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Traditional Chinese medicine and natural small molecules for pain treatment via voltage-gated sodium channels: a review

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Abstract

Background Voltage-gated sodium channels (VGSCs) are essential for generating and propagating action potentials in excitable cells. They are considered to be promising potential targets for analgesics acting on nociceptive neurons. However, the translation of animal model analgesic data to humans makes VGSCs-targeting analgesic drug development challenging. Starting with human experience to find analgesics can reduce such failures. Traditional Chinese medicine (TCM), a traditional medical system, has rich human experience of analgesics, which means many Traditional Chinese Medicine Herbs (TCMH) are worth exploring for analgesic drug development. However, studies of the analgesic mechanisms of TCMH need to be conducted at the cellular and molecular level for a VGSC perspective.

Purpose In this review, we provide an overview of the TCMH analgesics and molecules from TCMH, that act on VGSCs, especially subtype $Na_v1.3$, $Na_v1.7$, and $Na_v1.8$, along with a brief discussion on pharmaceutical potential for pain management. We also provide references for Chinese medicine to study pain relief mechanisms at the molecular level of sodium ion channels.

Methods Using Web of Science, the PubMed, and China National Knowledge Infrastructure databases, we conducted a comprehensive search of literature and data on TCMH and VGSCs published before October 2024.

Conclusion While $Na_v1.3$, $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ are involved in the development and maintenance of pain, $Na_v1.8$ can be studied as a potential drug target. The traditional Chinese medicine herbs involved sodium ion channels are primarily categorized into seven types, including 30 well-defined natural ingredients and 33 TCMH extracts. Studying the interactions between the components of TCMH is an important prerequisite for further exploration of how a specific analgesic TCM or TCM formula modulates ion channels or whether it binds to specific sites on these channels.

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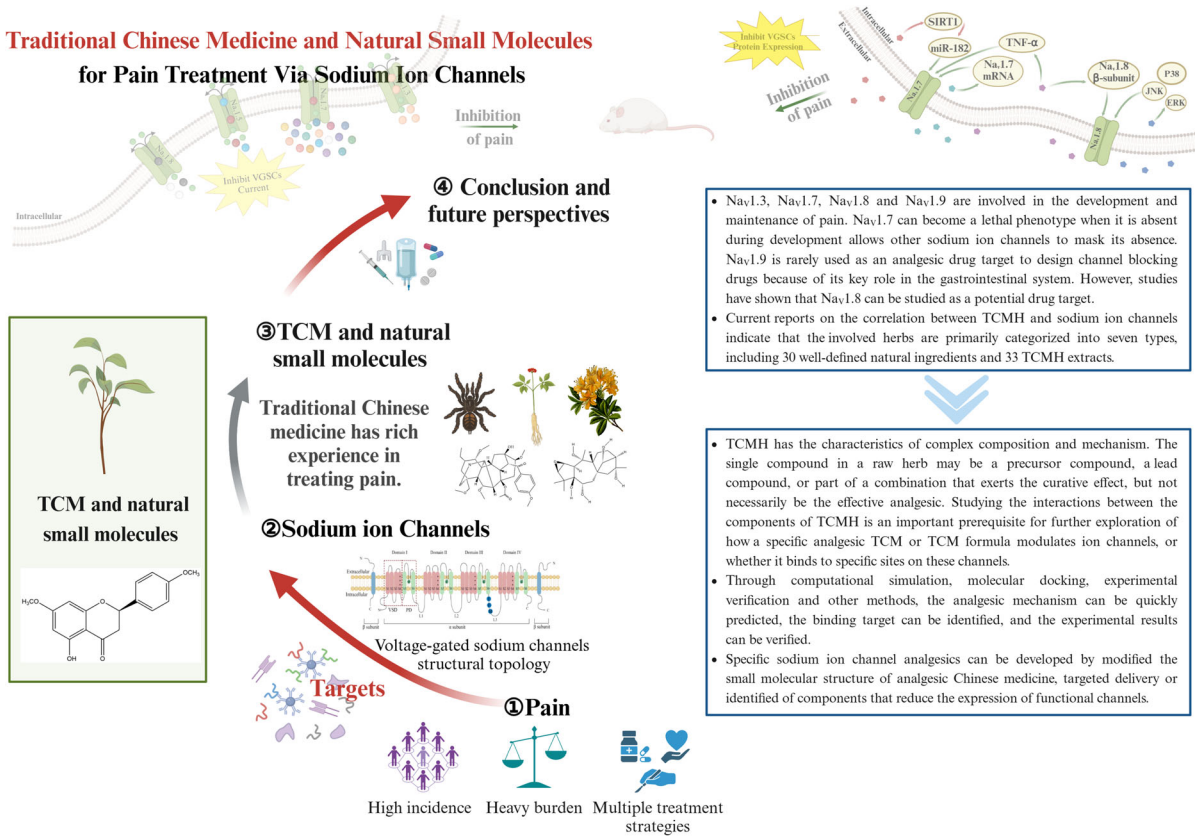
Graphic abstract



Keywords VGSCs · Pain · Traditional Chinese medicine · Herb medicine · Natural compound · Analgesic drug

Abbreviations

AGAP	Antitumor–analgesic peptide
Amm	*Androctonus mauretanicus mauretanicus*
ANEP	Anti-neuroexcitation peptide
BLA	Bulleyaconitine A
GJG	Goshajinkigan
HNTX-IV	Hainantoxin-IV
HWTX-IV	Huwentoxin-IV
JZTX-34	Jingzhaotoxin-34
LCA	Licochalcone A
MkTx-3	Makatoxin-3
NSAIDs	Non-steroidal anti-inflammatory drugs
PA	Processed aconite root
PDPN	Painful diabetic peripheral neuropathy
ProTxII	Protoxin-II
RJ-III	Rhodojaponin III
SNI	Spared nerve injury
Ssm6a	μ-SLPTX-Ssm6a
TCM	Traditional Chinese medicine
TCMH	Traditional Chinese medicine herbs
TTX	Tetrodotoxin
TTX-R	Tetrodotoxin-resistance
TTX-S	Tetrodotoxin-sensitive
VGSCs	Voltage-gated sodium channels

Introduction

The International Association for the Study of Pain define pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (Merskey and Bogduk 1994; Loeser and Melzack 1999). Pain is a common symptom of many disorders and a

common reason for a physician visit. Indeed, as an important survival mechanism to protect the body from harm, and promote healing of damaged tissues, the importance of pain perception is incontestable. However, pain syndromes resulting from chronic inflammatory disease or nerve damage seems to serve no useful function (Cregg et al 2010). Studies show that pain severely affects about half the population with a substantial number of people suffering daily intense pain (Sexton et al. 2018). Pain disorders have become the greatest clinical challenge of the age in terms of incidence and quality of life.

Since the beginning of modern era of pain research 80 years ago, analgesic drug development program has never stopped. The two major classes of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) acting on arachidonic acid metabolism, and opioids acting through endogenous G-protein-coupled receptor systems whilst useful, are often limited by side effects including tolerance, addiction, digestive tract hemorrhage and so on (Cregg et al. 2010). For instance, opioids are frequently and inappropriately prescribed for chronic pain and this led to an epidemic of opioid addiction. Over 80,000 individuals died of opioid overdoses in the United States alone in 2021, creating a tragedy of enormous proportions (Haroun et al. 2023). NSAIDs are reported for their adverse effect on inhibiting osteoblast growth and so on (Díaz-Rodríguez et al. 2012). Thus, to tease out distinct mechanisms of pain and tractable analgesic drug targets thereby developing new analgesic drugs and analgesic program has become an urgent problem to be solved.

Distinct types of sensory neurons can be distinguished based on immunocytochemical differences. Moreover, the expressed transcriptome in different types of neurons can be provided by RNA sequencing. Cell surface ion channels have been teased out as tractable drug targets, especially voltage-gated sodium channels (VGSCs) to control pain (Momin and Wood 2008). However, the uncertain animal-to-human translation keeps the data application of animal models to human pain pathology for analgesic drug development challenging. For instance, antagonists of substance P acting at the NK1 receptor are analgesic in mice but not humans (Raouf et al. 2010; Hill 2000). This problem might be solved using ancient clinical experience, for many traditional medical systems have been handed down based on human experience, rather than animal models.

Traditional Chinese medicine (TCM), an ancient medicine, has a long history of more than 2000 years in treating pain syndromes since the classic Huangdi Neijing was written, in Warring States period of the Qin and Han dynasties of ancient China. Traditional Chinese Medicine Herbs (TCMH) and acupuncture are all effective approaches to treat pain syndromes. Importantly, this is based on human experience. Therefore, a lot of TCMH are worthy of our attention and exploration for the treatment of pain. Indeed, abundant studies demonstrated some TCMH have the ability to relieve pain perception, for instance, the TCMH alkaloid and saponin components. Some of this research is at the cellular and VGSC molecular level. However, most research on the analgesic mechanism of traditional Chinese medicine are only at the behavioral or tissue level, and need molecular understanding.

In this review, we discuss the main types of sodium ion channels that may be tractable analgesic drug targets, and the current research progress of TCM focusing on sodium ion channels for analgesia. The results provide clues for the development of novel drugs targeting VGSCs in TCMH and in natural ingredients.

Pain incidence, burden, treatment principle

According to the China pain Medicine Development report (2020), the number of chronic pain patients in China is more than 300 million, and is increasing at an annual rate of 10 million to 20 million (Ai et al. 2023). A systematic review comprising studies done in the UK reported a pooled chronic pain prevalence rate of 43.5%, with the rate of moderate-to-severe disabling pain ranging from 10.4 to 14.3% (Cohen et al. 2021; Fayaz et al. 2016). A newer report found the average cost per year for one of the 15.4% of Australian people living with chronic pain to be AU$22,588-$42,979, when non-financial costs were considered (Ai et al. 2023). In America, chronic pain affects 116 million adults, that is more than one in three Americans, and the number is greater than the total of heart disease, cancer, and diabetes combined, costing between US$560 and US$635 billion per year in medical costs and lost productivity (Steglitz et al. 2012).

Pain is a complex multi-dimensional experience involving physical, psychological and social factors. It can be categorized as nociceptive (from tissue injury), neuropathic (from nerve injury), or nociplastic (from a sensitised nervous system) (Cohen et al. 2021), and many experts consider pain classification as a continuum because in practice there is considerable overlap in the different types of pain mechanisms within and between patients. The principle of personalized multimodal, interdisciplinary in clinical treatment is recommended. The common treatment strategies for pain include drug therapy, psychological therapy, surgery/interventional therapy, physiotherapy, adjuvant replacement therapy, and self-help strategies (Ai et al. 2023), and combined use of the above strategies, to formulate personalized treatment plans achieves the best treatment effect.

Pain and voltage-gated sodium channels

Noxious thermal, mechanical and chemical stimuli induce electrical signaling from nociceptors-specialized peripheral sensory neurons. These modality-specific sets of nociceptors respond to these stimuli to activate pain pathways in the central nervous system (Abrahamsen et al. 2008). VGSCs are crucial determinants of electrical signaling transduction and transmission in nociceptors, playing a central role in chronic pain.

Molecular studies revealed that the class of VGSCs comprise 10 pore forming α-subunits and 4 auxiliary β-subunits. The β-subunits modulate the localization, expression and functional properties of α-subunits (Isom 2001; Nassar et al. 2005). The α-subunits of human VGSCs are 1500-2000 amino acids in length and consist of four homologous repetitive domains DI-IV, being connected by three intracellular loops, L1-L3, between domains. Each domain has six transmembrane segments, S1-S6. The four amino acid motifs (DEKA) from DI-IV constitute the ion selective filter, while within L3 is the key inactivation gating region. With the change of membrane potential, there are three states of VGSCs, resting state, active state and inactivated state (Fig. 1).

