Pharmacological Effects of *Paeonia lactiflora* Focusing on Painful Diabetic Neuropathy

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ABSTRACT

Painful diabetic neuropathy (PDN) is a highly prevalent complication in patients suffering from diabetes mellitus. Given the inadequate pain-relieving effect of current therapies for PDN, there is a high unmet medical need for specialized therapeutic options. In traditional Chinese medicine (TCM), various herbal formulations have been implemented for centuries to relieve pain, and one commonly used plant in this context is *Paeonia lactiflora* (*P. lactiflora*). Here, we summarize the chemical constituents of *P. lactiflora* including their pharmacological mechanisms-of-action and discuss potential benefits for the treatment of PDN. For this, *in silico* data, as well as preclinical and clinical studies, were critically reviewed and comprehensively compiled. Our findings reveal that *P. lactiflora* and its individual constituents exhibit a variety of pharmacological properties relevant for PDN, including antinociceptive, anti-inflammatory, antioxidant, and antiapoptotic activities. Through this multifaceted and complex combination of various pharmacological effects, relevant hallmarks of PDN are specifically addressed, suggesting that *P. lactiflora* may represent a promising source for novel therapeutic approaches for PDN.

Introduction

Diabetes mellitus is one of the most serious pandemics of the 21st century. The global prevalence was estimated to be 11% in 2021, which corresponds to more than 500 million people. By 2045, the global number of people affected is predicted to rise to up to 12%, with around 90% of the patients suffering from diabetes mellitus type 2 (DMT2) [1, 2]. DMT2 leads to numerous complications, including cardiovascular effects, renal disease, and retinopathy [2]. Notably, one of the most common chronic complications is peripheral neuropathy, with a highly variable lifetime prevalence of up to 50% of diabetic patients, depending on the country, as well as on age and the duration of the diabetes [3–5]. Pain is a common clinical manifestation associated with neuropathy, affecting approximately 20% of the patient population [6, 7]. However, these statistics are most likely underestimated. For example, the PROTECT study, carried out in Germany between 2013 and 2016, analyzed the presence and prior diagnosis of distal sensory neuropathy in 1850 patients with or without a history of diabetes. Apparently, 43% of DMT2 patients had been diagnosed with painful sensory neuropathy, while 62% actually demonstrated neuropathic pain during the medical examination, a discrepancy suggesting a noticeably higher number of undiagnosed patients with PDN [8]. Overall, as PDN significantly reduces the quality of life, there is a high unmet medical need to alleviate or even prevent the symptoms [9–11].

Diabetic neuropathy leads to various structural and functional alterations of the peripheral nervous system (PNS), including reduced nerve fiber density in the epidermis, axonal atrophy, and demyelination, while sensory neurons are predominantly affected. The cell bodies of the sensory neurons are localized in the dorsal

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* These authors contributed equally to this work.

ABBREVIATIONS

5-HT	serotonin
A1R	adenosine A1 receptor
ADR	aldose reductase
AGEs	advanced glycation end products
Akt	protein kinase B
BDNF	brain-derived neurotrophic factor
CAT	catalase
CCI	chronic constriction injury
CFA	complete Freund's adjuvant
CHOP	C/EBP homologous protein
CNS	central nervous system
DAG	diacylglycerol
DHAP	dihydroxyacetone phosphate
DMT2	diabetes mellitus type 2
DRG	dorsal root ganglia
ER	endoplasmic reticulum
F6P	fructose-6-phosphate
FADH2	dihydroflavine-adenine dinucleotide
FFA	free fatty acids
G3P	glyceraldehyde-3-phosphate
GlcN6P	glucosamin-6-phosphate
GLUT	glucose transporter
GSH	glutathione
IL	interleukin
IRS	insulin receptor substrate
LC-MS	liquid chromatography–mass spectrometry
LDL	low-density lipoprotein
LOX1	oxidized low-density lipoprotein receptor 1
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinases
MGO	methylglyoxal
NF-*κ*B	nuclear factor kappa B
NLRP3	nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) pyrin domain containing 3
OSF	open science framework
PDN	painful diabetic neuropathy
PI3K	phosphoinositide 3-kinase
PKC	protein kinase C
PNS	peripheral nervous system
PPAR*γ*	peroxisome proliferator activated receptor gamma
RAGE	receptor for advanced glycation end products
ROS	reactive oxygen species
SNRI	serotonin-norepinephrine reuptake inhibitors
SOD	superoxide dismutase
TCA	tricarboxylic acid
TCM	Traditional Chinese Medicine
TGP	total glycoside of paeony
TLR4	toll-like receptor 4
TNF-*α*	tumor necrosis factor-*α*
TRP	transient receptor potential
TRPA1	transient receptor potential ankyrin 1
TRPM8	transient receptor potential melastatin 8
TRPV1	transient receptor potential vanilloid 1
TRPV4	transient receptor potential vanilloid 4
UDP-GlcNAC	uridine diphosphate *N*-acetylglucosamine

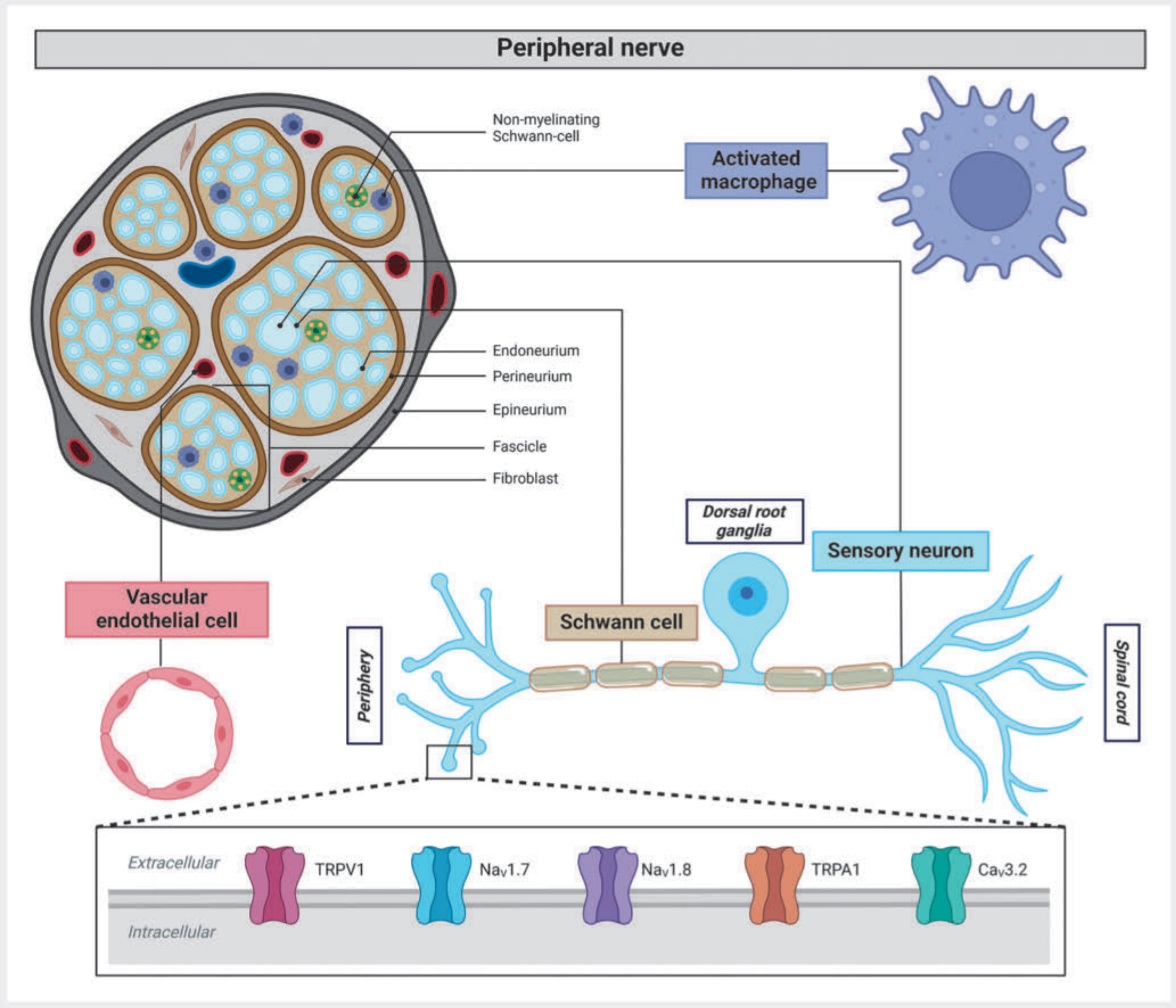
root ganglia (DRG), with long axons extending far into distal areas of the body (▸ **Fig. 1**) [12, 13]. Highly specialized sensory neurons, the so-called nociceptors that can be divided into thinly myelinated Aδ fibers and unmyelinated C fibers, are relevant for the development of pain [14]. Nociceptors express ion channels such as voltage-gated sodium channels, particularly Na_V 1.7 and Na_V 1.8, transient receptor potential vanilloid 1 (TRPV1), and transient receptor potential ankyrin 1 (TRPA1), as well as voltage-gated calcium channels like Ca_V 3.2 and many others (▸ **Fig. 1**) [15]. The activation of these channels triggers an action potential, thereby generating further nociceptive signaling to the central nervous system (CNS) [14]. Notably, impaired sensory neurons can become hyperexcitable, resulting in spontaneous activity in the absence of a triggering signal, which is associated with subsequent central sensitization and nociception [16]. Schwann cells, major players for the structural and functional integrity of neurons in the PNS, also appear to have an impaired metabolism in diabetic patients, causing further destabilization of the axons (▸ **Fig. 1**) [17, 18]. Furthermore, dysfunction of the vascular endothelia cells can lead to deficiencies in blood supply and hypoxia, subsequently causing damage to sensory neurons and Schwann cells [13]. Ultimately, cell injury in the PNS leads to the activation of macrophages [19]. ▸ **Fig. 1** presents the anatomy of a peripheral nerve and the cell types relevant for the pathophysiology of PDN.

