The Role of Saponins in the Neuropathic Pain

Subjects: Pharmacology & Pharmacy

Contributor: Bei Tan, Xueqing Wu, Jie Yu, Zhong Chen

Neuropathic pain is a chronic pain caused by tissue injury or disease involving the somatosensory nervous system, which seriously affects the patient's body function and quality of life. Saponins are a class of compounds with diverse structures, consisting of sapogenin and glycosyl groups. The common ones of the saccharides that make up saponins are D-glucose, D-galactose, D-xylose, L-arabinose, and L-rhamnose, etc.

Keywords: neuropathic pain ; saponins ; mechanism

1. Ginsenosides

Ginsenosides are the major biologically active components of *Ginseng*, which have a wide range of pharmacological activities. According to the skeleton of their aglycones, ginsenosides can be classified into two groups, tetracyclic triterpene dammarane-type saponins (protopanaxadiol (PPD)-, protopanaxatriol (PPT)-type) (**Figure 1**A) and tetracyclic triterpene oleanane-type saponins [1][2][3]. So far, more than 100 different ginsenoside monomers have been isolated, such as ginsenosides Rb1, Rb2, Rc, Rd, Re, Rg1, and Rf, the pharmacological and pharmacokinetic properties of which are different [4][5].

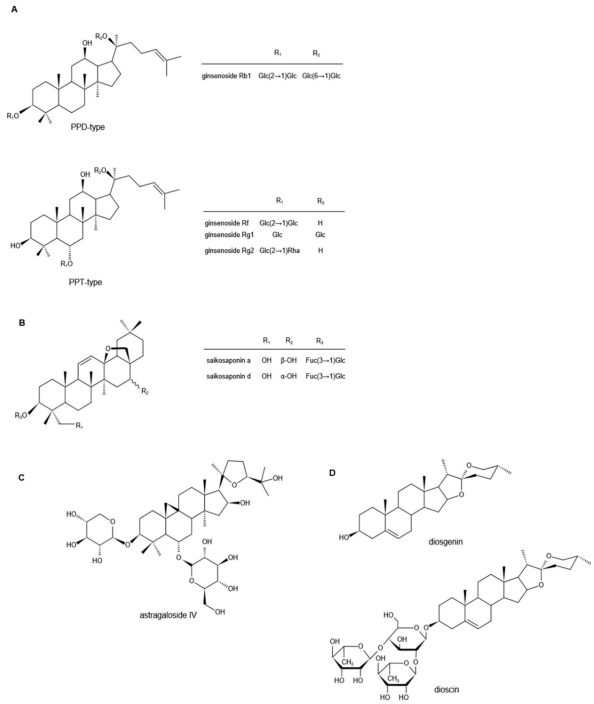

Figure 1. Chemical structures of ginsenosides (**A**), saikosaponins (**B**), astragaloside IV (**C**), and diosgenin and dioscin (**D**) (Note: PPD, protopanaxadiol; PPT, protopanaxatriol; Glc, glucoside; Rha, rhamnoside; Fuc, fructoside).

Data based on animal models have shown that ginsenosides play a beneficial role in neuropathic pain. In a study conducted by Jee Youn Lee et al. [6], peripheral and central neuropathic pain was induced by tail nerve injury or contusive spinal cord injury (SCI) in male SD rats, respectively. Remarkable analgesic effects were shown after the application of oral total saponin extract (TSE), ginsenoside Rb1. The research found that TSE and ginsenoside Rb1 inhibited the activation of microglia/astrocytes, and attenuated inflammatory factors levels, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). Further results demonstrated that TSE, ginsenoside Rb1, and Rb1-metabolite-compound, K, also exerted analgesic effects that might be mediated through the estrogen receptor. Other research conducted by Gao Chao et al. reported that intrathecal injection of ginsenoside Rg1 significantly inhibited chronic constrictive injury (CCI)-induced thermal hyperalgesia in a dose-dependent manner. It might

be mediated by inhibiting the expression of phosphorylated p38 mitogenactivated protein kinase (p-p38MAPK) and nuclear factor kappa-B (NF-κB) subunit phosphorylated p65, and the activation of ionized calcium binding adaptor molecule-1 (IBA-1) in the spinal microglia, resulting in downregulation of the central sensitization [7]. In addition, other studies showed that ginsenoside Rf robustly decreased IL-1β and IL-6, but increased the expression of IL-10 in the dorsal root ganglion (DRG), in both the spinal cord and DRG of CCI rats [8]. Thus, ginsenoside Rf may adjust the balance between proinflammatory and anti-inflammatory factors to promote its antinociceptive effect in neuropathic pain.