The VGSCs gene family comprises nine homologous members SCN1A to SCN11A, which encode the sodium selective ion channels $Na_V1.1$ to $Na_V1.9$. Nax, encoded by SCN6A/SCN7A, though structurally related to VGSCs, is not activated by membrane depolarization, but rather by altered sodium concentrations (Eijkelkamp et al. 2023). Many natural neurotoxins are blockers of Na_V channels, such as Tetrodotoxin (TTX) (Agnew et al. 1980; Akopian et al. 1996), that can physically block voltage-gated extracellular channel pores of sodium channels. The subtypes of VGSCs family can be divided into two categories by its sensitivity to TTX blocking, TTX-S (sensitive) such as $Na_V1.1$, 1.2, 1.3, 1.4, 1.6, 1.7 with TTX IC50 < 30 nM, and TTX-R (resistance), including $Na_V1.5$, 1.8 and $Na_V1.9$ with TTX IC50 > 30 nM. Different subtypes with a specific distribution are enriched in distinct tissues (Fig. 2).

It is clear that VGSCs play a pivotal role in chronic pain and other disorders such as epilepsy, muscle and immune disorders, cardiovascular complications, cancer, neurodegeneration, multiple sclerosis, autism and so on (Eijkelkamp et al. 2012; Wood and Iseppon 2018) (Table 1). Different VGSC α-subunits have distinct pharmacological properties. $Na_V1.1$ and $Na_V1.2$ mutations are genetically linked to epilepsy and related central nervous system diseases (Sourbron et al. 2017; Lauxmann et al. 2013). Periodic paralysis and five hereditary sodium channelopathies of skeletal muscle, hyperkalaemic periodic paralysis, hypokalaemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonia and congenital myasthenic syndrome, are caused by $Na_V1.4$ mutations (Eijkelkamp et al. 2012; Jurkat-Rott et al. 2010). Several syndromes leading to sudden cardiac death have been linked to mutations in $Na_V1.5$ (Eijkelkamp et al. 2012). $Na_V1.6$ knockout mice exhibit a range of motor disorders including tremor, ataxia, dystonia and paralysis, as well as sleep pattern disorders such as chronic impairment of REM sleep and enhanced spatial memory (Papale et al. 2010). $Na_V1.8$ may play an important role in the regulation of the expression of $Na_V1.5$ and Brugada syndrome (Wood and Iseppon 2018; Hu et al. 2014). The existence of $Na_V1.3$, $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ in human and animal sensory neurons has aroused people's interest in their potential role in pain transmission (Baker and Wood 2001; Zhang et al. 2013). Targeting different VGSC subtypes as a route to treating different types of pain is attractive. Nowadays, many studies on TCMH analgesic effects also revealed their mechanism of blocking sodium ion channels to treat pain disorders.

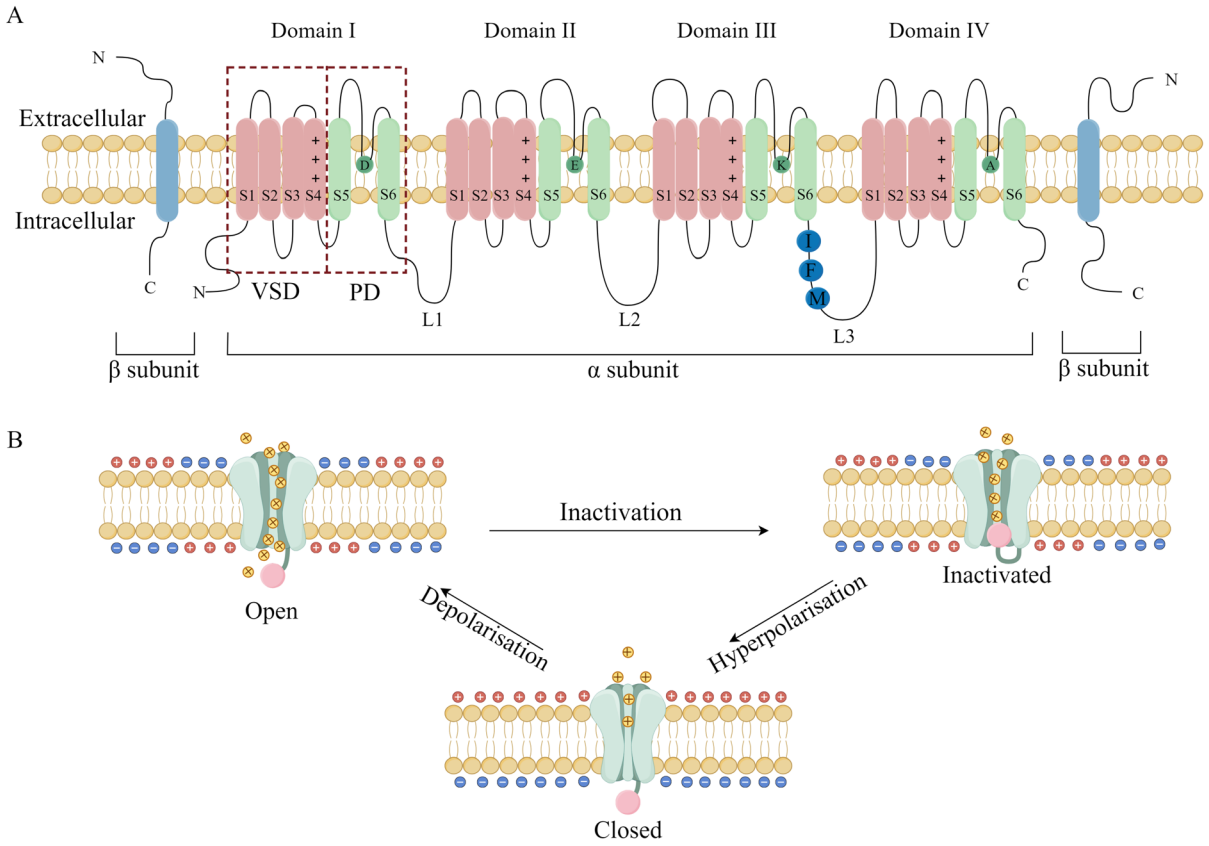


Fig. 1 Overall structures of voltage-gated sodium channels and the typical open-inactivated-closed cycle. **A** VGSCs structural topology; **B** typical gating mechanism of VGSCs (Created with *www.figdraw.com*)

Traditional Chinese medicine mediates voltage-gated sodium channels to treat pain disorder

Traditional Chinese medicine and pain

Pain is one of the important fields of TCM treatment. In TCM theory, the occurrence of pain is closely related to the obstruction of Qi (force) and blood, the blockage of meridians and the disorder of Zang-Fu organs. TCM emphasizes more fundamentally relieving pain by adjusting the balance of the whole body rather than relieving symptoms. Meanwhile, the TCMH for treating pain mostly belongs to wind-dampness dispelling herbs, interior-warming herbs, wind-dispelling and antispasmodic herbs, blood-activating and stasis-resolving herbs, tonifying herbs, exterior-releasing herbs, etc. All the names represent a series of herbal medicines in TCM. Therefore, looking for analgesic drugs from the TCMH resource bank can also focus on these herbs. Since the efficacy and mechanism of TCMs needs to be better understood with modern technology, there are an increasing number of studies conducted on the molecular and cellular levels for TCM analgesia effect, especially concerning VGSCs (Table 2).

Focusing on $Na_V1.3$ to treat pain disorders

$Na_V1.3$ is widely expressed in the central nervous system and is important for neuronal development. The expression of $Na_V1.3$ mRNA in DRG is high in embryonic but is much lower in adult rats, and it is expressed at higher levels in the developing nervous system than in adults (Luiz and Wood 2016; Hains and Waxman 2007). Research suggests that the $Na_V1.3$ channel may play a role in the pathogenesis of neuropathic pain, migraine, and epilepsy (Wood et al. 2002; Boucher et al. 2000). Wind-damp dispelling herbs and interior-warming herbs are commonly used in TCM to treat epilepsy, rheumatoid

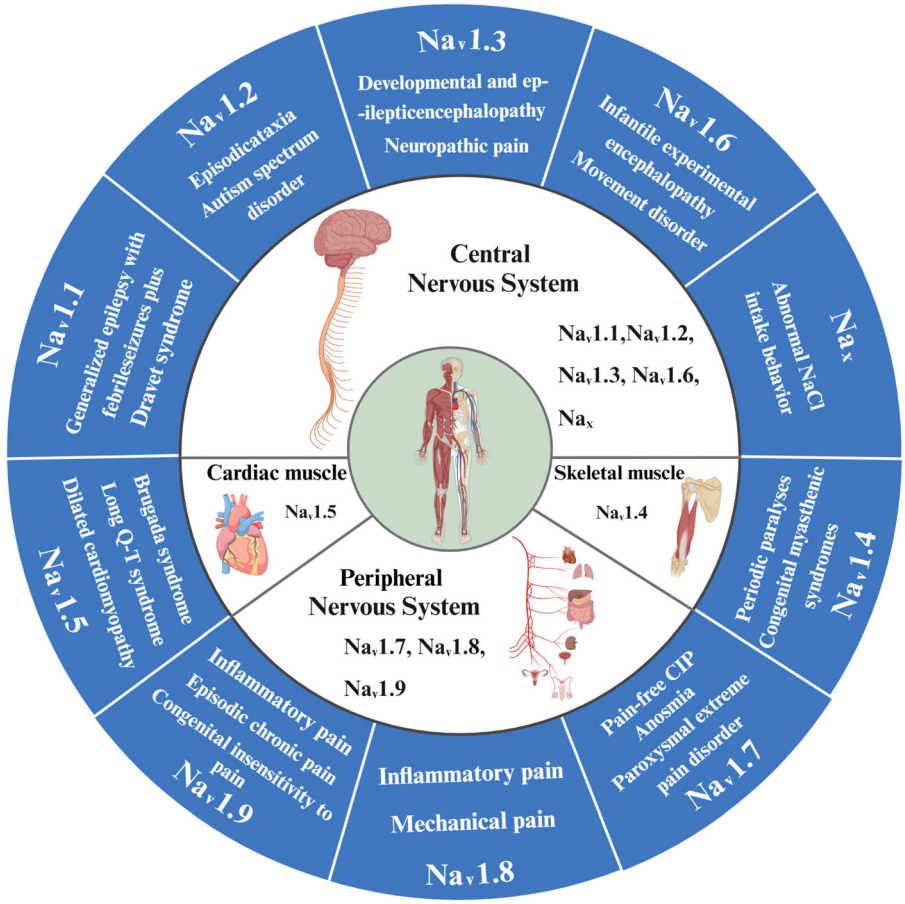


Fig. 2 Schematizes the tissue distribution of human VGSCs α-subunits (Created with *app.biorender.com*)

arthritis, and related pain. ACONITI KUSNEZOFFII RADIX (Cao Wu in Chinese, dried root tuber of *Aconitum kusnezoffii* Reichb.) and ACONITI RADIX (Chuan Wu in Chinese, dried taproot of *Aconitum carmichaelii* Debx.) are wind-dampness dispelling herbs. ACONITI LATERALIS RADIX PRAEPARATA (Fu Zi in Chinese, dried lateral root products of *Aconitum carmichaelii* Debx.) is an interior-warming herb. They are traditionally used to treat chronic pain and rheumatoid arthritis in China. Bulleyaconitine A (BLA) (Fig. 3(1)), a diterpenoid alkaloid with the site-2 neurotoxin pharmacological property, is a component extracted from *Aconitum* herbs. Cryo-EM combined with electrophysiological research reveal its mechanism for the modulation of $Na_V1.3$. BLA access to the receptor site is likely through the open activation gate where it binds to the highly conserved central cavity. The P-loops and S6 helices from DI and DII tightly pack the receptor site for BLA. Once bound, BLA stabilizes the open conformation of S6 helices from both DI and DII, and prevents them shifting back to a closed conformation. Meanwhile the entrance of the bulky BLA blocks the ion path, and the peak current is reduced. Therefore, BLA can strongly reduce neuronal Na^+ currents with effects on pain disorders (Li et al. 2022; Yang et al. 2023; Wang et al. 2007). Other research shows that BLA use-dependently blocks $Na_V1.3$, $Na_V1.7$ but not Nav1.8 at IC50 concentrations. The strongest effect is observed on $Na_V1.7$, less on $Na_V1.3$. This selective use-dependent blockage character explains the anti-neuropathic pain effect of BLA (Xie et al. 2018).

