulted in the presence of α-thujone (65 %) main component and other flavonoids (borneol, kaempferol, proanthocyanidins, myricetin, quercetin) having anti-inflammatory and antioxidant properties.[17,18,58,66] As evidenced, the active constituent borneol, thujone, myrcene, quercetin, myricetin, kaemferol and proanthocyanidin of *Thuja occidentalis* inhibits p38/MAPK, ERK signaling pathway and decreased inflammation and apoptosis.[46,64,49,55] Therefore, the current review proposed *Thuja occidentalis* as an effective natural remedy for preventing diabetes nephropathy and neuropathy by inhibiting p38MAPK/ERK pathway-mediated renal fibrosis and peripheral nerve damage.

The figure illustrates the protective effects of *Thuja occidentalis* against diabetic neuropathy and nephropathy. Rich in essential oils, flavonoids, and polyphenolic compounds, *Thuja occidentalis* exerts its therapeutic action by targeting key molecular pathways such as NF-κB, JAK, STAT, PIP3, and the MAPK pathway. These pathways are crucial in inflammation, oxidative stress, and tissue damage associated with diabetic complications. Through its multifaceted mechanisms, *Thuja occidentalis* acts as a potent agent in preventing diabetic neuropathy and nephropathy, offering promise in mitigating the debilitating effects of diabetes on nerve and renal function.

## 7. Toxicological assessment of ethanolic extracts of *Thuja occidentalis* (EFTO) and thujone in rat studies: implications for health and safety

Thujone, a compound found in various plants, has been studied for its toxic effects in different animals. The LD50 (lethal dose for 50 % of the population) of a combination of a- and b-thujone was approximately 192 mg/kg in rats, 230 mg/kg in mice, and 396 mg/kg in guinea pigs when administered orally.[59,69] When administered subcutaneously, alpha-thujone had an LD50 of 134 mg/kg in mice, while b-thujone's LD50 was estimated to be 442 mg/kg in mice. Intraperitoneal delivery of thujone at 180 mg/kg body weight caused convulsions and fatalities in rats.[201] In mice, the LD50 of alpha-thujone via abdominal injection was 45 mg/kg body weight, and when injected intravenously in rats, it was 0.031 mg/kg body weight.[69] In a 14-week oral administration study in rats, doses of 5, 10, or 20 mg/kg/day resulted in seizures and mortality at the highest dose, with a no-observed-effect level (NOEL) for convulsions established at 10 mg/kg in males and 5 mg/kg in females.[70] A

study by the National Toxicology Program (NTP) exposed mice and rats to thujone at doses ranging from 0 to 100 mg/kg/day for 14 days. Higher doses led to increased mortality rates and neurotoxic effects like heightened activity, tremors, and convulsions.[59] In a 3-month NTP trial, doses of 25–100 mg/kg/day were associated with seizures and elevated mortality. Although exact NOAELs (no-observed-adverse-effect levels) were not clearly stated, they were estimated to be around 30 mg/kg/day for the 14-day trials and 12.5 mg/kg/day for the 3-month studies.[218] Further, the acute, subacute, and chronic toxicological studies evaluated the ethanolic extracts of *Thuja occidentalis* (EFTO) conducted the effects of EFTO at varying dose levels, ranging from 1.0 to 20.0 g/kg of the rats for 30 days resulted in significant weight increase when the administered dosages exceeded the threshold of 20.0 g/kg.[70] At lower doses, EFTO consistently demonstrated a substantial increase in the body weight of the rats, suggesting a dose-dependent connection. However, this effect was not uniformly observed at higher doses, leaving the possibility of more complex physiological interactions.[218] Also, the studies showed that the rats treated with EFTO exhibited a decrease in plasma glucose and LDL-cholesterol concentrations, coupled with an elevation in HDL-cholesterol levels. These changes in lipid composition suggest that EFTO might have potentially positive impacts on metabolic and cardiovascular parameters.[223,224]Additionally, the EFTO administration had no significant effect on enzymes commonly used as indicators of liver function, such as aspartate aminotransferases (AST) and alanine aminotransferases (ALT). However, a concerning pattern emerged concerning renal function. The evaluation of creatinine levels, a marker of renal function, showed a consistent increase in all groups exposed to EFTO for prolonged used.[59,69,70]