Many studies have revealed the key role of proinflammatory cytokines in the pathophysiology of neuropathic pain [9][10][11][12]. The above studies all explained that related ginsenosides inhibited inflammation through different pathways to relieve neuropathic pain. Furthermore, other studies have shown that ginsenoside Rb1 inhibits neuronal apoptosis [13] and promotes the neurogenesis and regulates the expressions of brain-derived neurotrophic factor (BDNF) and caspase-3 to play a neuroprotective effect [14]. On the other hand, clinically chronic pain patients are often accompanied by depression, and some depressive patients also have chronic somatic pain symptoms [15]. Therefore, the relationship between pain and the occurrence of depression has become the focus of recent studies. It has shown that intraperitoneal injection of ginsenoside Rg2 not only alleviates the mechanical allodynia and thermal hyperalgesia, but also relieves anxiety and depression in CCI rats [16], though its underlying mechanism needs to be further explored. So far, most of the analgesic mechanisms of ginsenosides in the neuropathic pain are limited to the exploration of inflammatory factors, lacking in-depth analysis of its targeted molecular targets. In addition, whether the regulatory effects of ginsenosides are related with different neuropathic pain-related brain regions is still largely unknown. Further studies focusing on these points may provide a research basis for the precise regulation of drugs.

2. Saikosaponins

Saikosaponins are derived from *Bupleurum* or *Bupleurum* scorzonerifolium in the *Umbelliferae*, one of the traditional Chinese herbal medicines, and are the main active ingredients of *Bupleurum* [17]. So far, more than 100 kinds of saikosaponins have been isolated from *Bupleurum*, the main ones of which are oleanane and ursolic pentacyclic triterpene saponins [18][19][20][21][22]. According to their chemical structure, saikosaponins are divided into -A, -B, -C, -D, -M, -N, -P, and -T categories, and Saikosaponin D (SSD) is considered to be the most active one, followed by Saikosaponin A (SSA) [23][24]. Their chemical structures are shown in **Figure 1**B.

Both in vivo and in vitro experimental studies have shown that saikosaponins can inhibit the activation of transient receptor potential ankyrin 1 (TRPA1) and significantly reduce the nociceptive response of animals induced by allyl isothiocyanate (AITC) [25]. Molecular docking and site-directed mutagenesis analyses demonstrated that saikosaponins bind to the TRPA1 hydrophobic pocket near the Asn855 residue, which once mutated to Ser and was previously united with enhanced pain perception in humans [25][26]. Gyeongbeen also reported that multiple administrations of SSD could significantly relieve mechanical hypersensitivity induced by vincristine, which was carried out partially by suppressing the activity of TRPA1 [25]. Therefore, it can be further speculated that SSD might play a certain therapeutic role in the neuropathic pain that is induced by chemotherapeutics, diabetes, or CCI, in which the expression and sensitivity of TRPA1 were changed as well, resulting in abnormal pain response and perception [27][28][29][30][31]. However, the analgesic effect of SSD is different between streptozotocin (STZ)- and paclitaxel-induced pain models. Short-term oral administration was effective in the former, while multiple administrations were required for the pain relief of the latter [32]. This indicates that the analgesic effect of SSD may not only act as an antagonist of TRPA1, but also exert anti-inflammatory activity to reduce the oxidative stress caused by nerve damage. Related research reported that SSD could restrain the translocation of the glucocorticoid receptor to the mitochondria, and decrease the H_2O_2-induced phosphorylation of extracellular-regulated kinase (ERK), c-Jun N-terminal kinase (c-JNK), and p38MAPK to downregulate the activity of neuronal PC12 cells [33][34][35].

It is well known that activation of NF-κB in both DRG and spinal cord neurons is associated with the transduction and processing of nociceptive messages. Therefore, inhibition of NF-κB can alleviate chronic painful states [36]. Studies have shown that SSA alleviates neuropathic pain by inhibiting CCI-induced elevation of p-p38 MAPK and NF-κB levels in the spinal cord [37]. In addition, cytokine dysregulation is one of the characteristic manifestations of neuropathic pain symptoms [38]. It could also be found that SSA significantly inhibited the expression of certain immune-related cytotoxic factors, including COX-2 and iNOS, and, likewise, the pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. Meanwhile, the expression of the important anti-inflammatory cytokine IL-10 was significantly upregulated, suggesting that it had anti-inflammatory activity in lipopolysaccharide (LPS)-stimulated macrophages [39][40]. Further research showed that SSA blocked the NF-κB signaling pathway by preventing phosphorylation of the NF-κB inhibitor α (IκBα), thereby allowing p65 NF-κB to remain in the cytoplasm, preventing it from translocating to the nucleus. In addition, SSA inhibited the MAPK signaling pathway by downregulating the phosphorylation of p38 MAPK, c-JNK, and ERK to exert the anti-inflammatory