$Na_V1.7$ and pain disorders

$Na_V1.7$ is expressed in peripheral sensory neurons innervating the skin, viscera and orofacial region (dorsal root and trigeminal ganglia) as well as

Table 1 The present state of knowledge of VGSCs

Channel	Gene	Hox genes	Chromosome	Major expression	Expression in DRG	Pharmacological Features				
						Activators	Blockers	TTX-S/R	TTX IC50	Features
$Na_V1.1$	SCN1A	HoxD	2q24	CNS	Present	Veratridine Batrachotoxin	TTX (10 nM) Saxitoxin	TTX-S	10 nM	Fast inactivation(0.7 ms)
$Na_V1.2$	SCN2A	HoxD	2q23-24	CNS	Present	Veratridine Batrachotoxin	μ-Conotoxin (SIIIA) TTX (10 nM) Saxitoxin	TTX-S	10 nM	Fast inactivation (0.8 ms)
$Na_V1.3$	SCN3A	HoxD	2q24	CNS	Up-regulated in axotomy	Veratridine Batrachotoxin	TTX (2–15 nM) Saxitoxin	TTX-S	10 nM	Fast inactivation (0.8 ms)
$Na_V1.4$	SCN4A	HoxB	17q23-25	Skeletal muscle	Absent	Veratridine Batrachotoxin	μ-Conotoxin (GIIIA and PIIIA) TTX (5 nM) Saxitoxin	TTX-S	10 nM	Fast inactivation (0.6 ms)
$Na_V1.5$	SCN5A	HoxA	3p21	Cardiac muscle	Absent	Veratridine Batrachotoxin	TTX (2 μM)	TTX-R	1-10 μM	Fast inactivation (1 ms)
$Na_V1.6$	SCN8A	HoxC	12q13	CNS	Abundant	Veratridine Batrachotoxin	TTX (6 nM) Saxitoxin	TTX-S	< 10 nM	Fast inactivation (1 ms)
$Na_V1.7$	SCN9A	HoxD	2q24	PNS	Abundant	Veratridine Batrachotoxin	TTX (4 nM) Saxitoxin ProTx-II (0.3 nM)	TTX-S	10 nM	Fast inactivation (0.5 ms)
$Na_V1.8$	SCN10A	HoxA	3p21-24	PNS	Abundant	–	μO- Conotoxin MrVIB TTX (60 μM)	TTX-R	> 10 nM	Slow inactivation (6 ms)
$Na_V1.9$	SCN11A	HoxA	3p21-24	PNS	Abundant	–	TTX (40 μM)	TTX-R	1 μM	Slow inactivation (16 ms)
Na_X	SCN7A	HoxD	2q21-23	Circumventricular organs	Present	–	–	–	–	Concentration sensitive
β_1	SCN1B	–	–	CNS, Cardiac muscle	–	–	–	–	–	–
β_2	SCN2B	–	–	PNS	–	–	–	–	–	–
β_3	SCN3B	–	–	CNS, Cardiac muscle, Skeletal muscle	–	–	–	–	–	–
β_4	SCN4B	–	–	CNS, PNS	–	–	–	–	–	–

Table 1 continued

Channel	Function	Pain type	Diseases or syndromes	References
$Na_V1.1$	Participating in the inhibitory neural network	–	Dravet syndrome, Generalized epilepsy with febrileseizures plus, Febrile seizures, Developmental and epilepticencephalopathy, Familial hemiplegic migraine, Autism spectrum disorder	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Meisler et al. (2021); Zayat et al. (2022); Cummins et al. (2004); Krueger and Berg (2015); Fan et al. (2016); Spampanato et al. (2001)
$Na_V1.2$	Participating in the backward propagation of action potential	–	Benign familial neonatal seizures, Episodicataxia, Developmental and epilepticencephalopathy, Autism spectrum disorder, Intellectual disability, Generalized epilepsy with febrileseizures plus, Dravet syndrome	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Meisler et al. (2021); Liao et al. (2010); Spratt et al. (2019); Schwarz et al. (2019)
$Na_V1.3$	Participating in the brain development	NP	Familial focal epilepsy with variable foci, Developmental and epilepticencephalopathy, Neuropathic pain	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Zayat et al. (2022)
$Na_V1.4$	Participating in the muscle fiber contraction	–	Congenital myasthenic syndromes, Hyperkalemic periodic paralysis, Hypokalemic periodic paralysis, Normokalemic periodic paralysis, Myotonia congenita, Sudden infant death syndrome	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Zayat et al. (2022); Maggi et al. (2021); Männikkö et al. (2018)
$Na_V1.5$	Participating in the regulation of heart rhythm	–	Long Q-T syndrome, Brugada syndrome, Dilated cardiomyopathy, Familial atrial fibrillation, Heart block, Sick sinus syndrome, Progressive cardiac conduction defect, Arrhythmogenic right ventricular cardiomyopathy, Sudden unexpected death in epilepsy, Multiple sclerosis, Breast cancer	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Remme (2023); Lyu et al. (2023); Emery et al. (2016); Yuan et al. (2019); O'Malley et al. (2019); Patino et al. (2011); Liao et al. (2010); Krueger and Berg (2015); Fan et al. (2016); Spratt et al. (2019); Schwarz et al. (2019); Frosio et al. (2023); Remme (2013); Zou et al. (2019)
$Na_V1.6$	Participating in the initiation and transmission of action potential	MP	Cognitive impairment, Developmental and epilepticencephalopathy, Benign familial neonatal seizures, Mental retardation, Marie ataxia, Intellectual disability, Movement disorder, Autism spectrum disorder, Pancerebellar atrophy, Infantile experimental encephalopathy	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a, b, c); Meisler et al. (2021); Lyu et al. (2023)
$Na_V1.7$	Responsible for sensory conduction	IP, NP	Primary erythromelalgia, Paroxysmal extreme pain disorder, Small fiber neuropathy, Congenital insensitivity to pain, Anosmia	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Meisler et al. (2021); Emery et al. (2016); Zheng et al. (2018)

Table 1 continued

Channel	Function	Pain type	Diseases or syndromes	References
$Na_V1.8$	Responsible for sensory conduction	IP, NP	Paroxysmal extreme pain disorder, Pain noxious heat and cold, Small fiber neuropathy	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Emery et al. (2016)
$Na_V1.9$	Responsible for sensory conduction	IP	Paroxysmal extreme pain disorder, Sensory and autonomic neuropathy, Inflammatory pain, Peripheral neuropathy, Congenital insensitivity to pain, Episodic chronic pain	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Meisler et al. (2021); Emery et al. (2016)
Na_X	–	–	Abnormal NaCl intake behavior	Eijkelkamp et al. (2012); Luiz and Wood (2016); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a)
β_1	–	–	Dravet syndrome, Brugada syndrome, Atrial fibrillation, Generalized epilepsy with febrileseizures plus	Eijkelkamp et al. (2012); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Meisler et al. (2021); Remme (2023); Emery et al. (2016); Yuan et al. (2019); O'Malley et al. (2019); Patino et al. (2011); Spratt et al. (2019); Remme (2013)
β_2	–	–	Atrial fibrillation	Eijkelkamp et al. (2012); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a), Remme (2013)
β_3	–	–	Idiopathic ventricular fibrillation, Atrial fibrillation, Brugada syndrome, Sudden infant death syndrome	Eijkelkamp et al. (2012); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Remme (2013)
β_4	–	–	Long Q-T syndrome, Sudden infant death syndrome, Atrial fibrillation	Eijkelkamp et al. (2012); Wood et al. (2002); Wu (2023); Yan et al. (2017); Goldin (2001); Yang et al. (2019); Meng et al. (2011); Xie et al. (2013); Liu et al. (2012a); Remme (2023); Remme (2013)

DRG, Dorsal root ganglia; TTX-S, Tetrodotoxin-sensitive; TTX-R, Tetrodotoxin-resistant; IC50, Half maximal inhibitory concentration; CNS, Central nervous system; PNS, Peripheral nervous system; NP, Neuropathic pain; MP, Mechanical pain; IP, Inflammatory pain

Table 2 Present studies of analgesic traditional Chinese medicine herbs and their interactions with voltage-gated sodium channels

Channel	Name of TCMH	Scientific name	Chemical Composition	Attribute of Composition	Attribute of TCM	Binding Sites	Types of Pain	References
$Na_V1.3$	*Aconitum* plants;	–	Bulleyaconitine A	Alkaloids	Wind-dampness dispelling herbs, Interior-warming herbs, etc	The P-loops and S6 helices from DI and DII	Neuropathic pain	Li et al. (2022); Yang et al. (2023); Wang et al. (2007); Xie et al. (2018)
$Na_V1.7$	Lao Guan Cao	*Erodium stephanianum* willd *Geranium wilfordii* Maxim *Geranium carolinianum* L	Geraniol	Terpenes	Wind-dampness dispelling herbs	–	Neuropathic pain	Xing et al. (2017)
$Na_V1.7$	Nao Yang Hua	*Rhododendron molle* G. Don	Rhodojaponin III	Terpenes	Wind-dampness dispelling herbs	–	Nociceptive & neuropathic pain	Yang et al. (2022)
$Na_V1.7$	Chuan Shan Long	*Dioscorea nipponica* Makino	Dioscin	Steroids	Wind-dampness dispelling herbs	–	Neuropathic pain (Painful diabetic peripheral neuropathy)	Leng et al. (2018)
$Na_V1.7$	Can Sha	*Bombyx mori* Linnaeus	Phytol	Terpenes	Wind-dampness dispelling herbs	–	Neurovascular headache (Migraine)	Song et al. (2023)
$Na_V1.7$	*Aconitum* plants; Chuan Wu, Fu Zi, Cao Wu, etc	*Aconitum carmichaelii* Debx *Aconitum kusnezoffii* Reichb	Neoline	Alkaloids	Wind-dampness dispelling herbs, Interior-warming herb, etc	–	Neuropathic pain	Nakatani et al. (2020)
$Na_V1.7$	Zhe Bei Mu, Chuan Bei Mu, Ping Bei Mu	*Fritillaria thunbergii* Miq. *Fritillaria cirrhosa* D.Don *Fritillaria unibracteata* Hsiao et K. C. Hsia *Fritillaria przewalskii* Maxim. *Fritillaria delavayi* Franch. *Fritillaria taipaiensis* P. Y. Li *Fritillaria unibracteata* Hsiao et K. C. Hsiavar. Wabuensis (S. Y. Tang et S. C. Yue) Z. D. Liu, S. Wang et S. C. Chen *Fritillaria ussuriensis* Maxim	Peimine	Alkaloids	Phlegm-resolving herbs	–	–	Xu et al. (2016)

Table 2 continued

Channel	Name of TCMH	Scientific name	Chemical Composition	Attribute of Composition	Attribute of TCM	Binding Sites	Types of Pain	References
$Na_V1.7$	Chai Hu	*Bupleurum chinense* DC. *Bupleurum scorzonerifolium* Willd	Saikosaponin A	Saponins	Exterior-releasing herbs	–	Thermal pain & inflammatory pain	Xu et al. (2021)
$Na_V1.7$	Du Huo	*Angelica pubescens* Maxim. f. *biserrate* Shan et Yuan	Imperatorin	Phenylpropanoids	Wind-dampness dispelling herbs	–	Thermal pain & inflammatory pain	Xu et al. (2021)
$Na_V1.7$	Gan Cao	*Glycyrrhiza uralensis* Fisch. *Glycyrrhiza inflata* Bat. *Glycyrrhiza glabra* L	Licochalcone A	Flavonoids	Tonifying herbs	–	Inflammatory pain	Zhao et al. (2023b)
$Na_V1.7$	Ge Gen	*Pueraria lobata* (Willd.) Ohwi	Puerarin	Isoflavonoids	Exterior-releasing herbs	–	Neuropathic pain	Zhang et al. (2023)
$Na_V1.7$	Wu Wei Zi	*Schisandra chinensis* (Turcz.) Baill	Schisandrin B	Phenylpropanoids	Astringing herbs	–	Inflammatory pain	Zhao et al. (2024)
$Na_V1.7$	Vitaceae, Moraceae plants, etc	/	Resveratrol	Polyphenols	–	–	Neuropathic pain	Li et al. (2016b); Cao et al. (2003); Jia et al. (2020)
$Na_V1.7$	Quan Xie	*Buthus martensii* Karsch	MkTx-3	Peptides	Wind-dispelling and antispasmodic herbs	DIV S3-S4	Inflammatory pain	Chen et al. (2022)
$Na_V1.7$	Fei Wei Xie	*Androctonus australis*	AaH II	Peptides	Wind-dispelling and antispasmodic herbs	DIV S3-S4	–	Abbas et al. (2013)
$Na_V1.7$	Fei Wei Xie	*Androctonus mauritanicus*	Amm VIII	Peptides	Wind-dispelling and antispasmodic herbs	DIV S3-S4	–	Abbas et al. (2013)
$Na_V1.7$	Quan Xie	*Buthus martensii* Karsch	ANEP	Peptides	Wind-dispelling and antispasmodic herbs	DII S3-S4	Peripheral pain	Song et al. (2017)
$Na_V1.7$	Quan Xie	*Buthus martensii* Karsch	BmKBTx	Peptides	Wind-dispelling and antispasmodic herbs	–	–	Lin et al. (2017)