To date, the complex pathogenesis of diabetic neuropathy is not yet completely elucidated, but various key signaling pathways have been reported that can be assigned to the three main cell damaging pillars of DMT2: hyperglycemia, dyslipidemia, and insulin resistance [20, 21]. ▸ **Fig. 2** illustrates the complex signaling interplay of these three pillars.

In sensory neurons and Schwann cells, glucose as well as fatty acids are used as substrates in the energy metabolism to generate acetyl-CoA by glycolysis or by *β*-oxidation. Acetyl-CoA is then incorporated into the tricarboxylic acid (TCA) cycle in the mitochondria, producing the redox-active cofactors NADH and dihydroflavin-adenine dinucleotide ($FADH_2$), which are used to produce ATP by oxidative phosphorylation. Oxidative phosphorylation, however, is associated with the production of small amounts of reactive oxygen species (ROS), which are easily eliminated under physiological conditions by cellular antioxidant mechanisms [13].

Since glucose uptake in the PNS involves insulin-independent glucose transporters (GLUT) 1 and GLUT3, impaired insulin signaling in DMT2 is not associated with reduced glucose uptake in sensory neurons or Schwann cells, resulting in an increased activation of various glucose-dependent metabolic pathways in these cells in the presence of increased blood glucose levels (▸ **Fig. 2**) [13, 22]. As a consequence, elevated glycolysis can lead to a disruption of the respiratory chain due to a negative feedback loop. However, in the onset of DMT2, elevated glycolysis contributes to an increased formation of ROS that exceeds the capacity of the endogenous redox systems [12, 21].

During glycolysis, fructose-6-phosphate (F6P) is converted into glyceraldehyde-3-phosphate (G3P), which can be further transformed into the reactive glucose metabolite methylglyoxal (▸ **Fig. 2**) [23]. Both glucose and methylglyoxal lead to unspecific glycation of lipids, nucleotides, and proteins, forming so-called advanced glycation end products (AGEs) with altered function-



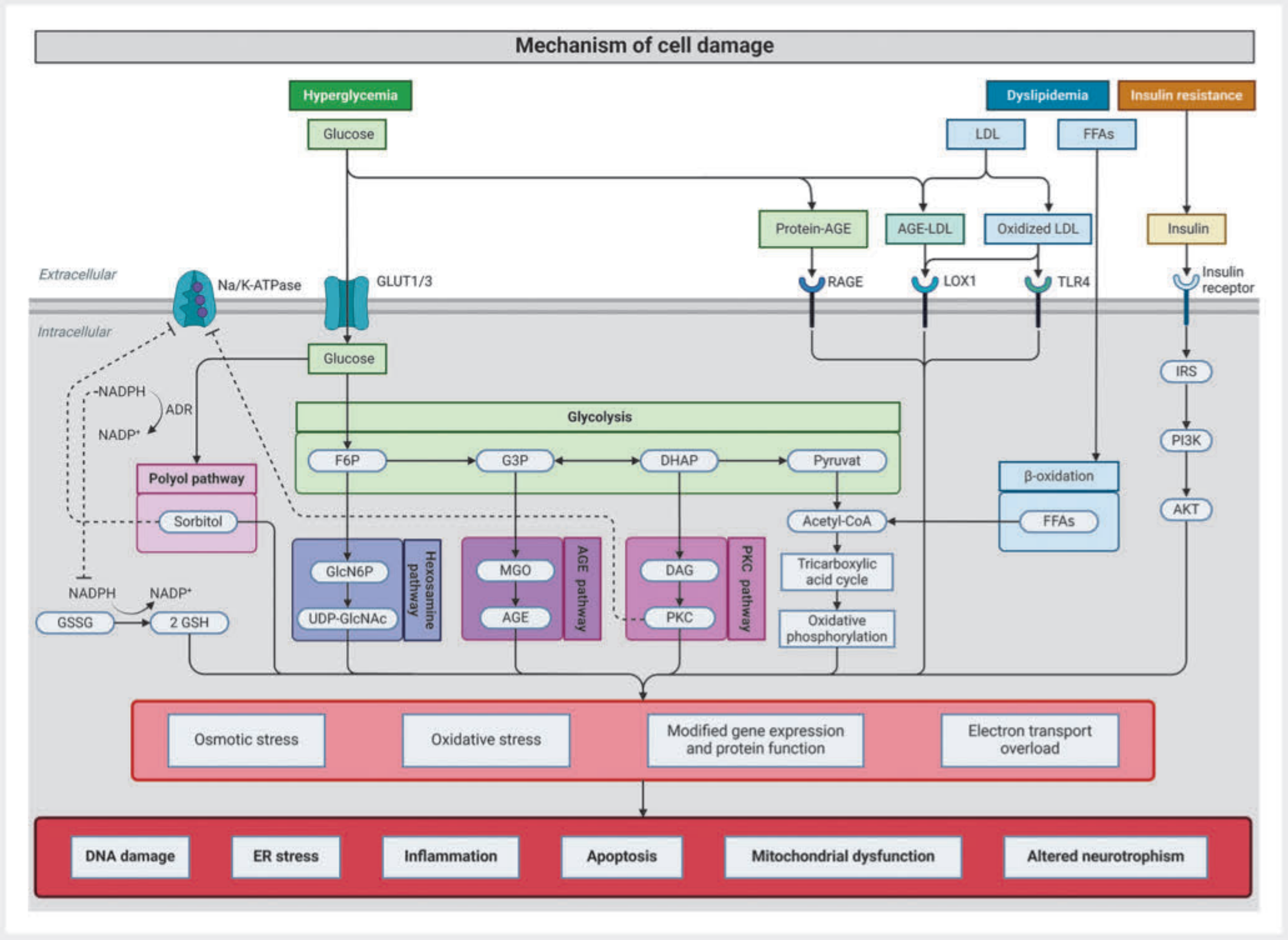
▸ **Fig. 1** Key cell types and ion channels involved in painful diabetic neuropathy. The figure displays cell types of the peripheral nervous system relevant for the development of painful diabetic neuropathy, including sensory neurons, Schwann cells, vascular endothelia cells, and immune cells. It also highlights specific ion channels expressed at the peripheral nerve endings of sensory neurons associated with the pain development. The figure has been created with BioRender.com. Abbreviations: Ca_V: voltage-gated calcium channel; Na_V: voltage-gated sodium channel; TRPA1: transient receptor potential ankyrin 1; TRPV1: transient receptor potential vanilloid 1. The figure was created with BioRender.com. [rerif]

ality [21]. Extracellular AGE can bind to receptors for AGE (RAGE), which are able to trigger downstream signaling pathways via the activation of the transcription factor nuclear factor κB (NF-κB) [24]. Similarly, ion channels at the terminals of nociceptors can undergo glycation, forming AGEs contributing to the hyperexcitability of sensory neurons as described above [15].

Furthermore, G3P is in equilibrium with dihydroxyacetone-phosphate (DHAP), which can be converted to diacylglycerol (DAG). DAG, on the other hand, is able to activate protein kinase C (PKC), which is associated with the disruption of the Na/K ATPase activity, a key protein for neuronal activity, and with the induction of endoplasmic reticulum (ER) stress [25, 26].

Moreover, the glycolysis intermediate F6P increases the synthesis of uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAC) via the hexosamine pathway (▸ **Fig. 2**). UDP-GlcNAC attaches either to transcription factors or to cytosolic proteins, thereby modifying gene expressions and protein functions linked to ER stress [27].