activity [40]. On the basis, SSA appeared to counteract the neurological function deficits after traumatic brain injury via inbiting aquaporin-4 (AQP-4) and matrix metalloprotein-9 (MMP-9) to account for its neuroprotective effects [41]. On the other hand, a study of Seong Shoon Yoon et al. expressed that SSA exhibited a significant inhibitory effect on morphine-reinforced behavior and drug addiction predominantly via mediating GABAB receptors [42][43]. Davoud Ahmadimoghaddam et al. reported that *Bupleurum falcatum* L. roots essential oil, of which SSA was one of the main constituents [44], exerted its antinociceptive and antiallodynic effects through the regulation of L-arginine-NO-cGMP-KATP channel pathways, as well as interaction with opioid, peroxisome proliferator-activated, and cannabinoid receptors [44]. The voltage-gated sodium channel Nav1.7 is a tetrodotoxin-sensitive sodium channel subtype and is encoded by SCN9A. It is well known that the dysfunction of Nav1.7 has the correlation with pain disorders [45]. Relevant research showed that SSA displayed the analgesic effects on the thermal pain and formalin-induced pain in mice via strong inhibitory effect on the peak currents of Nav1.7 [46].

The above studies have shown that SSD and SSA can exert analgesic effects in different neuropathic pain models through multiple pathways, and their mechanisms of action have similarities and differences. In the follow-up, authors can combine their structural characteristics with the mechanisms of action for deep analysis to provide a research basis for the precise regulation of the targets.

3. Astragalosides

Astragali Radix, the dried roots of *Astragalus membranaceus* (Fisch.) Bge. *var. mongholicus* (Bge.) Hsiao, or *Astragalus membranaceus* (Fisch.) Bge., is known as a high-grade traditional Chinese medicine [47]. There are three main types of compounds in astragalus: saponins, flavonoids, and polysaccharides, and triterpene saponins are the major constituents [48][49][50]. It is reported that more than 40 kinds of saponins have been isolated and identified from the dried astragalus roots via HPLC and GC-MS, such as astragalosides I–VIII, acetylastragaloside, isoastragaloside I, III, astramembrannin II, cycloastragenol, cycloascauloside B, brachyoside B, astrasieversianin X, etc. [51][52][53][54]. Among these, astragaloside IV (AS-IV) is known as the major active ingredient and qualitative control biomarker. AS-IV is 3-*O*-beta-d-xylopyranosyl-6-*O*-beta-d-glucopyranosyl-cycloastragenol (**Figure 1**C), the molecular formula is $C_{41}H_{68}O_{14}$ [55].

It is generally accepted that the transient receptor potential vanilloid 1 (TRPV1) channel is a polymodal receptor for various stimuli such as noxious heat and capsaicin, and is also an important pain sensor [56][57]. TRPV1 is overexpressed in Aδ fibers and C fibers in the situation of inflammation or nerve injury [58]. In addition, purinergic P2 × 3 receptors are ligand-gated nonselective cation channels, highly selectively expressed in small-diameter and medium-diameter sensory neurons related to nociceptive information, and play a key role in the generation and maintenance of pathological pain [59] [60]. In the research by Guo-Bing Shi et al., AS-IV not only dramatically downregulated the expression of TRPV1 in Aδ fibers to remarkably upregulate the nociceptive threshold, but also inhibited P2 × 3 expression in DRG neurons to attenuate the mechanical allodynia [61]. Meanwhile, AS-IV restored the histological structure of the damaged sciatic nerve by accumulating glial cell-derived neurotrophic factor family receptorα1 (GFRα1), the glial cell derived neurotrophic factor (GDNF) selective receptor, in the debris of myelin between the Schwann cells and the damaged axon [61]. It also reduced the levels of GFRα1 and GDNF in DRG, which were highly expressed and induced by CCI, contributing to the restoration of injured nerve fibers [62][63].