Table 2 continued

Channel	Name of TCMH	Scientific name	Chemical Composition	Attribute of Composition	Attribute of TCM	Binding Sites	Types of Pain	References
$Na_V1.7$	Quan Xie	*Buthus martensii* Karsch	BmNaL-3SS2	Peptides	Wind-dispelling and antispasmodic herbs	–	–	Lin et al. (2017)
$Na_V1.7$	Wu Gong	*Scolopendra subspinipes mutilans* L. Koch	Ssm6a	Peptides	Wind-dispelling and antispasmodic herbs	–	Thermal pain	Yang et al. (2013)
$Na_V1.7$	Zhi Zhu	*Chilobrachys jingzhao*	JZTX-34	Peptides	–	DII S3-S4	–	Zeng et al. (2018)
$Na_V1.7$	Zhi Zhu	*Thrixopelma pruriens*	ProTx-II	Peptides	–	DII S3-S4	–	Zeng et al. (2018)
$Na_V1.7$	Zhi Zhu	*Grammostola rosea*	GpTX-1	Peptides	–	–	–	Murray et al. (2015)
$Na_V1.8$	Xi Nan Ye Mu Gua	*Stauntonia brachyanthera* Hand. - Mazz	YM11	Terpenes	Wind-dampness dispelling herbs	–	Thermal pain & inflammatory pain	Meng et al. (2017)
$Na_V1.8$	Xi Nan Ye Mu Gua	*Stauntonia brachyanthera* Hand. - Mazz	EtOH extracts of *Stauntonia brachyanthera*	–	Wind-dampness dispelling herbs	–	Thermal pain & inflammatory pain	Meng et al. (2017)
$Na_V1.8$	Gan Song	*Nardostachys jatamansi* DC	(-)-NRG-DM	Flavonoids	Qi-regulating herbs	–	Inflammatory pain	Gu et al. (2022)
$Na_V1.8$	Ge Gen	*Pueraria lobata* (Willd.) Ohwi	Puerarin	Isoflavonoids	Exterior-releasing herbs	–	Neuropathic pain & chemotherapy-associated pain	Zhang et al. (2018)
$Na_V1.5$, 1.7	Lei Gong Teng	*Tripterygium wilfordii* Hook. f	Triptolide, Celastrol, Demethylzeylasteral	Terpenes	Wind-dampness dispelling herbs	–	Inflammatory & nociceptive pain	Xu et al. (2023)
$Na_V1.5$, 1.7	Lei Gong Teng	*Tripterygium wilfordii* Hook. f	Wilforgine	Alkaloids	Wind-dampness dispelling herbs	–	Inflammatory & nociceptive pain	Xu et al. (2023)
$Na_V1.5$, 1.7	Yan Hu Suo	*Corydalis yanhusuo* W.T. Wang	Dihydrosanguinarine	Alkaloids	Blood-activating and stasis-resolving herbs	–	–	Sun et al. (2022)

Table 2 continued

Channel	Name of TCMH	Scientific name	Chemical Composition	Attribute of Composition	Attribute of TCM	Binding Sites	Types of Pain	References
$Na_V1.5$, 1.7	Yan Hu Suo	*Corydalis yanhusuo* W.T. Wang	Dihydrochelerythrine	Alkaloids	Blood-activating and stasis-resolving herbs	–	–	Sun et al. (2022)
$Na_V1.7$, 1.8	Tian Ma	*Gastrodia elata* Bl	Gastrodin	Glycosides	Wind-dispelling and antispasmodic herbs	–	Neuropathic pain	Wang et al. (2021)
$Na_V1.2$, 1.3,1.7	Zhi Zhu	*Ornithoctonus huwena*	HWTX-IV	Peptides	–	DII S3-S4	–	Xiao et al. (2008)
$Na_V1.2$, 1.3,1.7	Zhi Zhu	*Ornithoctonus hainana*	HNTX-IV	Peptides	–	DII S3-S4	–	Liu et al. (2012b)
$Na_V1.4$, 1.5, 1.7, 1.8	Quan Xie	*Buthus martensii* Karsch	AGAP	Peptides	Wind-dispelling and antispasmodic herbs	–	Viscera and soma pain	Xu et al. (2017)
$Na_V1.2$, 1.3, 1.4, 1.5, 1.6	Zhi Zhu	*Phoneutria nigriventer*	PnTx4(5–5)	Peptides	–	–	Inflammatory & nociceptive pain	Oliveira et al. (2019)
$Na_V1.8$, 1.9	Shui Zhi	*Haemadipsa sylvestris*	HSTX-I	Peptides	Blood-activating and stasis-resolving herbs	–	Thermal pain & inflammatory	Wang et al. (2018)
Na_Vs	Quan Xie	*Buthus martensii* Karsch	BmK NT1	Peptides	Wind-dispelling and antispasmodic herbs	–	–	Zou et al. (2016)
Na_Vs	Quan Xie	*Buthus martensii* Karsch	BmK I	Peptides	Wind-dispelling and antispasmodic herbs	DIV S3-S4	–	Feng et al. (2015)
Na_Vs	Quan Xie	*Buthus martensii* Karsch	BmK AS-1	Peptides	Wind-dispelling and antispasmodic herbs	–	–	Tan et al. (2001)

Table 2 continued

Channel	Name of TCMH	Scientific name	Chemical Composition	Attribute of Composition	Attribute of TCM	Binding Sites	Types of Pain	References
$Na_V s$	Quan Xie	*Buthus martensii* Karsch	BmK AS	Peptides	Wind-dispelling and antispasmodic herbs	DII S3—S4	Inflammatory pain	Chen et al. (2006)
$Na_V s$	Hua Jiao	*Zanthoxylum schinifolium* Sieb. et Zucc. *Zanthoxylum bungeanum* Maxim	HJ-69	Alkaloids	Interior-warming herbs	–	Neuropathic pain & inflammatory pain	Wang et al. (2024a)
$Na_V s$	Mu Dan Pi	*Paeonia suffruticosa* Andr	Quercetin	Flavonoids	Heat-clearing herbs	–	Inflammatory pain	Liu et al. (2024)
$Na_V s$	Long Xue Jie	*Dracaena cochinchinensis* (Lour.) S. C. Chen *Dracaena cambodiana* Pierre ex Gagnep	Loureirin B	Flavonoids	Blood-activating and stasis-resolving herbs	–	–	Zhang et al. (2019); Xin et al. (2024); Liu et al. (2004)
$Na_V s$	Ma Qian Zi	*Strychnos nux-vomica* L	Brucine	Alkaloids	Blood-activating and stasis-resolving herbs	–	Thermal pain	Yu et al. (2019)
$Na_V s$	Hou Po	*Magnolia officinalis* Rehd.et Wils. *Magnolia officinalis* Rehd.et Wils.var.*biloba* Rehd.et Wils	Magnolol	Phenylpropanoids	Dampness-resolving herbs	–	Inflammatory pain	Zhanget al. (2021)
$Na_V s$	Chan Su	*Bufo bufo gargarizans* Cantor *Bufo melanostictus* Schneider	Bufalin	Steroids	Resuscitation herbs	–	Thermal pain	Tao et al. (2018)
$Na_V s$	Ren Shen	*Panax ginseng* C. A. Mey	(9R,10S)-epoxyheptadecan-4,6-diyn-3-one)	Polyacetylenic	Tonifying herbs	–	–	Choi et al. (2008)

sympathetic neurons and olfactory epithelia and the central nervous system. $Na_V1.7$ expressed within $Na_V1.8$-positive sensory neurons is important for acute noxious mechanosensation and inflammatory pain whilst $Na_V1.7$ expressed within sympathetic and sensory neurons contributes toacute noxious thermosensation (Eijkelkamp et al. 2012; Luiz and Wood 2016). Furthermore, $Na_V1.7$ in sympathetic neurons plays a role in the development of neuropathic pain. Overall, it is an important analgesic drug target, particularly as Nav1.7 null humans and mice are pain-free. Weiss et al. demonstrated that $Na_V1.7$ is also an essential requirement for odor perception in both mice and humans (Weiss et al. 2011).

Current reports on the correlation between TCMH and $Na_V1.7$ indicate that the involved herbs are primarily categorized into seven types, wind-dampness dispelling herbs, interior-warming herbs, phlegm-resolving herbs, exterior-releasing herbs, tonifying herbs, astringent herbs, and wind-dispelling and antispasmodic herbs (Table 2). The related chemical components mainly include terpenes (including triterpenes), steroids, alkaloids, flavonoids and non-flavonoid polyphenols, phenylpropanoids, glycosides, and peptides.

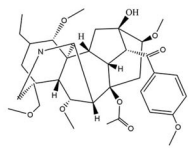
Terpenes, steroids, and wind-dampness dispelling herbs, exterior-releasing herbs

Geraniol (Fig. 3(2)), a monoterpenic alcohol compound, is a major chemical component in wind-dampness dispelling herbs, such as ERODII HERBA GERANII HERBA (Lao Guan Cao in Chinese, the dried ground part of Erodium stephanianum willd., Geranium wilfordii Maxim., or Geranium carolinianum L.), Lemongrass Herb (XiaoMao in Chinese, Cymbopon citratus (D C.) Stapf), and the plants sources from Cymbopogon, Litsea Lam., Rosaceae, Gardenia, and Gardenia, etc. Xing et al. established a neuropathic pain rat model of Spared Nerve Injury (SNI), and used HEK293 cells expressing $hNa_V1.7$ and hTRPA1 channels to measure changes in the threshold of paw withdrawal and in channel activities with or without geraniol. They showed that geraniol may lowere hypersensitivity of mechanical pain in the SNI model by specifically inhibiting $Na_V1.7$ channel activity (Xing et al. 2017).

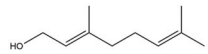
RHODODENDRI MOLLIS FLOS (Nao Yang Hua in Chinese), the dried flower of Rhododendron molle G. Don, is categorized to wind-dampness dispelling herbs in TCM with the effect of relieving pain. One of the main pharmacological activity and toxic component is Rhodojaponin III (RJ-III, Fig. 3(3)), a diterpenoid compound. Its antinociceptive and anti-neuropathic pain effects have been evaluated in four classic nociceptive pain models and whole-cell patch clamp technology (Yang et al. 2022). This work shows RJ-III can inhibit $Na_V1.7$ and $Na_V1.8$ in a significant dose-dependent way, 143 μM and more than 200 μM respectively, these are relatively high concentrations but arfe similar to lidocaine with an IC50 of 104 μM and 450 μM on $Na_V1.7$ and $Na_V1.8$. Particularly worth mentioning is its problem of lowering blood pressure and reducing heart rate, and doses of 0.375 mg/kg RJ-III and above may cause hepatotoxicity and leukopenia that should be fully considered in analgesic drug development.

