# 基于TRPV通道的辛味中药药理作用研究进展

王佳佳[1], 杨志军[1,2,3*], 杨秀娟[1,2,3*], 牛鹏贤[1], 李 硕[1,2,3], 段国建[1,2,3],
田一虹[1], 吉庆云[1]

(1. 甘肃中医药大学, 甘肃 兰州 730000; 2. 西北中藏药省部共建协同创新中心, 甘肃 兰州 730000;
3. 陇药产业创新研究院, 甘肃 兰州 730000)

**摘要**: 瞬时受体电位香草酸 (TRPV) 作为一类重要的非选择性阳离子通道, 与多种生理和病理过程密切相关。辛味是中药五味学说中的重要性味之一, 具有解表、行气、活血等作用, 主治病证多样。现代研究表明, 众多辛味中药中的活性成分具有调节TRPV离子通道的功能。本文旨在从TRPV通道的生物学特性, 辛味中药现代研究进程及其在炎症、疼痛等病理过程中的作用机制来探讨基于TRPV通道的辛味中药药理作用研究进展, 以期揭示辛味中药的科学内涵, 亦为中药药性的现代研究提供新的研究思路和模式。

**关键词**: 辛味中药; 瞬时受体电位香草酸通道; 药理作用; 临床应用; 物质基础

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# Research progress in the pharmacological effects of pungent Chinese medicine based on TRPV channels

WANG Jia-jia[1], YANG Zhi-jun[1,2,3*], YANG Xiu-juan[1,2,3*], NIU Peng-xian[1], LI Shuo[1,2,3],
DUAN Guo-jian[1,2,3], TIAN Yi-hong[1], JI Qing-yun[1]

(*1. Gansu University of Traditional Chinese Medicine, Lanzhou 730000, China; 2. Northwest China-Tibetan Medicine Co-construction and Collaborative Innovation Center, Lanzhou 730000, China; 3. Gansu Pharmaceutical Industry Innovation Research Institute, Lanzhou 730000, China*)

**Abstract**: Transient receptor potential vanilloid (TRPV), an important class of non-selective cation channels, is closely associated with a variety of physiological and pathological processes. Pungent flavour is one of the important flavours in the doctrine of five flavours in traditional Chinese medicine, which has the functions of relieving the epidermis, moving the Qi, activating the blood and so on, which has a variety of main treatments. Modern research has shown that the active ingredients in numerous pungent Chinese medicine have the ability to modulate TRPV channels. The purpose of paper is to explore the biological characteristics of TRPV channels, the modern research process of pungent Chinese medicine and its mechanism in inflammation, pain and other pathological processes. This paper discusses the research progress of the pharmacological action of pungent Chinese medicine based on TRPV channel, in order to reveal the scientific connotation of spicy traditional Chinese medicine, and also provide new research ideas and models for the modern research of Chinese medicine.

**Key words**: pungent Chinese medicine; transient receptor potential vanilloid channel; pharmacological action; clinical application; material basis

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*通讯作者 E-mail: yangzhijun1971@yeah.net;
Tel: 86-931-5161162, E-mail: yangxiujuants@163.com

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瞬时受体电位香草酸 (transient receptor potential vanilloid, TRPV) 作为一类非选择性阳离子通道, 广泛分布于哺乳动物的组织器官之中[1], TRPV家族由6个成员构成, 分别是温度敏感型的TRPV1～4通道以及细胞内Ca$^{2+}$敏感型的TRPV5和TRPV6, 其中TRPV3能响应非伤害性的温热刺激 (≥33 ℃), 并展现出独特的敏化特性[2]。