In the peripheral nervous system, the appropriate dose of AS-IV could also greatly promote the regeneration of peripheral nerves [64]. Growth-associated protein 43 is lower in spinal cord segments L4–6 but active in growing neuronal axons in normal Balb/c mice. As a particular biomarker in nerve injury, it plays a vital role in nerve growth, and strongly associates with neuronal axon growth [55][65][66][67]. Previous research showed that AS-IV significantly upregulated the expression of growth-related protein 43 in regenerated nerve tissue, thereby increasing the number and diameter of myelinated nerve fibers in the sciatic nerve of mice, while elevating motor nerve conduction velocity and action potential amplitude [65]. Moreover, AS-IV also conducted analgesic effects on peripheral neuropathy in STZ-induced diabetic rats. Firstly, it reduced blood glucose and glycosylated hemoglobin (HbA_1C) levels, and increased plasma insulin levels in diabetic rats [68]. It is crucial to control the levels of HbA_1C because its concentration is closely related to the incidence of diabetes-related complications, which has been proven by clinical trials [69]. Secondly, AS-IV enhanced the activity of glutathione peroxidase in nerves, suppressed the activation of aldose reductase in erythrocytes, and decreased the accumulation of advanced glycation end products in both nerves and erythrocytes, which might not only activate the cellular antioxidant defense system, but also aggrandize the ability of antioxidative stress injury on peripheral nerves. Thirdly, AS-IV acted as the AR inhibitor, and then enhanced Na^+, K^+-ATPase activity, improved the delayed motor nerve conduction velocity, increased nerve blood flow, and prevented structural nerve fiber damage to correct peripheral nerve defects [68].

4. Diosgenin

Diosgenin is a naturally occurring steroidal sapogenin and is abundant in nature. Primary sources of diosgenin include the three *Dioscorea* species and one *Heterosmilax* species, namely, *D. zingiberensis*, *D. septemloba*, *D. collettii*, and *H. yunnanensis* [70]. Diosgenin can also be obtained from fenugreek (*T. foenum graecum Linn*) and *Costus speciosus* [71][72][73]. It is a C27 spiroketal steroid sapogenin, 3β-hydroxy-5-spirostene (**Figure 1**D), and its molecular formula is $C_{27}H_{42}O_3$ [74]. As a representational phytosteroid, diosgenin is an important basic raw material for the production of steroid hormone drugs and has received increasing attention in the pharmaceutical industry for decades [75]. In addition, diosgenin itself has a wide range of biological effects. The following studies mainly describe its role in neuropathic pain.

Neuropathic pain, one of the common complications of diabetes mellitus, manifests as increased sensitivity to noxious stimuli [76]. To evaluate the effects of diosgenin in the treatment of diabetes-induced neuropathic pain, an in vivo study was performed on a rat model of STZ-induced diabetes. It was demonstrated that diosgenin upturned mechanical and thermal nociceptive thresholds and lowered pain scores at the late phase of the formalin test in diabetic rats [77]. Since elevated oxidative stress is one of the key factors in diabetes-related neurological dysfunction, it can lead to vascular dysfunction, resulting in intraneural hypoxia, which can lead to impaired motor and sensory nerve function [78][79]. Studies showed that diosgenin could reduce the content of malondialdehyde (MDA) in serum, DRG, and sciatic nerve of diabetic rats and restored the activities of superoxide dismutase (SOD) and catalase, thereby inhibiting oxidative stress and enhancing the function of the antioxidant defense system [77]. Furthermore, NF-κB, an important nuclear transcription factor, is responsible for the control of genes encoding inflammation and nociception-related mediators [80]. Upregulation of NF-κB in the DRG neurons of diabetic rats has been proven, and its inhibition significantly reduces nociceptive responses [81][82][83]. It reported that diosgenin downregulated the NF-κB p65/p50 signaling pathway in the LPS-induced lung injury model [84]. However, based on the available reports, there is no specific experimental research regarding whether diosgenin exerts its analgesic effect in diabetes-induced neuropathic pain by regulating NF-κB, and related research needs to be further developed. Nerve growth factor (NGF), as a neurotrophic factor, is a protein factor that plays a vital role in the maintenance of the growth, development, and function of sympathetic and sensory neurons. It stimulates the axon growth, maintains the axon size, prevents the postinjury death of mature neurons, and regulates various functions of the nervous system, including synaptic plasticity and neurotransmission [85][86]. In diabetic neuropathy, the function of NGF is impaired and the expression of NGF-related genes is modified, which are important factors in the progress of diabetic neuropathic pain. A study conducted by Tong Ho KANG et al. revealed that diosgenin upregulated the level of NGF in the sciatic nerve of diabetic rats. The comparable effects also reported that diosgenin increased the neurite outgrowth of PC12 cells, enhanced the sciatic nerve conduction velocity of diabetic mice by inducing NGF, reduced myelin disturbance, increased the area of myelinated axons, and improved the signal transmission of damaged axons, thereby alleviating diabetic neuropathic pain [87].