Dioscin (Fig. 3(4)), a steroid compound, is the main component of Dioscoreaceae R. Br., which is the source of many TCM. DIOSCOREAE NIPPONICAE RHIZOMA (Chuan Shan Long in Chinese) is a wind-dampness dispelling herb in TCM, it is the dried root of Dioscorea nipponica Makino. Leng et al. observed the effect on painful diabetic peripheral neuropathy (PDPN) rats by examining the mRNA expression of $Na_V1.7$ with dioscin extracted from DIOSCOREAE NIPPONICAE RHIZOMA. They showed that both high and low doses of dioscin can down-regulate the expression of $Na_V1.7$ mRNA in Wistar rats' sciatic nerve (Leng et al. 2018). Unfortunately, the electrophysiology research of 1.7 was not conducted in this study.

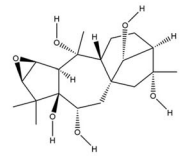
Tripterygium wilfordii Hook. f. (Lei Gong Teng in Chinese) is a wind-dampness dispelling herb in TCM widely used as analgesic and anti-inflammatory drug but with cardiotoxicity. Triptolide (Fig. 3(5)), celastrol (Fig. 3(6)), demethylzeylasteral (Fig. 3(7)), and wilforgine (Fig. 3(8)) are four main molecules in this herb. Xu et al. considered the involvement of VGSCs in pain and heart-related diseases, and the fact that *Tripterygium wilfordii* also exhibits both good analgesic activity and cardiac risk. They used computational autodocking to calculate the binding energy and show the binding modes and sites of the four monomers of *Tripterygium wilfordii* on $Na_V1.7$(related to pain) versus $Na_V1.5$(related to cardiotoxicity). They examined the pharmacology of the peak currents and kinetic properties on $Na_V1.7$/$Na_V1.5$, analgesic



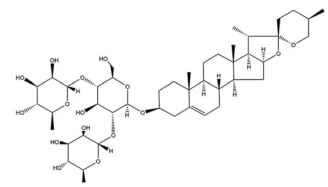
Bulleyaconitine A (1)



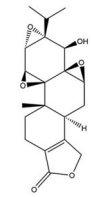
Geraniol (2)



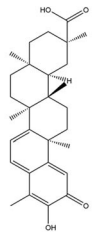
Rhodojaponin III (3)



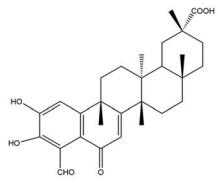
Dioscin (4)



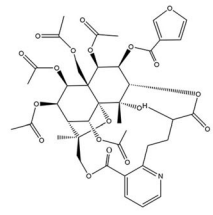
Triptolide (5)



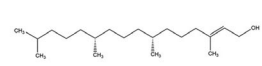
Celastrol (6)



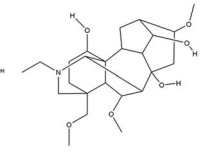
Demethylzeylasteral (7)



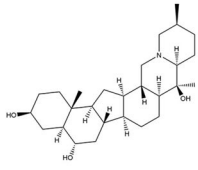
Wilforgine (8)



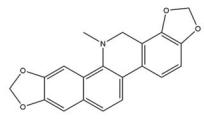
Phytol (9)



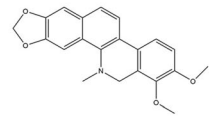
Neoline (10)



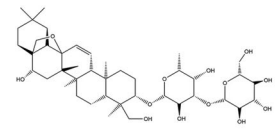
Peimine (11)



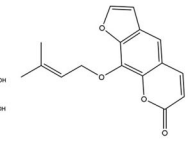
Dihydrosanguinarine (12)



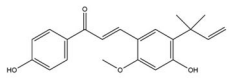
Dihydrochelerythrine (13)



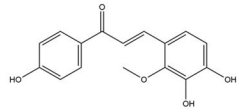
Saikosaponin A (14)



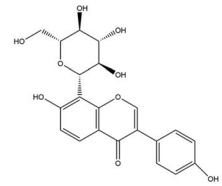
Imperatorin (15)



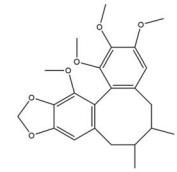
Licochalcone A (16)



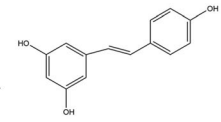
Licochalcone B (17)



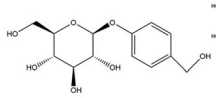
Puerarin (18)



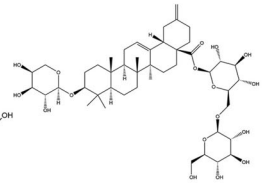
Schisandrin B (19)



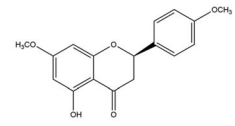
Resveratrol (20)



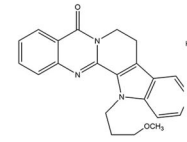
Gastrodin (21)



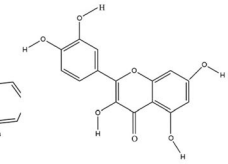
YM11 (22)



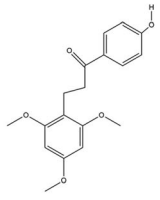
(-)-Naringenin 4',7-dimethyl Ether (23)



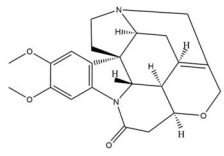
HJ-69 (24)



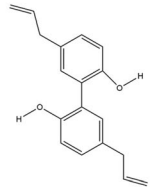
Quercetin (25)



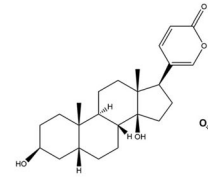
Loureirin B (26)



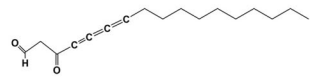
Brucine (27)



Magnolol (28)



Bufalin (29)



(9R,10S)-epoxyheptadecan-4,6-diyn-3-one (30)

◀**Fig. 3** The chemical structure of TCM molecules studied in this research

effects in formalin-induced model, as well as the acute heart toxicity in vivo. They demonstrated VGSCs are targets of *Tripterygium wilfordii.* The four monomers show strong inhibitory effects on both $Na_V1.7$ and $Na_V1.5$. Triptolide has a better analgesic effect at a lower dose, and Demethylzeylasteral is mainly related to the cardiac risk of *Tripterygium wilfordii.* Notably, they consider that $Na_V1.7$ might not be the most important pathway for the analgesic mechanism of *Tripterygium* wilfordii. (Xu et al. 2023).

FECULAE BOMBYCIS (Can Sha in Chinese, the dried faeces of *Bombyx mori* Linnaeus, a wind-dampness dispelling herb) is a common medication for migraine as recorded in the classic ancient Chinese medical book "Compendium of Materia Medica". Some scholars have studied the analgesic mechanism of FECULAE BOMBYCIS. It was found that phytol (Fig. 3(9)), a terpene compound, the main active ingredient in FECULAE BOMBYCIS, could reduce the excitability of trigeminal ganglion neurons by inhibiting $Na_V1.7$, thereby relieving migraine. Moreover, phytol was more likely to act on the inactive state of $Na_V1.7$ rather than on the off and on states (Song et al. 2023).

Alkaloids, and wind-dampness dispelling herbs, interior-warming herbs, phlegm-resolving herbs

Alkaloids plays an important role in TCM as the effective components of many herbs. Many categories of TCMH have analgesic, antibacterial, and anti-inflammatory effects and so on because of alkaloids, such as wind-dampness dispelling herbs, interior-warming herbs, wind-dispelling and antispasmodic herbs, and blood-activating and stasis-resolving herbs. Neoline (Fig. 3(10)) is an alkaloid from many TCMH, such as ACONITI RADIX (Chuan Wu in Chinese, the dried taproot of Aconitum carmichaelii Debx., a wind-dampness dispelling herb), ACONITI LATERALIS RADIX PRAEPARATA (Fu Zi in Chinese, the dried lateral root products of Aconitum carmichaelii Debx., an interior-warming herb), and ACONITI KUSNEZOFFII RADIX (Cao Wu in Chinese, the dried root tuber of Aconitum kusnezoffii Reichb., a wind-dampness dispelling herb). Nakatani et al. identified neoline as the active ingredient of both Goshajinkigan (GJG, a traditional Japanese formula first described in "Ji sheng fang", a TCM classic published in 1253 in Southern Song Dynasty of China) and Processed aconite root (PA) that is responsible for effects on oxaliplatin-induced neuropathic pain in mice. The electrophysiological properties of the three medicines on $Na_V1.7$, and the ameliorative effects on diabetic peripheral neuropathic pain were evaluated. It turns out that neoline, GJG, and PA could inhibit $Na_V1.7$ current and the mechanical threshold is increased in diabetic mice, but not in non-diabetic mice, which suggests that neoline might only affect lowered mechanical nociceptive thresholds (Nakatani et al. 2020). Nonetheless, many other alkaloids except neoline were demonstrated as the main effective ingredients in aconite root, for example, Benzoylmesaconitine, Benzoylhypaconine, Benzoylaconitine, and Talatisamine, etc., which may also worth exploring for effects on pain.

Alkaloids are also the effective components of phlegm-resolving herbs. Fritillaria is a sort of phlegm-resolving herb, and there are three major members: Fritillaria thunbergii Miq. (Zhe Bei Mu in Chinese), Fritillaria cirrhosa D.Don (Chuan Bei Mu in Chinese), and Fritillaria ussuriensis Maxim. (Ping Bei Mu in Chinese). An isosteroidal alkaloid component peimine (verticine, Fig. 3(11)) is explored having the character of blocking $Na_V1.7$, but the mechanism is similar to lidocaine. It binds the channel pore region, which is highly conserved region among sodium channel families. This means the inhibition of peimine on $Na_V1.7$ is likely not specific for only this sodium channel (Xu et al. 2016). However, this research lacks classical pain animal model research to further explain the pharmacological character of peimine.

A study of computer simulation prediction and experimental validation provides an efficient way to process large amounts of TCMH compound data and quickly locate targets. CORYDALIS RHIZOMA (Yan Hu Suo in Chinese, the dried rhizome of Corydalis yanhusuo W.T. Wang) is an essential analgesic herb in TCM, and is often regarded as the TCM morphine. There are large numbers of active alkaloids in it. Sun et al. conducted a prediction and verification work to target two important alkaloids which strongly bind both $Na_V1.7$ and $Na_V1.5$. The active components screen platform (Traditional

Chinese Medicine Database and Analysis Platform) and target databases (Swiss target prediction, etc.) were applied to target key compounds and biological targets. Then the relationship of compounds and targets is visualized and computational docked. The result shows 33 components could bind to $Na_V1.7$ and $Na_V1.5$ with different binding energies. Then patch clamp was applied to show that the top two strongly binding alkaloids dihydrosanguinarine (Fig. 3(12)) and dihydrochelerythrine (Fig. 3(13)) could inhibit peak currents and promote the activation phases of both $Na_V1.5$ and $Na_V1.7$ by direct blocking of the pore-forming region (Sun et al. 2022).

Above are the cases for varies single components in TCMH Many researches are conducted with single herbs or herbal formulas because the composition of TCM is relatively complex. BUPLEURI RADIX (Cai Hu in Chinese, the dried root of Bupleurum chinense DC. or Bupleurum scorzonerifolium Willd.) and ANGELICAE PUBESCENTIS RADIX (Du Huo in Chinese, dried root of Angelica pubescens Maxim. f. biserrate Shan et Yuan) are two representative analgesics in TCM. Xu et al. selected five monomers of saikosaponins from Cai Hu and five monomers from Du Huo to represented the two herbs, and examine the pain-regulating effects. Whole-cell patch-clamp results reveals all five saikosaponins in Cai Hu and all five monomers in Du Huo inhibit the peak currents of $Na_V1.7$ in a concentration-dependent manner. Saikosaponin A Fig. 3(14)) in Cai Hu has the strongest inhibitory effect and makes $Na_V1.7$ more easily activated and difficult to return to the resting state, whilst imperatorin (Fig. 3(15)), a phenylpropanoid compounds in Du Huo, makes $Na_V1.7$ more difficult to activate and inactivate with difficulties in returning to its resting state, thus delaying the regulation process of $Na_V1.7$ channel (Xu et al. 2021). This is probably useful for the ability of sodium channel blockers to distinguish the resting channels from the inactivated channels. Interestingly, the two compounds have inhibitory effects on the thermal pain and formalin-induced pain in mice.