Glucose can also be metabolized to sorbitol via the polyol pathway. Sorbitol damages the cells due to its osmotic effect and inhibits the expression of Na/K ATPase by decreasing intracellular myoinositol [23]. Additionally, a depletion of NADPH leads to a reduction in glutathione (GSH), a major detoxification system of our cells, resulting in an increased susceptibility to oxidative stress [25].



▶ **Fig. 2** Pathogenesis of diabetic neuropathy. The figure illustrates the signaling interplay of the three damaging pillars of diabetes mellitus type 2: hyperglycemia, dyslipidemia, and insulin resistance. These factors activate numerous pathways, including the polyol pathway, the hexosamine pathway, the AGE pathway, and the PKC pathway. This activation of signaling pathways leads to DNA damage, endoplasmic reticulum stress, inflammatory signaling, mitochondrial dysfunction, apoptosis, and loss of neurotrophic signaling, ultimately resulting in cell damage that contributes to painful diabetic neuropathy. The figure has been created with BioRender.com. Abbreviations: ADR: aldose reductase; Akt: protein kinase B; AGE: advanced glycation end products; DAG: diacylglycerol; DHAP: dihydroxyacetone-phosphate; ER: endoplasmic reticulum; FFAs: free fatty acids; F6P: fructose-6-phosphate; GLUT: glucose transporter; GSH: glutathione; GSSG: glutathione disulfide; G3P: glyceraldehyde-3-phosphate; GlcN6P: glucosamin-6-phosphate; IRS: insulin receptor substrate; LDL: low-density lipoprotein; LOX1: oxidized LDL receptor 1; MGO: methylglyoxal; PI3K: phosphatidylinositol 3-kinase; PKC: protein kinase C; RAGE: receptors for AGE; TLR4: toll-like receptor 4; UDP-GlcNAC: *N*-acetylglucosamine. The figure was created with BioRender.com. [rerif]

Additionally, dyslipidemia plays a role in the development of PDN. Plasma lipoproteins, low-density lipoprotein (LDL) in particular, can undergo glycation or oxidation (▶ **Fig. 2**) [21]. These modified molecules, like AGE-LDL and oxidized LDL, can bind to extracellular receptors such as oxidized LDL receptor 1 (LOX1), toll-like receptor 4 (TLR4), or RAGE, triggering a variety of signaling cascades, including the activation of caspase 3 and the DNA degradation, leading to apoptosis. It also leads to an increased NADPH oxidase activity, resulting in oxidative stress [28, 29].

Finally, insulin resistance interferes with the phosphoinositide 3-kinase/protein kinase B (PI3K-Akt) signaling pathway (▶ **Fig. 2**). Insulin resistance leads to reduced phosphorylation of the insulin receptor substrate (IRS), thereby inhibiting downstream signaling cascades, including the activation of PI3K and ultimately Akt, which is associated with neurotrophic effects such as regeneration, survival, and axonal growth [12, 30].

Due to the complex pathophysiology and the limited understanding of the exact mechanistic interplay leading to PDN, current treatments remain inadequate [31]. In the absence of a disease-modifying treatment strategy, current guideline therapy is mainly restricted to the alleviation of pain symptoms [32]. First-line therapy options include anticonvulsants, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors (SNRI), but the exact mechanism-of-action in neuropathic pain is not yet fully elucidated [24, 33]. The most common therapeutic approach is the anticonvulsant pregabalin, which inhibits voltage-dependent calcium channels of presynaptic neurons in the CNS. This prevents the release of neurotransmitters like glutamate, noradrenaline, and substance P and the subsequent transmission of nociceptive stimuli [20, 33]. Moreover, a study hypothesized an effect on the PNS by inhibiting NF-κB activation in rat DRG pre-treated with substance P [34]. Tricyclic antidepressants and SNRI, on the other hand, influence the reuptake of neurotransmitters in the CNS [20]. However, these treatments are only effective to a limited extent, with only one-third of patients achieving significant pain relief [35]. Additionally, systemically applied therapies carry a high risk of adverse effects, especially in patients with polypharmacy like diabetic patients with increasing age [12]. In conclusion, there is a high unmet medical need for specialized therapeutic options [36].

Paeonia lactiflora (*P. lactiflora*) belongs to the family of Paeoniaceae and has been applied in traditional Chinese medicine (TCM) for centuries for the treatment of various disorders including pain symptoms [37]. In TCM, the dried root is used, which can be separated according to its processing method into *Paeoniae radix alba* 'white peony root' (*baishao*) and *Paeoniae radix rubra* 'red peony root' (*chishao*) [38]. Monographs of these drugs are not only listed in the Chinese but also the European Pharmacopoeia [39, 40].

Numerous pharmacological properties are attributed to the constituents of *P. lactiflora* that have an influence on the key factors affected in PDN: the nervous system, the vascular system, and the immune system. These characteristics include antinociceptive, anti-inflammatory, antioxidant, and antiapoptotic effects [41, 42]. Paeoniflorin, for example, the main constituent of *P. lactiflora*, is reported to show analgesic effects on different types of pain, including PDN. These effects are mediated via different pathways, amongst them the modulation of nociceptor excitability and the inhibition of inflammatory response [43]. Studies on Schwann cells also demonstrated that apoptosis induced by oxidative stress in the form of hydrogen peroxide is inhibited by paeoniflorin through inhibition of the phosphorylation of p38 mitogen-activated protein kinases (p38MAPK) and a reduction in the levels of caspase3, cleaved-caspase3, and cleaved-caspase7 [44]. On the other hand, paeonol presented pain-relieving activity in diabetic mice by enhancing antioxidant enzymes, thereby reducing oxidative stress [45]. Both paeonol and kaempferol additionally reduced neuroinflammation due to the modulation of microglia activation by switching M1 macrophages with a pro-inflammatory phenotype to M2 macrophages with an anti-inflammatory phenotype [46, 47].

The clinical relevance of *P. lactiflora* was demonstrated in a recently published meta-analysis that evaluated the efficacy and safety of herbal formulations from TCM with respect to the treatment of PDN [35]. Noteworthy, *P. lactiflora* turned out to be one of the most frequently used plants in prescriptions for PDN. For the herbal formulations in general, higher clinical efficacy and a lower rate of adverse effects compared to corresponding control groups with "classical" pharmaceuticals are reported [35].

Despite the given evidence for the use of *P. lactiflora* in PDN, to date, there is no review highlighting the potential of *P. lactiflora* as a substantial treatment strategy. Thus, this article provides a systematic insight into the existing research on the constituents of *P. lactiflora* and their pharmacological effects presented in various pain models, which also play a potential role in the treatment of PDN.

Search Strategy

We considered relevant articles from the following electronic databases until July 2024: PubMed, Springer, Web of Science, Google Scholar, Science Direct, and China National Knowledge Infrastructure. The search terms included "painful diabetic neuropathy", "analgesic", "antinociceptive", "neuroprotective", "clinical trial", and "network pharmacology", combined with the plant name or the names of main constituents. *In silico* data, as well as preclinical and clinical studies, were reviewed and analyzed.