## 8. Pre-clinical evaluation of *Thuja occidentalis* for diabetes neuropathy and nephropathy: our pharmacology laboratory findings

In our laboratory, we conducted *in-vivo* studies to explore the therapeutic potential of *Thuja occidentalis* in addressing diabetes-related neuropathy and nephropathy. To assess its effectiveness, we employed a hydroalcoholic ethanolic extract of *Thuja occidentalis* at varying doses: 50 mg/kg, 100 mg/kg, and 200 mg/kg.[94,117] Our investigation involved the use of a Streptozotocin (STZ) rat model, which demonstrated that the hydroalcoholic ethanolic extract of *Thuja occidentalis* (administered orally at 50, 100, and 200 mg/kg) exhibited preventive effects against neuropathy and nephropathy.[94,117] This was achieved by effectively reducing inflammatory markers and oxidative stress indicators. Specifically, there was a significant, dose-dependent reduction in pro-inflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6, highlighting the potent anti-inflammatory activity of *Thuja occidentalis*.[94,117] Moreover, we observed a decrease in oxidative stress, as evidenced by decreased thiobarbituric acid reactive substances (TBARs) and enhanced antioxidant enzyme activities (catalase, GSH, SOD) in the brain tissue of the treated rats, indicating the antioxidant properties of *Thuja occidentalis*.[94,117] Furthermore, our research revealed an anti-apoptotic effect of *Thuja occidentalis* in diabetes neuropathy and nephropathy, as indicated by reduced Transforming Growth Factor-β (TGF-β) levels. Complementing our experimental findings, in-silico studies supported the anti-inflammatory mechanism of *Thuja occidentalis*. Docking studies demonstrated strong binding interactions of Thujone, a component of *Thuja occidentalis*, with TNF-alpha, IL-1beta, IL-6, and TGF-beta, reinforcing its potential as an effective treatment for diabetes-related neuropathy and nephropathy. To advance the clinical applicability of *Thuja occidentalis*, future endeavors may include clinical trials to validate its safety and efficacy in human subjects, a deeper exploration of the underlying molecular mechanisms, optimization of pharmaceutical formulations, and pursuit of regulatory approvals. In conclusion, our current investigation presents *Thuja occidentalis* as a promising avenue for developing a novel and effective therapeutic approach for individuals afflicted with diabetes neuropathy and nephropathy.

## 9. Conclusion

Intensive literature-based evidence of dry plant *Thuja occidentalis* has provided information on active components like isothujone, thujone, fenchone, borneol, camphene, fenchone, limonene, myricene, α-Terpine, terpinolene, sabines, α-pinene, catechine, gallocatechine, proanthocyanidin compounds (procyanidin B-3, prodelphinidin) possessing antioxidant and anti-inflammatory biological activity. Furthermore, looking into the pathogenesis of diabetes-induced nephropathy and neuropathy, the oxidative stress-mediated multiple inflammatory (nuclear factor kappa beta (NF-κB), JAK-STAT, ERK, MAPK) and apoptosis signaling molecules (JNK, P38, JAK-STAT) results in renal and peripheral nerve damage. The evidence of medical plant-based research, on the other hand, lacks knowledge of cellular and molecular mechanisms and the selection of the medicinal plant *Thuja occidentalis* as a safer and more effective therapy in diabetic complications (neuropathy and nephropathy). Therefore, the current review presents mechanisms of the medicinal plant *Thuja occidentalis* comprising a wide variety of phytochemicals modulating intracellular cascades involved in the pathogenesis of diabetes complications (neuropathy and nephropathy) correlating the molecular mechanisms of *Thuja occidentalis* as an effective therapy for diabetic complications.

### Ethics approval and consent to participate

Not applicable.

### Compliance with ethical standards

Not applicable.

### Consent to participate

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### Availability of data and materials

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### Declaration of competing interest

We certify that we have obtained written permission for the use of text, tables, and/or illustrations from any copyrighted source(s), and we declare no conflict of interest.

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