Flavonoids, phenylpropanoids, polyphenols, and tonifying herbs, exterior-releasing herbs, astringent herbs

GLYCYRRHIZAE RADIX ET RHIZOMA (Gan Cao in Chinese, Liquorice root) is the dried roots or rhizomes of Leguminosae plants, such as Glycyrrhiza uralensis Fisch., Glycyrrhiza inflata Bat., and Glycyrrhiza glabra L. Licorice is called an essential herbal medicine because of the usage and compatibility, and it is often used as a detoxifying analgesic (Jiang et al. 2020). Licochalcone A (LCA, Fig. 3(16)), a flavonoid compound, is the characteristic chemical component of Licorice in tonic medicines (Wang et al. 2020). Zhao et al. priority use patch-clamp recordings to measure the effect of LCA on DRG neurons of mice. They found that LCA can significantly inhibit sodium currents in DRG neurons, and inhibit the excitability of DRG neurons through reduction of the frequency of action potentials and their amplitude. Subsequently, they used HEK293T cells expressing $Na_V1.7$ to further measure changes of LCA on $Na_V1.7$. They showed that LCA can either inhibit $Na_V1.7$ current, or shift the I-V curve in the direction of depolarization. Finally, a formalin pain model was established, and it was found that LCA could reduce the pain response in the first and second stages of formalin test, which verified the regulatory effect of LCA on $Na_V1.7$. In addition, Zhao et al. also selected LCB (Fig. 3(17)), with a chemical structure that is similar to LCA, to conduct the same experiment. But these results showed that LCB could not inhibit the Nav current in DRG neuron, and only alleviated the second phase of pain response in the formalin pain model. Combined with the chemical structures, LCA has an alkene side chain on the aromatic B-ring, but LCB does not. They speculated that the regulatory effect of LCA on $Na_V1.7$ may be closely related to its alkene side chain on the aromatic B-ring, this may be useful guidance for the development of novel $Na_V1.7$ inhibitors (Zhao et al. 2023b).

PUERARIAE LOBATAE RADIX (Ge Gen in Chinese, Lobed kudzuvine root, the dried root of *Pueraria lobata* (Willd.) Ohwi), is a commonly used exterior-releasing herb in clinical practice of TCM. Puerarin (Fig. 3(18)) is the main active component of lobed kudzuvine root, which is an isoflavonoid compound. Zhang et al. explored the effect of puerarin on the expression of $Na_V1.7$ in the DRG of lumbar disc herniation (LDH) rats, through various methods—autologous nucleus pulposus transplantation, immunofluorescence staining, etc. The results showed that puerarin could inhibit the expression of $Na_V1.7$, by reducing the protein expression of inflammatory factor TNF-α in DRG, to treat LDH-induced nervous radicular pain (Zhang et al. 2023). However, this study

lacks in vitro cell experiments, and further data at the cellular level will be more helpful for the subsequent development of puerarin.

Schisandrin B (Fig. 3(19)) is a phenylpropanoid compound extracted from SCHISANDRAE CHINENSIS FRUCTUS (Wu Wei Zi in Chinese, the dried ripe fruit of *Schisandra chinensis* (Turcz.) Baill., an astringent herb in TCM). It has significant analgesic effect and can effectively relieve pain caused by acetic acid, formalin and complete Freund 's adjuvant. The analgesic effect of schisandrin B is mainly achieved by blocking the $Na_V1.7$ sodium channel, especially the inhibitory effect on the inactivation state is more significant. However, it cannot be ruled out that other sodium channels may be involved in its analgesic mechanism, which needs further study to clarify (Zhao et al. 2024).

Resveratrol (Fig. 3(20)), a polyphenolic component, is widely found in a variety of plants, such as the plants sources from Vitaceae, Moraceae, Liliaceae, Leguminosae, etc. (Li et al. 2016b; Cao et al. 2003). Jia et al. explored the mechanism of resveratrol that regulates $Na_V1.7$ to alleviate neuropathic pain, through the rat model of neuropathic pain that established by chronic constriction injury surgery. The study found that resveratrol may increase the expression of microRNA 182 (the downstream effector of Sirt1) to inhibit the expression of $Na_V1.7$ and relieve neuropathic pain, by activating silent information regulator 1(Sirt1) (Jia et al. 2020). However, the current changes of $Na_V1.7$ in DRG neurons were not further explored in this study.

Peptides, glycosides, and wind-dispelling and antispasmodic herbs

SCORPION (Quan Xie in Chinese, the dried body of *Buthus martensii* Karsch, BmK) has been used as a wind-dispelling antispasmodic drug in China for thousands of years. According to the Chinese authoritative pharmaceutical monograph *Compendium of Materia Medica* compiled by Li Shizhen in 1578, scorpion is used to treat stroke, hemiplegia, epilepsy, etc. (Zou et al. 2016). Its venom plays an important role in TCM and it can be used to treat a variety of pains. Most scorpion toxins isolated from venom are polypeptides composed of 60–80 amino acid residues. It has been reported that targeting VGSCs may be their main mechanism of analgesia. They can be divided into Scorpion α-toxins and Scorpion β-toxins according to the gating effect and binding characteristics of scorpion toxins on the channel. Scorpion α-toxins may be activators of VGSCs, causing pain, while Scorpion β-toxins exert analgesic effects by inhibiting VGSCs (Xu et al. 2018). For example, BmK NT1, BmK I, Makatoxin-3 (MkTx-3), Scorpion α-toxins purified from *Buthus martensii* Karsch induce pain by regulating sodium channels (Zou et al. 2016; Chen et al. 2022; Feng et al. 2015). Interestingly, in addition to enhancing the activity of $Na_V1.7$ to induce pain, MkTx-3 can also significantly reduce the pain induced by formalin, acetic acid and complete Freund 's adjuvant after increasing the concentration, and its analgesic mechanism is also related to the activation of $Na_V1.7$. However, the mechanism by which MkTx-3 exerts pain and analgesia by regulating $Na_V1.7$ at different concentrations still needs further study (Chen et al. 2022). In addition to Buthus martensii Karsch, other scorpion venoms have also been found to induce pain by regulating sodium channels. For example, the toxic protein AaH II purified from *Androctonus australis* (AaH) and Amm VIII purified from *Androctonus mauretanicus mauretanicus* (Amm) can bind to the channel isoforms at the domain IV S3-S4 linker region and induce pain by enhancing the tetrodotoxin-sensitive (TTX-S) Na_V current of DRG. In DRG neurons, $Na_V1.7$ is a major TTX-S subtype, and Amm VIII and AaH II can lead to rapid inactivation of $Na_V1.7$ current (Alami et al. 2003; Abbas et al. 2013). Antitumor-analgesic peptide (AGAP), Anti-neuroexcitation peptide (ANEP), BmK Ang M1, BmKBTx, BmNaL-3SS2, BmK AS, and BmK AS-1 are seven Scorpion β-toxins purified from *Buthus martensii* Karsch, which have been verified to have analgesic activity in rodent models (Liu et al. 2003, 2008; Xu et al. 2017; Li et al. 2016a; Song et al. 2017; Cao et al. 2004; Lin et al. 2017; Tan et al. 2001; Chen et al. 2006; Liu et al. 2012c; Shao et al. 2008). It was found that AGAP could exert analgesic effects by inhibiting the activity of $Na_V1.7$ and $Na_V1.8$, while the mutant W38G of AGAP mainly exerted analgesic effects by inhibiting $Na_V1.8$. Although the channels of the two effects were different, the analgesic effects of the two were similar. Therefore, AGAP may exert analgesic effects mainly by inhibiting $Na_V1.8$. In addition, AGAP can also significantly inhibit $Na_V1.4$ and $Na_V1.5$, but the inhibitory effect of W38G is weak, which may explain

why the toxicity of W38G to skeletal muscle and myocardium in vivo is lower than that of AGAP. These results suggest that Trp38 may be a key amino acid involved in the biological activity of AGAP (Xu et al. 2017). Song et al. conducted a series of experimental studies on the binding mode of ANEP and its mutants with $Na_V1.7$. They also found that changing some amino acids can achieve better efficacy and fewer side effects. This suggests that in future studies, we need to pay attention to the interaction between residues, and when examining the analgesic effect of peptides, we also need to examine the selective study of other sodium channel subtypes associated with side effects, such as $Na_V1.4$, $Na_V1.5$, to reduce adverse reactions (Song et al. 2017). BmKBTx and BmNaL-3SS2 were found to have analgesic activity in mouse writhing experiments, and could reduce the amplitude of sodium currents in a concentration-dependent manner and inhibit $Na_V1.7$ (Lin et al. 2017). However, BmK AS and BmK AS-1 can inhibit TTX-R and TTX-S sodium channel currents in rat DRG neurons, and BmK AS can produce significant analgesic effects not only in the periphery but also in the spinal cord (Tan et al. 2001; Chen et al. 2006; Liu et al. 2008).

μ-SLPTX-Ssm6a (Ssm6a) is a polypeptide purified from venom of SCOLOPENDRA (Wu Gong in Chinese, the dried body of *Scolopendra subspinipes mutilans* L. Koch), which consists of 46 residues with three disulfide bonds. Shilong Yang et al. found that Ssm6a was preferentially active on NaV1.7 by using rat DRG neurons and HEK293 cells, and showed high selectivity and strong inhibitory activity. The analgesic effect of Ssm6a was more effective than morphine in the formalin-induced pain model. In the heat and acetic acid-induced pain model, Ssm6a and morphine were similarly effective at reducing thermal pain and abdominal writhing. Ssm6a had no obvious side effects at a dose up to 10 times higher than the analgesic effect, so can be developed as a potential drug targeting $Na_V1.7$ in the future. It is expected that in future experiments, more complex rodent models will be used to detect the analgesic activity of Ssm6a, then better simulate human pain and evaluate its analgesic mechanism in more detail (Yang et al. 2013).

GASTRODIAE RHIZOMA (Tian ma in Chinese, from the dry tuber of *Gastrodia elata* Bl.) is an important medicine for the treatment of pain in traditional Chinese medicine, and its main component gastrodin (Fig. 3(21)) is a glycoside compound. It was found that gastrodin can increase the pain threshold of chemotherapy-induced neuropathic pain rat model constructed by vincristine. The mechanism may be related to decrease the hyperexcitability of vincristine-induced DRG neurons, inhibiting the current density of $Na_V1.7$ and $Na_V1.8$ Sodium Channels, and down-regulation the protein expression of $Na_V1.7$ and $Na_V1.8$ channels. Particularly worth mentioning is the three-dimensional structures of $Na_V1.7$ and 1.8 were constructed by homology modeling method and molecular dynamics. Site i 1 may be the action site of gastrodin on $Na_V1.7$, and the binding of gastrodin to $Na_V1.7$ was more stable than that of $Na_V1.8$ (Wang et al. 2021).

Spider venom is rich in desmin. It is reported that about one-third of spider desmin plays an analgesic role against sodium channels (Wang et al. 2024a). Huwentoxin-IV (HWTX-IV) from *Ornithoctonus huwena* venom and Hainantoxin-IV (HNTX-IV) from *Ornithoctonus hainana* venom inhibited TTX-S sodium channels in rat DRG cells, preferentially inhibiting $Na_V1.2$, $Na_V1.3$ and $Na_V1.7$, with the highest sensitivity to $Na_V1.7$. Moreover, HWTX-IV and HNTX-IV have high sequence consistency, indicating that they may share a binding site on the sodium channel and inhibit the $Na_V1.7$ current by binding to the DIIS3-S4 junction of $Na_V1.7$ in a closed state (Xiao et al. 2008; Liu et al. 2012b; Cai et al. 2015). Jingzhaotoxin-34 (JZTX-34), isolated from *Chilobrachys jingzhao* venom, showed potent analgesic effect in thermal and noxious chemical-induced animal pain models. It inhibited TTX-S sodium currents, but had no significant effect on TTX-R sodium currents in rat dorsal root ganglion neurons. It was found that JZTX-34 inhibited the sodium channel subtype $Na_V1.7$ by binding to the neurotoxin receptor 4 site in the closed structure, but had little effect on other sodium channel subtypes (Zeng et al. 2018; Chen et al. 2009). In contrast, GpTX-1, which was isolated from *Grammostola rosea* venom, not only has a strong inhibitory effect on $Na_V1.7$, but also has good selectivity againstother key Na_V subtypes (selectivity to $Na_V1.4$ and $Na_V1.5$ is more than 20 times and 1000 times, respectively). Protoxin-II (ProTxII) isolated from *Thrixopelma pruriens* venom can inhibit the activation of the Nav1.7 channel by binding to a voltage sensor to lock the channel in a closed

conformation (Murray et al. 2015). In addition, PnTx4(5–5), isolated from Phoneutria nigriventer venom, was found to exert analgesic effects in animal pain models induced by PGE2, carrageenan or glutamate, and to block mammalian $Na_V1.2$ to $Na_V1.6$ sodium currents, with the highest inhibition of $Na_V1.3$ currents (Oliveira et al. 2019).