Phytochemical Characteristic of *Paeonia lactiflora*

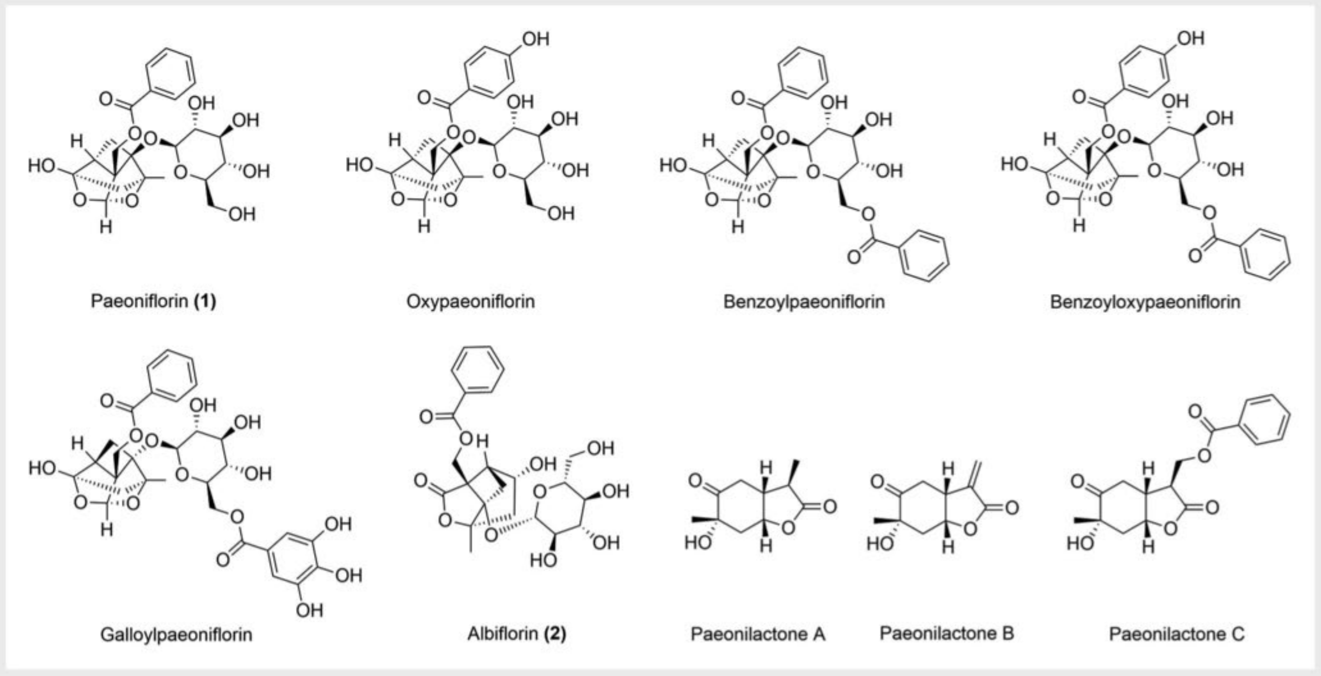
To date, approximately 300 compounds have been isolated and structurally identified from *P. lactiflora*, including monoterpenes and their glycosides, sesquiterpenes, triterpenes and steroid compounds, tannins, flavonoids, lignans, stilbenes, volatile oils, and other compounds [48–50]. Among them, monoterpenes and their glycosides are considered to be the predominant active components in *P. lactiflora* that have been shown to possess significant therapeutic effects in various nervous system diseases, including neuropathic pain, neuroinflammation, and neurotoxicity. As illustrated in the following chapters, the reported components from *P. lactiflora* exert pharmacological activities through multilateral mechanisms, such as antinociceptive, anti-inflammatory, antioxidant, and antiapoptotic activities [51, 52].

Monoterpenes and their glycosides

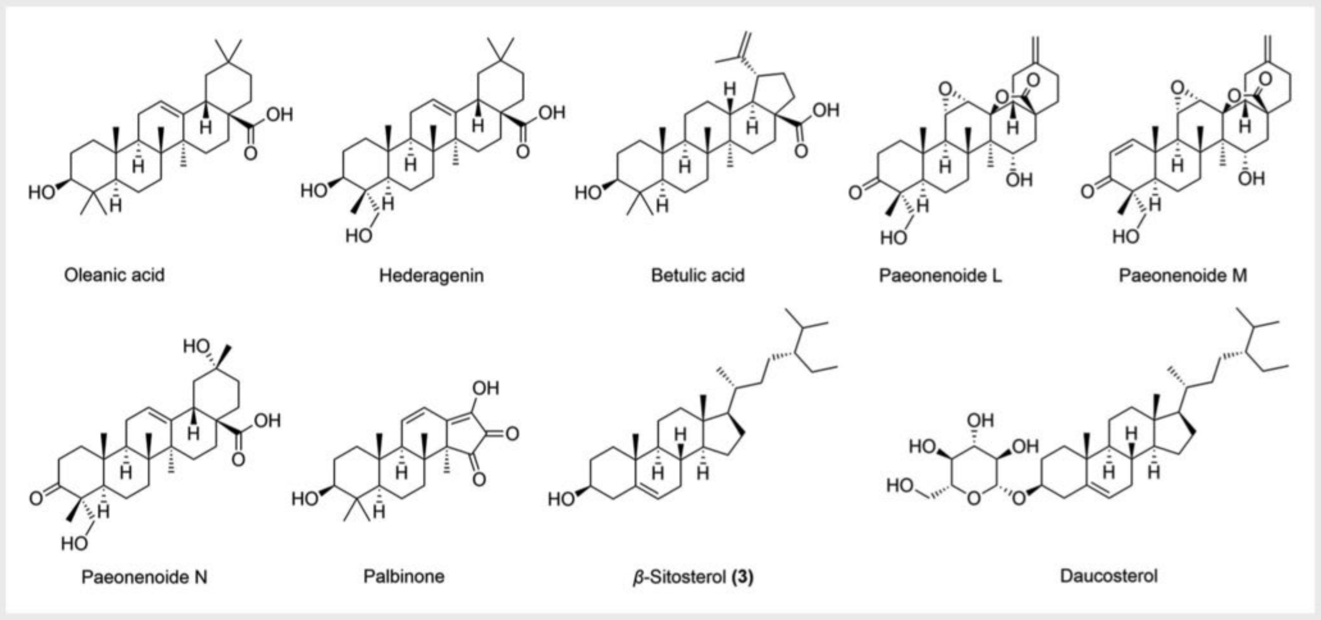
Symbol structures for the genus *Paeonia* and the basis for the plant's pharmacological effects are the pinane type and *p*-menthane type monoterpene glycosides. In particular, pinane-type monoterpene glycosides, such as the primary compounds paeoniflorin (**1**) and albiflorin (**2**), have been extensively studied and demonstrated to have neuroprotective, anti-inflammatory, antioxidant, and analgesic effects that play an important role in the treatment of PDN [51, 52]. Pinane-type monoterpenes are characterized by their "cage-like" pinane skeleton and exist as monocargo dibenzoate of monoterpene glycosides, which differ in the aromatic ring substitutions or sugar moieties and various stereocenters in the pinane skeleton, forming abundant varieties (▶ **Fig. 3**) [49, 53]. For example, in contrast to paeoniflorin, the isomer albiflorin (**2**) exhibits a lactone ring in the pinane skeleton. Furthermore, oxypaeoniflorin, benzoylpaeoniflorin, benzoyloxypaeoniflorin, and galloylpaeoniflorin have similar structures to paeoniflorin but with different substituents. The other important type of monoterpene glycosides in *P. lactiflora*, the *p*-menthane type, includes paeonilactone A–C (▶ **Fig. 3**) [54]. In addition, numerous novel types of monoterpene glycosides were isolated in recent years, such as nor-monoterpenes, labile monoterpenes, or dimeric monoterpenes [49].

Terpenes and steroids

In addition to monoterpenes, sesquiterpenes and triterpenes can also be isolated from *P. lactiflora*. Most triterpenes are pentacyclic triterpenoids, such as oleanolic acid, hederagenin, and betulinic