In addition to the diabetic neuropathy model, the role of diosgenin in the treatment of neuropathic pain has also been reported in the CCI rat model. In 2017, Wei-Xin Zhao et al. performed an in vivo study, and the results demonstrated that diosgenin could upregulate CCI-reduced mechanical withdrawal threshold and thermal withdrawal latency. This was due to the fact that diosgenin not only inhibited CCI-induced elevation of proinflammatory cytokines TNF-α, IL-1β and IL-2, but also suppressed oxidative stress in the spinal cord. Moreover, diosgenin remarkably restrained the expression of p-p38 MAPK and NF-κB in the spinal cord and eased neuropathic pain in CCI rats by inhibiting the activation of p38 MAPK and NF-κB signaling pathways [88]. In other research [89], sciatic-crushed-nerve injury in rats decreased the sciatic function index, which was widely used to evaluate functional gait [90], increased the c-Fos expression in the ventrolateral periaqueductal gray and paraventricular nucleus, restrained recovery of locomotor function caused by the overexpression of BDNF, and aggrandized expressions of COX-2 and iNOS that responded to inflammation. Fortunately, diosgenin was able to significantly improve the above pathological states, and exploited potential abilities in pain control and functional recovery after peripheral nerve injury.

5. Saponin-Rich Extracts of *O. sanctum*

In addition to the analgesic effects of the above four plant saponins that have been identified with clear structures, saponin-rich extracts of *O. sanctum* have also been found with similar effects. *O. sanctum* is the aerial part of Ocimum basilicum, a plant of the Labiatae family. Modern pharmacological studies have illustrated that the chemical composition of *O. sanctum* is complex and the types are diverse, including volatile oils, flavonoids and their glycosides, coumarins, phenylpropanoids, and fatty acids, mainly volatile oils and flavonoids and their glycosides [91]. In addition, a variety of saponins have been isolated from the alcoholic extract of *O. sanctum* [92], the most important of which are pentacyclic triterpenoid saponins that are dominated by ursolic and oleanolic acids [93][94][95], and have a wide range of pharmacological effects.

Oxidative stress [96] and alterations in calcium homeostasis [97] are thought to be closely associated with neuropathic pain. During neurological disorders, dysfunction of the intracellular calcium regulatory system produces oxidative stress [98], and increases in free radicals lead to neuronal degeneration and apoptosis. On the other hand, metabolic abnormalities [99], formation of protein aggregates [100], and changes in membrane permeability [101] caused by oxidative stress all increase calcium levels, and they act together to promote the deterioration of neuropathic pain. *O. sanctum* has a good antioxidant effect [102][103], protects against free radical damage [104], and is able to reduce calcium levels [105]. *O. sanctum* is used as a neurotonic in parts of India for the relief of headache, joint pain, and muscle pain. In the experiments conducted by Muthuraman et al., the administration of *O. sanctum* attenuated sciatic nerve transection-induced peripheral neuropathy and motor in-co-ordination, attenuated the amputation-induced reduction in thiobarbituric acid reactive species, total calcium, and glutathione levels in a dose-dependent manner [105]. It suggested that the analgesic effect of *O. sanctum* might be related to its antioxidation and reduction of calcium levels. Additionally, in other studies, treatment with *O. sanctum* and its saponin-rich fraction reduced neuropathic pain caused by chronic constrictive injury and chemotherapeutic agent vincristine, associated with its effects on the oxidative stress and calcium levels [105][106]. Based on the above findings, it can be observed that the downregulation of calcium levels by *O. sanctum* administration may be due to a direct effect on or secondary to a decrease in oxidative stress. Then, it produces an antinociceptive or antiapoptotic effect on neurons. It has been reported that Saponins have antioxidant [107] and calcium lowering effects [108]. Thus, the antinociceptive effect of *O. sanctum* saponins may be constructed through direct or indirect reduction of calcium levels.

There is also evidence that *O. sanctum* leaves and seeds reduce uric acid levels in rabbits [109], and elevated uric acid levels are associated with gouty arthritis and other joint inflammation [110]. The ethanolic extract of *O. sanctum* can be antinociceptive, and involves the interaction of neurotransmitter systems such as opioid receptors and norepinephrine [111]. These studies support the traditional use of *O. sanctum* for the treatment of inflammation and pain, without excluding the effects of other active ingredients such as flavonoids and phenols.

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