$Na_V1.8$ as a pain target

$Na_V1.8$ is highly selectively expressed in the peripheral nervous system, mainly in small (with small and medium diameter) nociceptive sensory neurons, and acts as a major contributor to the upstroke of action potentials (Akopian et al. 1999; Renganathan 2001). A fragment of $Na_V1.8$ has a functional role in the heart through regulation of the expression of the cardiac channel $Na_V1.5$ (Wood and Iseppon 2018). As a TTX-resistant sodium channel subtype, the inactivation of $Na_V1.8$ is cold resistant (Eijkelkamp et al. 2012), whereas the slow inactivation of TTX-sensitive channels enhanced in response to cooling. This makes $Na_V1.8$ essential in maintaining the excitability of nociceptors at low temperatures, becoming the sole electrical impulse generator at temperatures < 10 °C (Wood and Iseppon 2018). Mice in which $Na_V1.8$-expressing sensory neurons are ablated present deficits in inflammatory and mechanical pain behavior, yet they respond normally to heat (Luiz and Wood 2016).

Two studies revealed the mechanism of TCM treating inflammatory pain by inhibiting $Na_V1.8$. *Stauntonia brachyanthera* Hand. -Mazz. (Xi Nan Ye Mu Gua in Chinese) is widely used in the southern provinces of China for pain and inflammatory diseases. The EtOH extracts (EESB) of *Stauntonia brachyanthera* and a nor-oleanane triperpenoids compound, YM11 ((Fig. 3(22)), which is the most characteristic component because of its highest content, are demonstrated to have analgesic activity. The results showed that EESB could provide responses to two different grades of noxious stimuli including chemically induced and thermal stimulus tissue damage, and the anti-inflammation effect of EESB and YM11 are higher than that of aspirin in anti-inflammatory test at doses of 400 mg/kg and 20 mg/kg, respectively. However, the results suggested that YM11 was not a centrally acting analgesic because no significant difference in the results. EESB exhibited an almost similar analgesic effect to morphine, and the inhibition rate (38.6%) was even stronger than that of morphine (35.7%) after 2 h, indicating its long persistent period of antinociceptive effect. Besides, the significant increase of TTX-R sodium currents of small-sized DRG neurons isolated from mice in formalin test ($Na_V1.8$ in L4-6 DRGs) could be efficaciously ameliorated after the administration of YM11. They speculated that the analgesic effect of YM11 mainly comes from the suppression of the expression of $Na_V1.8$ in L4-6 DRGs due to the inhibitions of p38, c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinases (ERK) (Meng et al. 2017). *Nardostachys jatamansi* DC. (Gan Song in Chinese) has been widely used as a qi-regulating analgesic herb in TCM. (−)-Naringenin4',7-dimethyl ether ((−)-NRG-DM, (Fig. 3(23)), a flavonoid isolated from *Nardostachys jatamansi* DC.,that can dose dependently ($30 \sim 50$ mg/kg) relieve inflammatory pain. In acutely isolated mice dorsal root ganglion neurons, (−)-NRG-DM ($1 \sim 30$ μM) potently dampens the stimulated firing, reduce the action potential threshold and amplitude, and it dramatically inhibit heterologously expressed $K_V2.1$ and $Na_V1.8$ channels (Gu et al. 2022).

Effective pain management remains a problem for patients diagnosed with cancer, for cancer-induced bone pain and chemotherapy-associated pain are painful side effects of cancer itself. Although paclitaxel is used to treat various types of cancers, it often brings chemotherapy-associated pain that mainly manifests as tingling, numbness, cold, and burning/shooting pain. Puerarin (Fig. 3(18)) is an isoflavonoid extracted from an exterior-releasing herb, *Pueraria montana* (Willd.) Ohwi. Zhang et al. revealed the effect of puerarin treating neuropathic pain caused by chemotherapy paclitaxel. The result shows the blocking effects of puerarin on Nav channels in DRG neurons were stronger in neuropathic pain state than that in normal state, and this selective inhibitory effect depends on the β1 subunit. This finding suggests the possibility that the β1 subunit is a potential target of puerarin, and it may preferentially inhibit the β1 subunit of $Na_V1.8$ and reduce the excitability of DRG neurons contributes to its anti-paclitaxel induced neuropathic pain effect. Meanwhile, puerarin potently blocked $Na_V1.8$ channels in resting and inactivated states in a neuropathic pain state, suggesting that puerarin may be effective for the relief of severe pain.

In addition, they suspect puerarin may act on potassium channels of DRG neurons (Zhang et al. 2018).

Haemadipsa sylvestris (Shui Zhi in Chinese), a blood-activating and stasis-resolving herb, has a rapid, effective and lasting analgesic effect and can treat a variety of pain syndromes. The polypeptide HSTX-I purified from *Haemadipsa sylvestris* has shown significant analgesic effects in many animal models such as formalin-induced claw licking, acetic acid-induced abdominal writhing and hot plate test, suggesting that HSTX-1 effect on both neurogenic and inflammatory pain. The mechanism may be related to the inhibition of $Na_V1.8$ and $Na_V1.9$ currents. However, the effects of HSTX-I on these two sodium channels are slightly different, which may be due to the different binding regions of HSTX-I to the two channels. Further mutation studies are needed to explore the specific domains of the two channels. The selectivity of HSTX-1 on $Na_V1.8/1.9$ and its significant analgesic effects shows it is useful for $Na_V1.8$ and $Na_V1.9$ studies and analgesic development (Wang et al. 2018).

Targetting Navs to treat pain disorders

Currently, many TCM analgesic herb studies are conducted at the level of Na_V channels rather than specific subtypes, which remains to be further inspected. For example, ZANTHOXYLI PERICARPIUM (Hua Jiao in Chinese, the dried citrus peel of *Zanthoxylum bungeanum* Maxim. or *Zanthoxylum schinifolium* Sieb. Et Zucc.) is a basic analgesic herb in TCM for treating arthritis and toothache conditions. Wang et al. first isolated and identified a novel isoquinoline alkaloid named HJ-69 (Fig. 3(24)) from this herb. And this monomer notably relieved pain behaviors in the formalin-induced mouse model with intraperitoneal application of 30 and 100 mg/kg. HJ-69 can dramatically suppress the excitability of acutely isolated small-diameter mouse DRG neurons by inhibiting Na_V and activating Kv currents. Further, in line with the potent inhibition of endogenous Na_V currents, HJ-69 exhibited significant state-dependent inhibitory effects on $Na_V1.7$ and $Na_V1.8$ expressed in heterologous HEK293 cells. The state-dependent inhibition property of HJ-69 corresponded to that described for some Na_V channel inhibitors, such as CNV1014802 and vixotrigine, that might contribute to its inhibitory effect on the high-frequency firing of neurons in pain conditions without affecting other tissues (Wang et al. 2024a).

MOUTAN CORTEX (Tree peony bark, Mu Dan Pi in Chinese, the dried root bark of *Paeonia suffruticosa* Andr.) is a kind of heat-clearing drugs, commonly used in the treatment of febrile and inflammatory diseases in TCM clinical practice. Quercetin (Fig. 3(25)), a flavonoids component, was identified as the main active component of MOUTAN CORTEX in the treatment of chronic orofacial pain by network pharmacology. Furthermore, chronic orofacial pain in a rat model and patch-clamp techniques were used to evaluate the effects of quercetin on inflammation and electrophysiology of trigeminal ganglion neurons. It was found that quercetin could inhibit inflammation in trigeminal ganglion neurons by inhibiting the current density of Na channels on trigeminal ganglion neurons, thereby relieving inflammatory pain (Liu et al. 2024). However, how quercetin directly or indirectly acts on VGSCs is still unclear.

RESINA DRACONIS (Long Xue Jie in Chinese), a blood-activating and stasis-resolving herbs, is a kind of resin obtained by extraction from xylem in *Dracaena cochinchinensis* (Lour.) S. C. Chen or *Dracaena cambodiana* Pierre ex Gagnep. It contains a variety of flavonoid components (Zhang et al. 2019; Xin et al. 2024). Liu et al. study the antinociceptive effects of RESINA DRACONIS and its main active component, loureirin B (Fig. 3(26)), and found that high concentrations of RESINA DRACONIS (0.05% of the content of loureirin B) and loureirin B (0.2 mmol/L) not only reduced the peak current of TTX-S sodium channels in a dose-dependent manner, but also shifted the potential corresponding to the maximum peak current and the half activation potential to depolarization, and the half inactivation potential to hyperpolarization. Thus, it affects the generation of action potentials and interferes with the transmission of noxious stimuli. The effect of high concentrations of loureirin B on TTX-S currents is extremely similar to that of some neurotoxins, but the molecular structure of loureirin B is not similar to these neurotoxins; therefore, Liu speculated that there may be unknown differential receptor sites sensitive to loureirin B in TTX-S channels (Liu et al. 2004).

Another blood-activating and stasis-resolving herb commonly used in clinical practice of TCM to relieve pain is STRYCHNI SEMEN (Ma Qian Zi, Maqianzi in Chinese, the dried mature seed of *Strychnos nux-*

vomica L.), and one of its active ingredients is brucine (Fig. 3(27)), a toxic alkaloid. Brucine can significantly reduce the current of VGSCs, inhibit the excitability of DRG neurons, and have a significant inhibitory effect on nociceptive thermal and mechanical stimuli, and this inhibitory effect is stronger than the classical anti-pain neurotrasnmitter GABA gamma-aminobutyric acid (Yu et al. 2019).

Magnolol (Fig. 3(28)) is a phenylpropanoid compound extracted from MAGNOLIAE OFFICINALIS CORTEX (Hou Po in Chinese, the dry bark, root bark and branch bark of *Magnolia officinalis* Rehd.et Wils. or *Magnolia officinalis* Rehd.et Wils. var. *biloba* Rehd.et Wils.), a plant which has anti-inflammatory, anti-tumor and other biological activities. It has been reported that magnolol can inhibit the current of VGSCs in a dose-dependent manner and inhibit the high excitability of DRG neurons induced by carrageenan, thereby alleviating inflammatory pain in model mice. However, there is still a lack of research to explore the inhibitory effect of magnolol on VGSCs at the molecular mechanism level (Zhang et al. 2021).