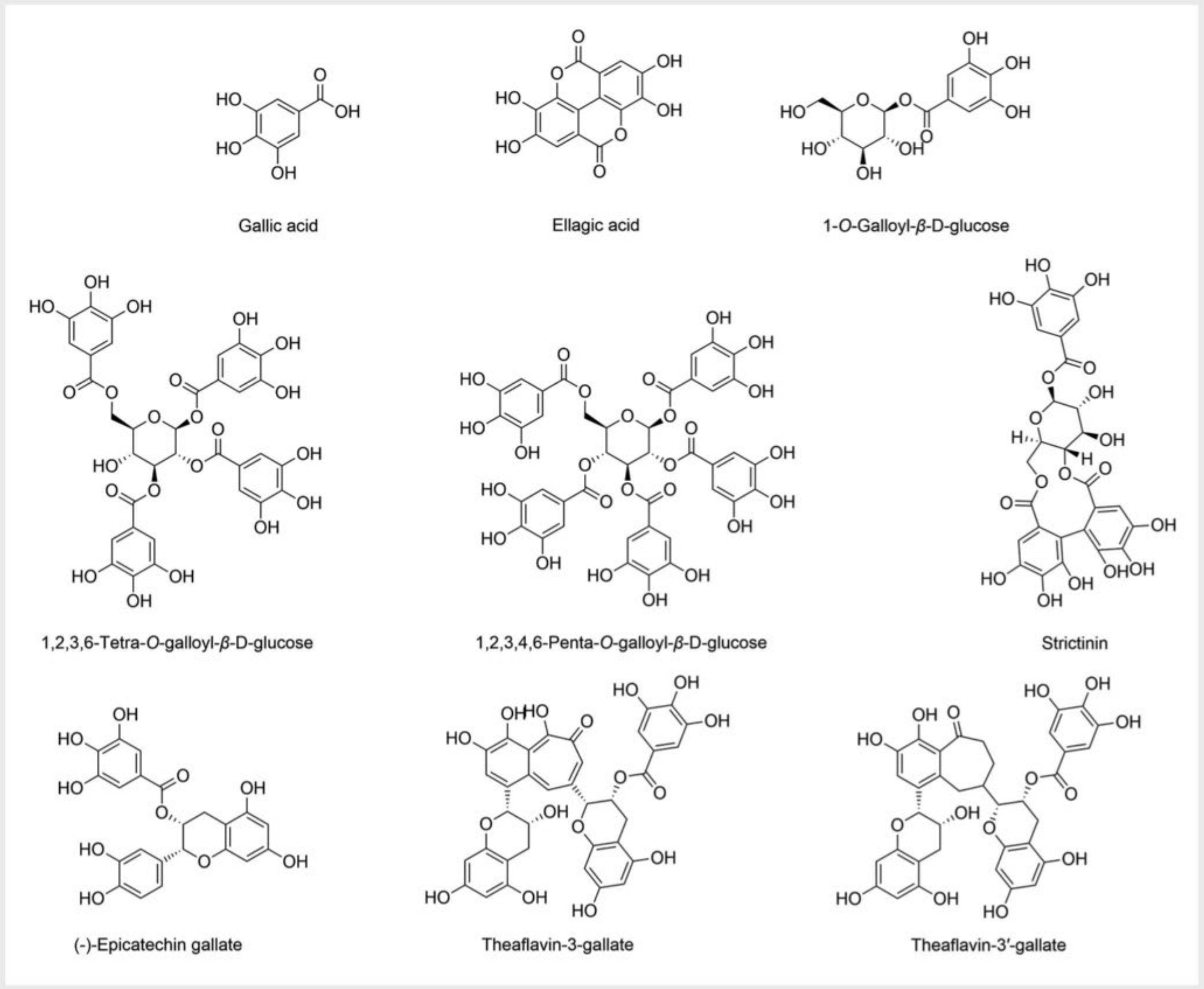


▶ **Fig. 3** Selected monoterpenes and their glycosides isolated from *P. lactiflora*. The most important constituents are marked with a number.



▶ **Fig. 4** Selected terpenes and steroids isolated from *P. lactiflora*. The most important constituents are marked with a number.

acid (▶ **Fig. 4**) [55]. Recently, three new 30-noroleanane triterpenoids paeonenoides L–N were isolated from the root section of *P. lactiflora* that show anti-inflammatory, antioxidant, and antidiabetic activities [56, 57]. Furthermore, the steroids palbinone, daucosterol, and *β*-sitosterol (**3**) were isolated from *P. lactiflora* (▶ **Fig. 4**) [58, 59]. Many clinical roles of steroids are related to their potent anti-inflammatory and immune-modulating properties [60]. For example, palbinone suppresses glucose-induced retinal inflammation and oxidative stress in a diabetic rat model [61], while *β*-Sitosterol improves glycemic control in type 2 diabetic rats and protects against oxidative damages in diabetic mice [62].



Gallic acid

Ellagic acid

1-*O*-Galloyl-*β*-D-glucose

1,2,3,6-Tetra-*O*-galloyl-*β*-D-glucose

1,2,3,4,6-Penta-*O*-galloyl-*β*-D-glucose

Strictinin

(-)-Epicatechin gallate

Theaflavin-3-gallate

Theaflavin-3′-gallate

▶ **Fig. 5** Selected tannins isolated from *P. lactiflora*.

Tannins

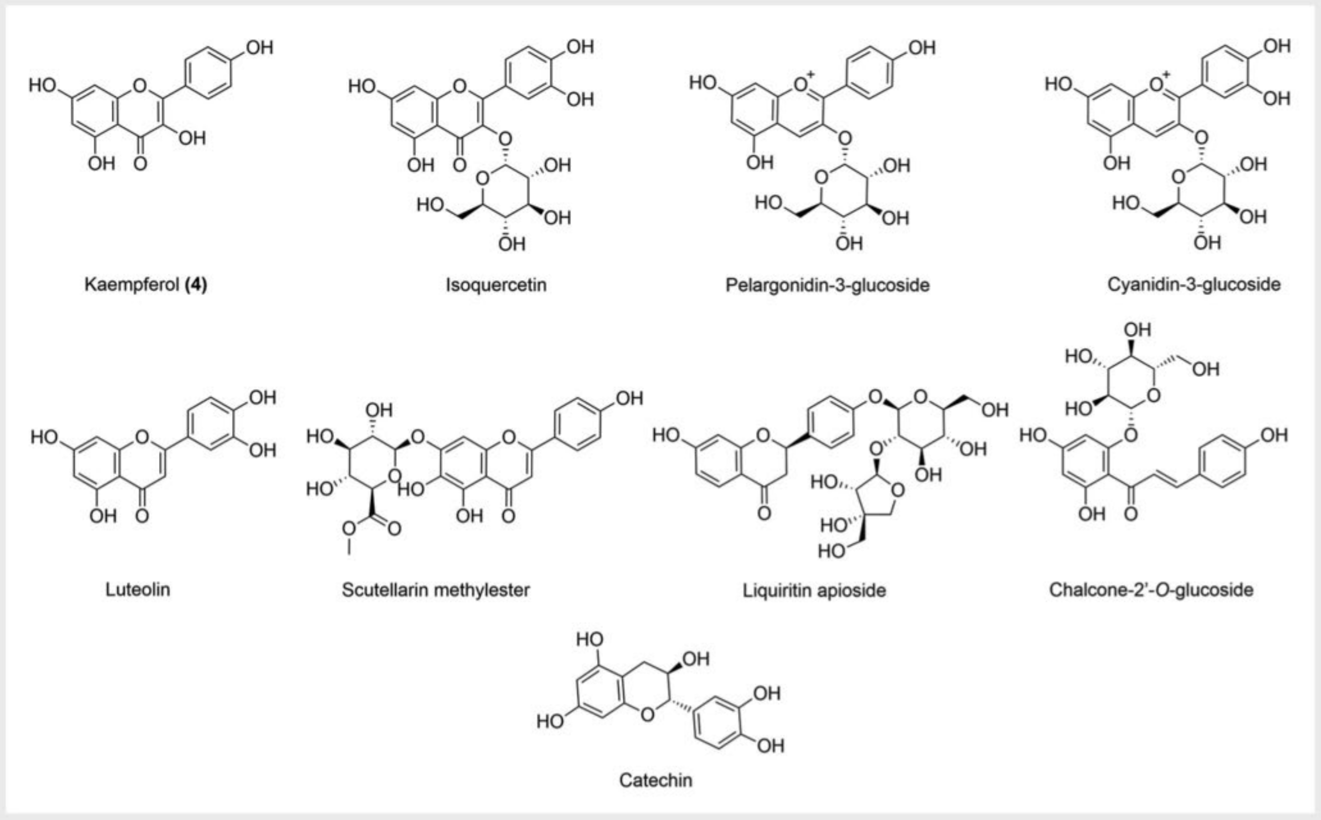
Recently, a study using high-resolution accurate-mass LC-MS instruments (UHPLC-Q-Exactive Orbitrap MS) identified 106 tannin constituents in the spectrum of the dried root of *P. lactiflora* [50]. Based on their structure, tannins can be divided into two types (▶ **Fig. 5**), hydrolyzed tannins and condensed tannins, and most of them present anti-inflammatory and antioxidant activities [63]. Gallic acid and its derivatives, gallotannins and ellagitannins, such as ellagic acid and strictinin, comprise the main group of tannins in *P. lactiflora* [38]. Among them, a series of high molecular weight hydrolyzed tannins, including tetra-, penta-, hexa-, hepta-, octa-, nona-, and deca-galloylglucoses displaying a 1,2,3,4,6-penta-*O*-galloyl-*β*-D-glucose core show potent glucose-lowering activity [64, 65]. Moreover, many condensed tannins, such as (−)-epicatechin gallate, theaflavin-3-gallate, and theaflavin-3′-gallate were isolated from *P. lactiflora* [50]. Condensed tannins, also referred to as proanthocyanidins, are oligomers or polymers of flavan-3-ols, which are characterized by immunomodulatory, antidiabetic, and neuroprotective properties [66].

Flavonoids

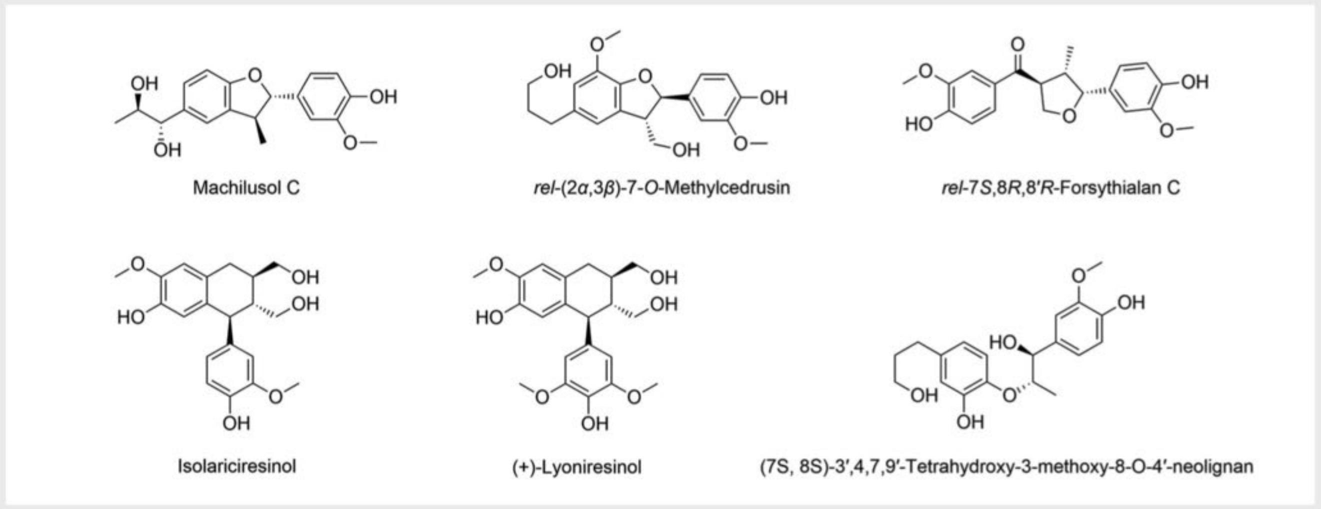
Flavonoid extracts of *P. lactiflora* are known for their antioxidant, anti-inflammatory, anticancer, and antibacterial activities [67, 68]. They can be divided into several structural classes (▶ **Fig. 6**), including the following: flavonols, such as kaempferol (**4**) and isoquercetin [69]; anthocyanidins, such as, for example, pelargonidin-3-glucoside and cyanidin-3-glucoside [70]; flavones, such as luteolin [71] and scutellarin methylester [69]; flavanone, including liquiritin apioside [72]; chalcone, such as chalcone-2′-*O*-glucoside [67]; and flavan-3-ol, such as, for example, catechin [73].

Lignans

Most of the lignans isolated from *P. lactiflora* display a benzofuran or tetrahydrofuran substructure (▶ **Fig. 7**), such as machilusol C, *rel*-(2*α*,3*β*)-7-*O*-methylcedrusin, and *rel*-7*S*,8*R*,8′*R*-forsythialan C,



▶ **Fig. 6** Selected flavonoids isolated from *P. lactiflora*. The most important constituent is marked with a number.

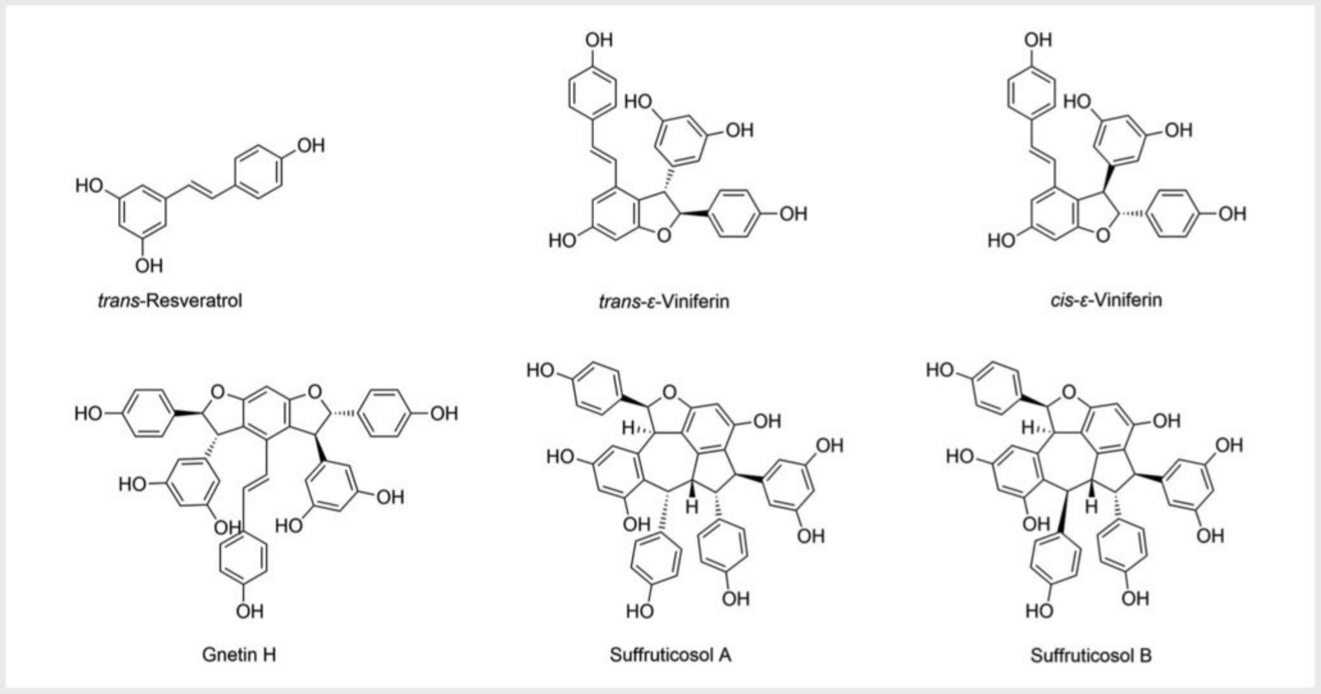


▶ **Fig. 7** Selected lignans isolated from *P. lactiflora*.

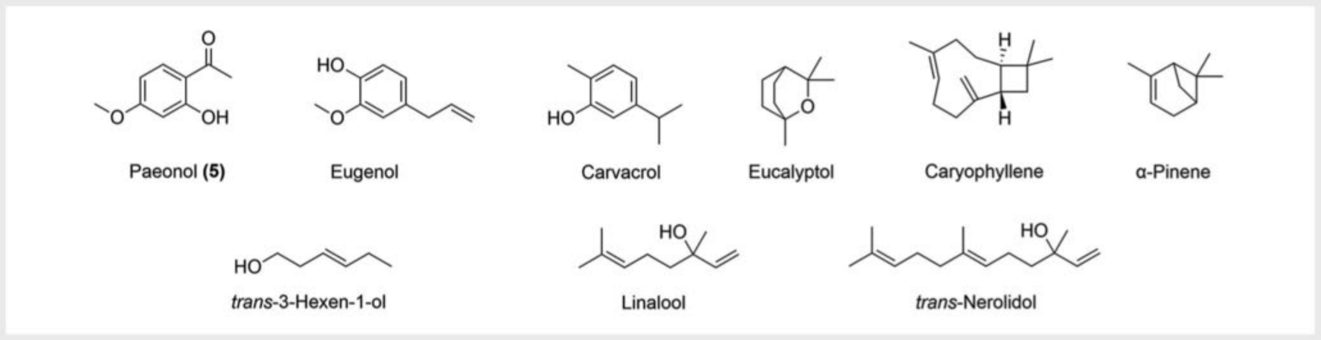
while some representatives have a 1-phenyltetralin skeleton, such as, for example, isolariciresinol and (+)-lyoniresinol [48], and some belong to neolignans, such as (7*S*, 8*S*)-3′,4,7,9′-tetrahydroxy-3-methoxy-8-*O*-4′-neolignan [74]. Lignans exhibit diverse biological effects, including anti-inflammatory and antioxidant activities.

Stilbenes

Stilbenes are a group of specialized compounds with a C6-C2-C6 structure usually composed of two isomers. To date, less than 500 naturally occurring stilbenes have been isolated from plants and only a few from *P. lactiflora*. Stilbenes discovered in seeds of *P. lactiflora* represent resveratrol oligomers, including *trans*-resveratrol



▶ **Fig. 8** Selected stilbenes isolated from *P. lactiflora*.



▶ **Fig. 9** Selected volatile oils and other compounds isolated from *P. lactiflora*. The most important constituent is marked with a number.

and its glycosides, *trans*-ε-viniferin, *cis*-ε-viniferin, gnetin H, suffruticosol A, and suffruticosol B (▶ **Fig. 8**). For stilbenes, a variety of biological activities have been reported including neuroprotective, antidiabetic, antioxidant, and anti-inflammatory effects [75]. For example, suffruticosol A demonstrates anti-inflammatory activity by inhibiting the production of nitric oxide, as well as the expression of inducible nitric oxide synthase and pro-inflammatory cytokines in lipopolysaccharide (LPS)-stimulated macrophages [76].

Volatile oils and other compounds

More than 70 different types of volatile oils and other compounds are described and distributed in all parts of *P. lactiflora* including phenols, benzenoids, phenylpropanoids, alkyl hydrocarbons, fatty acid derivatives, coumarin, anthraquinone, and others [48, 77]. Some of them are the main constituents of the plant's fragrance [78, 79]. Paeonol (**5**) (▶ **Fig. 9**) is an important bioactive phenolic compound of *P. lactiflora*. Despite its simple structure, it has great pharmacological potential with regard to the treatment of PDN including anti-inflammatory, antidiabetic, and neuroprotective effects [80–82].