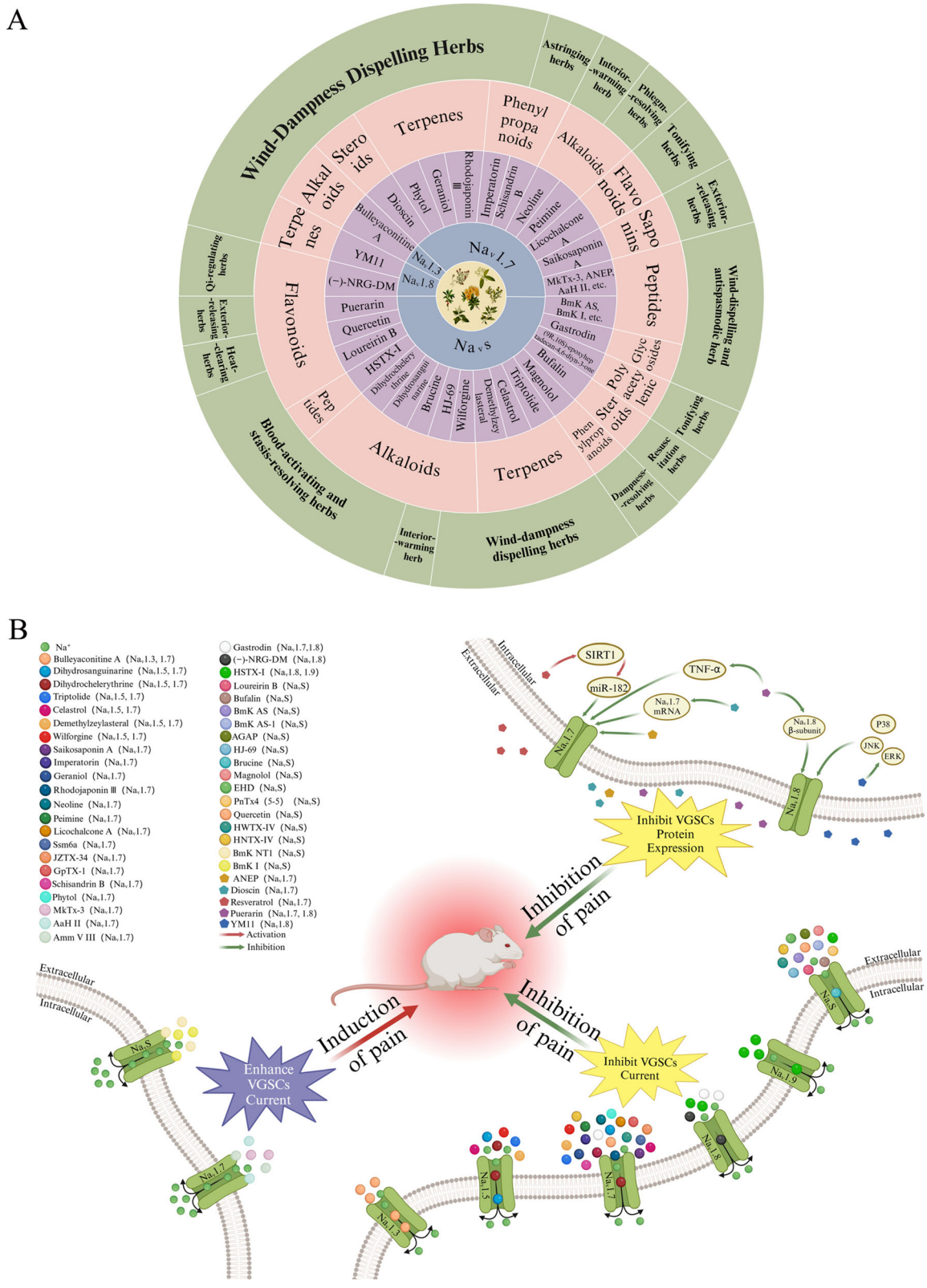
Toad venom (BUFONIS VENENUM, Chan Su in Chinese, the dry secretions of *Bufo bufo gargarizans* Cantor or *Bufo melanostictus* Schneider) is a classic Chinese painkiller, has a variety of effects such as detoxification and pain relief. Bufalin (Fig. 3(29)), the main component of bufalin, is considered to be the active ingredient responsible for its analgesic effect. Bufalin (1–1000 nM) dose-dependently inhibits the peak currents of VGSCs in ND7-23 cells (dorsal root ganglion neuroblastoma) and is effective in relieving spontaneous pain, mechanical hyperalgesia, and thermal hyperalgesia. On this basis, Jie et al. also found that there may be two distinct receptor sites for bufalin in VGSCs, one responsible for reducing peak current and promoting activation, while the other partially inhibits inactivation and reduces recovery, but the exact two receptor sites remain to be determined (Tao et al. 2018).

Ginseng (GINSENG RADIX ET RHIZOMA, Ren Shen in Chinese, the dried roots or rhizomes of *Panax ginseng* C. A. Mey.), is a typical representative medicine for tonic medicine. Various active components of ginseng have been shown to have antinociceptive effects (Nah et al. 2000; Choi et al. 2003). (9R,10S)-epoxyheptadecan-4,6-diyn-3-one (EDH, (Fig. 3(30)), a polyethyl compound derived from ginseng that inhibits Na + currents in a concentration-dependent manner in DRG neurons. However, the inhibitory effect of EDH on TTX-S and TTX-R was not the same. The inhibitory effect of EHD increased with the increase of depolarizing stimulus frequency in TTX-S VGSCs, but not in TTX-R VGSCs (Choi et al. 2008). This implies that EHD regulates these two types of VGSCs as different mechanisms, so the inhibitory effect on TTX-S and TTX-R of EHD can be further studied at the molecular mechanisms level.

Future perspectives and conclusion

The mouse knockout studies and human mutations prove the involvement of $Na_V1.3$, $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ in the development and maintenance of acute and chronic pain. In this study, we show that the reported studies on the intervention of TCM in pain by mediating sodium ion channels mainly focus on $Na_V1.7$ subtype, with some studies on $Na_V1.8$ and $Na_V1.3$, and few studies on $Na_V1.9$. The genetic evidence of a role for Nav1.7 in human pain is compelling, but loss of Nav1.7 in development allows other sodium channels to mask what is normally a lethal phenotype in the absence of Nav1.7 (Iseppon et al. 2024). Channel blocking drugs act no only on the pain system, but also on the autonomic nervous system and centrally to produce disastrous side effects. In addition, Nav1.9 has such a key role in the gastrointestinal system that is also of little interest as an analgesic drug target (Zhao et al. 2023a). However, Nav1.8 is a very attractive drug target, as demonstrated by the dramatic actions of a new orally active drug suzatrigine that inhibits Nav1.8 activity (Jones et al. 2023).

In this paper, we have summarized the studies and the mechanisms on the intervention of sodium ion channels mediated by TCM, of which 30 are defined molecular components and 33 extracts of TCMH (Fig. 4). However, hundreds of TCMH have been recorded in the Chinese Pharmacopoeia at present, and countless drugs have been recorded in the classical books of Chinese medicine. There are dozens of representative drugs closely related to pain in each of the seven categories of Chinese medicines which are mentioned in this paper. In contrast, there is still very little research on Chinese medicines for pain relief through sodium ion channel blockade. Some drugs


A
Wind-Dampness Dispelling Herbs
Astringing herbs
Interior-warming herb
Phlegm-resolving herbs
Tonifying herbs
Exterior-releasing herbs
Wind-dispelling and antispasmodic herb
Tonifying herbs
Resuscitation herbs
Dampness-resolving herbs
Wind-dampness dispelling herbs
Interior-warming herb
Blood-activating and stasis-resolving herbs
Peptides
Exterior-releasing herbs
Heat-clearing herbs
Qi-regulating herbs
Terpenes
Alkaloids
Flavonoids
Phenyl propanoids
Alkaloids
Flavonoids
Saponins
Peptides
Glycosides
Polyacetylenic Sterols
Phenylpropanoids
Terpenes
Alkaloids
Peptides
Sterols
Alkaloids
Terpenes
Rhodojaponin Ⅲ
Imperatorin
Schisandrin B
Neoline
Peimine
Licochalcone A
Saikosaponin A
MkTx-3, ANEP, AaH II, etc.
BmK AS, BmK I, etc.
Gastrodin
Bufalin
Magnolol
Celastrol
Triptolide
Demethylzeylasteral
Wilforgine
HJ-69
Brucine
Dihydrosanguinarine
Dihydrochelerythrine
HSTX-I
Loureirin B
Quercetin
Puerarin
(−)-NRG-DM
YM11
Bulleyaconitine A
Dioscin
Phytol
Geraniol
Nav1.7
Nav1.3
Nav1.8
Nav s
B
Na+
Bulleyaconitine A (Nav1.3, 1.7)
Dihydrosanguinarine (Nav1.5, 1.7)
Dihydrochelerythrine (Nav1.5, 1.7)
Triptolide (Nav1.5, 1.7)
Celastrol (Nav1.5, 1.7)
Demethylzeylasteral (Nav1.5, 1.7)
Wilforgine (Nav1.5, 1.7)
Saikosaponin A (Nav1.7)
Imperatorin (Nav1.7)
Geraniol (Nav1.7)
Rhodojaponin Ⅲ (Nav1.7)
Neoline (Nav1.7)
Peimine (Nav1.7)
Licochalcone A (Nav1.7)
Ssm6a (Nav1.7)
JZTX-34 (Nav1.7)
GpTX-1 (Nav1.7)
Schisandrin B (Nav1.7)
Phytol (Nav1.7)
MkTx-3 (Nav1.7)
AaH II (Nav1.7)
Amm V III (Nav1.7)
Gastrodin (Nav1.7,1.8)
(−)-NRG-DM (Nav1.8)
HSTX-I (Nav1.8, 1.9)
Loureirin B (Nav.S)
Bufalin (Nav.S)
BmK AS (Nav.S)
BmK AS-1 (Nav.S)
AGAP (Nav.S)
HJ-69 (Nav.S)
Brucine (Nav.S)
Magnolol (Nav.S)
EHD (Nav.S)
PnTx4 (5-5) (Nav.S)
Quercetin (Nav.S)
HWTX-IV (Nav.S)
HNTX-IV (Nav.S)
BmK NT1 (Nav.S)
BmK I (Nav.S)
ANEP (Nav.1.7)
Dioscin (Nav.1.7)
Resveratrol (Nav.1.7)
Puerarin (Nav.1.7, 1.8)
YM11 (Nav.1.8)
Activation
Inhibition
Intracellular
Extracellular
SIRT1
miR-182
TNF-α
Nav1.7 mRNA
Nav1.8 β-subunit
P38
JNK
ERK
Nav1.7
Nav1.8
Inhibit VGSCs Protein Expression
Inhibition of pain
Induction of pain
Enhance VGSCs Current
Inhibit VGSCs Current
Nav.S
Nav1.7
Nav1.3
Nav1.5
Nav1.9

◀**Fig. 4** The mechanism of interaction between monomers of TCM and sodium ion channels. **A** The information of TCM monomer compounds and their regulation of ion channels; **B** the mechanism of TCM monomer compounds regulating ion channel to mediate pain disorder (Created with *app.biorender.com*)

with obvious analgesic effect, such as Chuanxiong, Paeoniae, notoginseng, Coptis, do not affect their analgesic ations through sodium ion channels.

Moreover, as natural products, TCM exhibit complex characteristics of multi-component, multi-target, multi-pathway, and multi-level interactions. Commonly, the components in TCM effect collaborate synergistically rather than in isolation. Furthermore, a monomer in a raw herb could be a precursor compound, a lead compound, or part of a combination. During the extraction and identification process, individual compounds may even undergo natural synthesis to form new compounds that exert analgesic effects. Therefore, from the perspective of studying individual components, a single isolated compound from a TCM may not necessarily be the effective analgesic agent. To gain a deeper understanding of how a specific analgesic TCM or TCM formula modulates ion channels, or whether it binds to specific sites on these channels, the interactions among the components of the TCM should be investigated first.

For the molecules reported in this paper, only a few of their binding targets with sodium ion channels have been studied, and the others mostly focused on the electrophysiology of sodium ion channels or the regulation of ion channel protein expression. In future studies, computational simulations, molecular docking, and experimental validation can be used to rapidly and purposefully predict mechanisms of action and identify binding targets, while also verifying the results. Additionally, structural modifications of small molecules in the analgesic TCM can be explored, along with targeted delivery or the identification of components that reduce the expression of functional channels, to develop specific channel analgesics based on ensuring their natural without side effects.

In summary, VGSCs are essential for many electrophysiological processes and pain disorders, and currently more and more studies have shown that the active ingredients of many TCMH can act through sodium ion channels. As an ancient form of traditional medicine, TCM has a potential wealth of clinical applications, and its analgesic agents are a significant source for discovering and developing natural analgesics with minimal toxicity and side effects. Sodium ion channels also represent an important pathway for elucidating the molecular mechanisms by which TCM treats pain.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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