In Silico Data

The network pharmacology approach reflects a systematic data analysis where networks of drug-target interactions and disease-target phenotypes are correlated, offering the opportunity of mapping active substances with pathophysiological pathways to uncover possible modes-of-action [83, 84].

Noteworthy, a recent study revealed potential mechanisms of the antinociceptive effect of *P. lactiflora* using *in silico* methods. In this study, 11 active constituents were identified that may exert analgesic effects, mainly via an inflammation-regulated transient receptor potential (TRP) channel pathway, including TRPV1, which is sensitive to heat pain, or the calcium signaling pathway, as well as the serotonin (5-HT) receptor [85]. The effect of the monoterpene glycoside albiflorin (▶ **Fig. 3**) on 5-HT receptors has already been investigated in more detail. A high affinity of albiflorin to 5-HT and to norepinephrine receptors has been reported, hinting at a mechanism-of-action similar to that of antidepressants [86]. Furthermore, Hu et al. demonstrated that the steroid compound *β*-sitosterol (▶ **Fig. 4**) could be one of the key active constituents acting on neuroinflammation and immune regulation by binding to the peroxisome proliferator-activated receptor gamma (PPAR*γ*) and to TNF-*α* [87]. Another study assessed the mechanisms-of-action of the herb pair *P. lactiflora* and *Ramulus cinnamomi (cassiae)* in chronic pain with comorbid anxiety and depression. The main pathways involved were the AGE-RAGE axis and the TNF signaling pathway, which contribute to neuroinflammation [88]. In addition to peaoniflorin, albiflorin, palbinone, *β*-sitosterol, and kaemferol were identified as active compounds inhibiting neuropathic and inflammatory pain [85, 87, 88].

Preclinical Data

Neuropathic pain caused by diabetes mellitus

Diabetes and diabetic peripheral neuropathy can be induced in rats using streptozotocin, leading amongst other things to a decreased threshold for mechanical and thermal pain [89]. Adki et al. used this model to demonstrate that treatment with the phenolic constituent paeonol (▶ **Fig. 9**) resulted in the suppression of mechanical allodynia and hyperalgesia, as well as thermal hyperalgesia and improved sensory nerve conduction velocity. Furthermore, they showed the antioxidant effect of paeonol by increasing the content of the antioxidant enzymes GSH, superoxide dismutase (SOD), and catalase (CAT) and the anti-inflammatory effect by decreasing NF-*κ*B activity in the sciatic nerve. All these effects of paeonol had a comparable significance to the control treatment with pregabalin [45]. Similar effects have been shown for treatment with the flavonoid kaempferol (▶ **Fig. 6**). Mechanical hyperalgesia and allodynia were alleviated in diabetic rats by modulating oxidative stress, especially by increasing GSH levels, and by reducing the formation of AGE, leading to decreased concentrations of the proinflammatory cytokines TNF-*α* and IL-1*β* [90].

Neuropathic pain caused by nerve injury

One of the most researched constituents of *P. lactiflora* is paeoniflorin, which also represents the major active monoterpene of the total glycoside of paeony (TGP) (▶ **Fig. 3**). To verify the inflammatory mediator regulation of TRP channels found in the pharmacological network analysis [85], a study analyzed mRNA levels of different TRP channels, as well as the phosphorylation of p38MAPK (p-p38MAPK) in a rat model of chronic construction injury (CCI) in comparison to the positive control pregabalin. Expression levels of TRPA1, TRPV1, transient receptor potential vanilloid 4 (TRPV4), transient receptor potential melastatin 8 (TRPM8), and p-p38MAPK in rat DRG in combination with serum levels of pro-inflammatory cytokines, such as IL-6 and TNF-*α*, decreased in the presence of paeoniflorin, demonstrating the antinociceptive effect via the reduction in inflammatory factors by inhibiting the p38MAPK pathway. The antinociceptive effect was confirmed in behavioral tests, in which paeoniflorin attenuated mechanical pain and thermal pain [91].

Moreover, Zhou et al. also showed that paeoniflorin, as well as albiflorin (▶ **Fig. 3**), could relieve neuropathic pain in a model of mechanical hyperalgesia induced by CCI in rats by inhibiting microglia activation in the CNS by reducing the activated p38MAPK signaling pathway. This led to reduced IL-1*β* and TNF-*α* levels, suggesting that the reported antinociceptive effect of paeoniflorin and albiflorin is mediated via the inhibition of neuroinflammation [92]. In this context, the role of the NOD-like receptor protein 3 (NLRP3) inflammasome and the influence of paeoniflorin were elucidated. Paeoniflorin was found to reduce the activation of the NLRP3 inflammasome in the spinal cord, which mediates the development of neuropathic pain. Paeoniflorin also suppressed NF-*κ*B activity in the spinal cord, thereby inhibiting neuroinflammation [93]. Likewise, the isolated constituent albiflorin reduced the expression of NLRP3, the levels of IL-1*β* and ROS, and the activity of NF-*κ*B, thereby alleviating pain [94].

The CCI model of neuropathic pain was additionally used to assess the analgesic effect of *β*-sitosterol (▶ **Fig. 4**) with the nonsteroidal anti-inflammatory drug ibuprofen as a positive control. In this study, *β*-sitosterol was able to relieve mechanical pain, presumably by decreasing TLR4 expression and NF-*κ*B activity, resulting in reduced levels of the proinflammatory cytokines IL-1*β* and IL-8. [95]. Moreover, paeonol (▶ **Fig. 9**) alleviated mechanical and thermal pain in the CCI model by reducing levels of TNF-*α*, IL-1*β*, and IL-6, associated with the inhibition of neuroinflammation [96].

In a mouse model for neuropathic pain and associated insomnia, where the sciatic nerve is partially ligated, paeoniflorin (▶ **Fig. 3**) has relieved both mechanical and thermal pain and improved sleep. Since administration of an adenosine A1 receptor (A1R) antagonist abolished the antinociceptive and hypnotic effects, it was hypothesized that the efficacy of paeoniflorin may be mediated by A1Rs [97].

To investigate postoperative pain, mice underwent plantar incision surgery. The subsequent administration of paeoniflorin was able to alleviate the mechanical pain. In addition, paeoniflorin was able to inhibit microglial activation by reducing p-p38MAPK and by preventing the upregulation of IL-1*β* in the spinal cord. The reduction in neuronal cFOS expression, a marker of the activation of nociceptive neurons in the spinal cord, was also reduced by paeoniflorin [98].

Neuropathic pain caused by chemotherapy

Noteworthy, a study focusing on the paclitaxel-induced model of peripheral neuropathic pain in mice demonstrated that not only the oral but also the repeated topical application of paeoniflorin (▶ **Fig. 3**) could attenuate mechanical pain [99]. Andoh et al. additionally reported that paeoniflorin downregulated the expression of the transcription factor C/EBP homologous protein (CHOP) in

▶ **Table 1** Representative phytochemical constituents of *P. lactiflora* in the treatment of nervous system indications.

Compound	Pain Model	Mechanisms	References
Paeoniflorin (1)	CCI neuropathic pain	↓ TRPM8, TRPA1, TRPV1, TRPV4, IL-6, TNF-*α*, p38 MAPK, IL-1*β*, NLRP3, NF-*κ*B, cFOS Effect as A1R agonist	[91–93, 97, 98]
	LPS-induced or CFA-induced inflammatory pain	↓ IL-1*β*, TNF-*α*, IL-6, intracellular Ca^{2+}, PKC, NF-*κ*B, TRPV1, NLRP3, substance P	[101–103]
	Paclitaxel-induced neuropathic pain	↓ CHOP Effect as A1R agonist	[100]
Albiflorin (2)	CCI neuropathic pain	↓ p38 MAPK, IL-1*β*, TNF-*α*, NLRP3, ROS, NF-*κ*B	[92, 94]
β-Sitosterol (3)	CCI neuropathic pain	↓ TLR4, NF-*κ*B, IL-1*β*, IL-8	[95]
Kaempferol (4)	Diabetic neuropathic pain	↓ AGEs, TNF-*α*, IL-1*β* ↑ GSH	[90]
Paeonol (5)	Diabetic neuropathic pain	↓ NF-*κ*B, MDA ↑ GSH, SOD, CAT	[45]
	CCI neuropathic pain	↓ TNF-*α*, IL-1*β*, IL-6	[96]

Abbreviations: CCI: chronic constriction injury; A1R: adenosine A1 receptor; AGEs: advanced glycation end products; CAT: catalase; CFA: complete Freund's adjuvant; CHOP: C/EBP homologous protein; GSH: glutathione; IL-1*β*: interleukin-1 beta; IL-6: interleukin-6; IL-8: interleukin-8; LPS: lipopolysaccharide; MDA: malondialdehyde; NF-*κ*B: nuclear factor kappa B; NLRP3: nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) pyrin domain containing 3; p38 MAPK: p38 mitogen-activated protein kinase; PKC: protein kinase C; ROS: reactive oxygen species; SOD: superoxide dismutase; TLR4: toll-like receptor 4; TNF-*α*: tumor necrosis factor-*α*; TRPA1: transient receptor potenzial ankyrin 1; TRPM8: transient receptor potenzial melastatin 8; TRPV1: transient receptor potenzial vanilloid 1; TRPV4: transient receptor potenzial vanilloid 4

Schwann cells, which is a marker of endoplasmic reticulum stress. As this effect could be counteracted by an A1R antagonist, they similarly suggested A1R to be a potential mediator of the analgesic effects of paeoniflorin [100].

Inflammatory pain

Another study focused on the effect of paeoniflorin on complete Freund's adjuvant (CFA)-induced inflammatory pain in mice, where paeoniflorin could inhibit the spinal microglial activation and reduce NF-*κ*B expression, leading to reduced production of the proinflammatory cytokines TNF-*α*, IL-6, and IL-1*β* in the CNS, both *in vivo* and *in vitro*. Behavioral tests also showed a relief of mechanical pain and thermal pain with paeoniflorin [101]. This is consistent with a study in which the DRG neurons of mice were examined in the CFA model. The authors hypothesized that the attenuation of inflammatory pain by paeoniflorin is partially due to the modulation of pyruvate and succinate dehydrogenase activity in the TCA cycle, resulting in a downstream inhibition of NLRP3 inflammasome expression. In addition, they found a reduction in serum IL-6, TNF-*α*, and IL-1*β* levels. Most importantly, they demonstrated that paeoniflorin could directly suppress the response of DRG neurons to capsaicin and reduce the release of substance P, a neurotransmitter relevant to pain perception [102].

Furthermore, paeoniflorin alleviated inflammatory pain in mice with LPS-induced pain by inhibiting the production of the proinflammatory cytokines IL-1*β*, TNF-*α*, and IL-6, as well as intracellular Ca^{2+} levels and PKC activity, in addition to NF-*κ*B activation and TRPV1 expression [103].

A detailed summary of the pharmacological effects of the key constituents of *P. lactiflora* acting on PDN and other pain-related disorders of different pathological genesis is summarized in ▶ **Table 1**.

Clinical Data

To date, for the highlighted monomers isolated from *P. lactiflora*, mostly preclinical data are available. However, P. lactiflora extracts have been used for centuries as an important ingredient in TCM formulations for the treatment of PDN. Many classical TCM formulations involved *P. lactiflora* as one of the predominant compositions, such as the Shaoyao Gancao decoction [104], Buyang Huanwu decoction [105], Danggui Sini decoction [106], Shentong Zhuyu decoction [107], Huangqi Guizhi Wuwu decoction [108], Yiqi Huoxue Tongmai decoction [109], or Mudan granules [110]. Among them, the Shaoyao Gancao decoction, which originated in the Dong Han Dynasty (25–220 A. D.), is one of the most influential classical TCM formulations. It consists of only two ingredients, *Paeoniae Radix Alba* (poeny) and *Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle* (licorice), with a ratio of 1 : 1. This formulation is widely used in Asian countries to treat various types of pain, including diabetic neuropathic pain [104]. Notably, in a recent literature review and meta-analysis, the effectiveness and safety of Chinese herbal medicine in the therapy of PDN were assessed in a total of 21 randomized controlled trials with 1737 PDN patients. Noteworthy, after analyzing all TCM formulations, *P. lactiflora* belonged to the top 10 (*Paeoniae Radix Rubra* ranked No. 4 and *Paeoniae Radix Alba* ranked No. 9) most frequently used herbal medicines in all formulations proven to enhance nerve conduction velocity, reduce pain, and promote clinical efficacy during the therapy of PDN [35].

Mudan granules are a patented TCM drug approved for diabetic peripheral neuropathy by the National Medical Products Administration in 2008 and listed in the National Health Insurance Catalogue as an urgently needed medicine in China [111]. The 2024 Expert Consensus of the China Association of Chinese Medicine summarizes the recent research and clinical effects of Mudan granules in treating diabetic peripheral neuropathy. This drug can significantly improve the syndrome of diabetic peripheral neuropathy, enhance peripheral nerve conduction velocity, and alleviate symptoms of peripheral sensory abnormalities in patients, including pain and numbness. Moreover, it can be used alone or in combination with other medicines to treat diabetic peripheral neuropathy. Therefore, Mudan granules were considered a highly recommended drug for the treatment of PDN [112].

The main components of Mudan granules are the roots of *P. lactiflora* (*Paeoniae Radix Rubra*), *Astragalus membranacea, Panax notoginseng, Corydalis yanhusuo* and five other medicinal herbs. In an ongoing clinical trial for Mudan granules that had been registered in the open science framework (OSF) in 2022, 93 PDN patients were recruited and randomly divided into a treatment group (Mudan granules combined with pregabalin) and a control group (placebo combined with pregabalin) to evaluate the efficacy and safety of Mudan granules in treating PDN [110]. Meanwhile, a post-marketing evaluation of Mudan granules as an intervention for type 2 diabetic peripheral neuropathy was initiated in 2021. This is a 14-center, double-blind, randomized, placebo-controlled, parallel-arm trial involving 402 people [113]. It is designed to evaluate the efficacy of Mudan granules in combination with methylcobalamin, an active form of vitamin B12 that has been proven in numerous clinical trials to alleviate the symptoms of peripheral diabetic neuropathy [114].

Summary and Conclusion

In general, the molecular interplay of oxidative stress and inflammation represents a major part in the pathogenesis of PDN, increasing the sensitivity of sensory neurons to nociceptive signals. Furthermore, the increased susceptibility to apoptosis is associated with a higher prevalence of the degeneration of sensory neurons. Overall, *in silico* and preclinical data, as well as clinical studies, strengthen the analgesic, anti-inflammatory, antioxidant, and antiapoptotic evidence of *P. lactiflora* extracts and its secondary metabolites as a great potential for the treatment of PDN.

Especially, the major monoterpene glycoside paeoniflorin exhibits antinociceptive effects in various pain models. This effect is mainly mediated by the suppression of inflammatory cytokines, by downregulating the expression of ion channels TRPM8, TRPA1, TRPV1, and TRPV4, relevant for the generation of pain signals, and by reducing the neurotransmitter substance P. Similarly, the monoterpene glycoside albiflorin exhibits analgesic properties by decreasing ROS and inflammatory signaling through the inhibition of the NLRP3 inflammasome and of the transcription factor NF-*κ*B. Both, the phenolic compound paeonol and the flavonoid kaempferol alleviate painful diabetic neuropathy analogously by reducing neuroinflammation via the inhibition of NF-*κ*B and the subsequent suppression of inflammatory cytokines. In addition, they increase a protective function against reactive oxygen species by enhancing antioxidant enzymes. Furthermore, the steroid *β*-sitosterol demonstrates anti-inflammatory properties by inhibiting the TLR4 signaling pathway and thereby relieving neuropathic pain.

Altogether, these synergistic effects of *P. lactiflora* metabolites allow a simultaneous influence on the key features of the complex pathophysiology of PDN including inflammation, oxidative stress, and hyperexcitability of neuronal cells, thereby offering the advantage of a holistic therapy. In line, the multi-target therapeutic approach used in TCM for centuries confirms a high efficacy and low toxicity in clinical studies, suggesting that *P. lactiflora* and its constituents might be a specific treatment option with a low rate of adverse effects. Furthermore, since the side effects of local medications are generally less than those of systemic medications, the topical antinociceptive effect of paeoniflorin might serve as a promising basis for the development of topical formulations of isolated, biologically active secondary metabolites in the future.

However, given the use of herbal formulations in TCM, one limitation in the assessment of the effects of *P. lactiflora* for the treatment of PDN is the small number of clinical studies focusing exclusively on *P. lactiflora*. Considering this lack of sufficient clinical evaluations, the need for randomized controlled clinical trials to confirm the promising effects has been identified.

In addition to the summarized secondary metabolites directly isolated from the plant, the next logical step is the investigation of endophytic fungi from *P. lactiflora* that may significantly impact its therapeutic potential. Endophytic fungi symbiotically inhabit plants without harming the host, and some fungi have developed pathways analogous to their host, synthesizing bioactive compounds that were originally associated with the plant [115]. This has already been demonstrated for taxol, a chemotherapeutic agent first isolated from the Pacific yew and later from the endophyte *Taxomyces andreanae* [116], suggesting that not only the individual plant *P. lactiflora* but also associated endophytic fungi might be valuable resources for the isolation of pharmacologically active compounds targeting PDN in the future.

Contributors' Statement

Y.G. and V. W. carried out the literature search, data collection and interpretation, produced the first draft. N.T. was responsible for conceiving the topic, provided funding and supervision, as well as reviewed and edited the final draft. All authors approved the manuscript in its final form.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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