中药五味理论是中药药性理论的核心内容之一, 辛味中药作为一类极具特色的中药, 其来源广泛、功效多样, 且配伍灵活, 对于保障中医临床的准确合理用药具有不可忽视的作用。研究表明, 众多能够调节TRPV离子通道的天然成分多数源自辛味中药[3,4]。此外, 辛味中药的功效与TRPV离子通道所参与的生物学效应及其药理作用存在着显著的相似性[5,6], 如辛味中药丁公藤可以降低膝骨关节炎模型大鼠的TRPV4蛋白表达量, 缓解膝骨关节炎大鼠冷刺激痛和机械刺激痛[7]; 白芷水提液通过抑制背根神经节神经元中TRPV1的表达和活性缓解弗式完全佐剂诱导的小鼠炎症性疼痛[8]。随着现代技术的快速发展, 研究者还利用电子舌仿生技术[9]、计算机辅助虚拟技术[10]及生物传感技术[11]等手段对辛味中药进行客观表征, 使辛味理论更加清晰、客观和标准化。

因此, 本文综述TRPV通道的生物学特性, 辛味中药现代研究进展及其在炎症、疼痛、瘙痒、癌症等病理过程中的作用机制, 并提出通过辛味中药与TRPV受体家族的关系认识辛味药性作用机制的研究思路。

## 1 TRPV通道

TRPV通道是TRP通道超家族的成员, 是感知机械和渗透刺激并参与跨细胞膜的Ca$^{2+}$信号传导的离子通道。TRPV通道在维持生物体的正常功能中起重要作用, TRPV通道功能的缺陷或异常会引起一系列疾病, 包括糖尿病、炎症、心血管、中枢神经和泌尿系统疾病[12]。TRPV家族的第一位创始成员TRPV1于1997年首次在神经元中对热和辣椒素的敏感性被鉴定[13], 其他5个家族成员后续都被鉴定。TRPV1～4被进一步分为热敏性 (thermoTRPV通道) 并且相当保守 (40%～50%序列同一性); TRPV5和TRPV6彼此高度同源 (75%序列同一性), 对温度不敏感, 并且在序列保守性方面与thermoTRPV不同 (30%序列同一性)[14]。TRPV离子通道作为一种同源四聚体结构, 由4个亚基构成, 每个亚基包含6个跨膜结构域 (S1～S6), 在S5和S6之间具有孔环, 及细胞内的N-和C-末端小区, N-末端含有6个锚蛋白重复序列 (A), C-端含有TRP盒[15], 如图1所示。

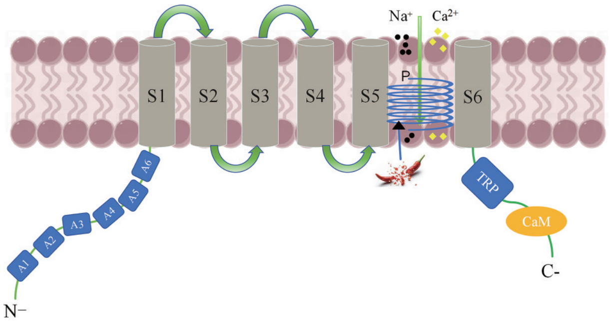

**Figure 1** Transient receptor potential vanilloid (TRPV) structure and interaction sites. S1 − S6 are 6 helical fragments in the transmembrane region; P is the hole ring; the black circles are Na$^{2+}$; the yellow diamonds are Ca$^{2+}$; A1−A6 are six ankyrin repeat units in the N-terminal

**1.1 温度敏感型的TRPV1～4通道** TRPV1～4通道受多种内源性刺激以及一系列天然和合成化合物的调节, 分布广泛, 可见于神经元、免疫细胞、脏器上皮细胞及角质形成细胞等, 主要分布区域为外周伤害性感觉神经元, 发出的感觉神经纤维主要包括无髓鞘的C类纤维和部分薄髓鞘的A$\delta$纤维[16]。TRPV1可以被大量的物理 (热、机械刺激) 和化学因素 (质子、辣椒素、树脂毒素和内源性配体内香草素等) 激活[17]。TRPV1在细胞内的作用包括细胞膜去极化和钙离子内流两个方面, 从而触发不同细胞类型的多种功能反应, 包括神经元兴奋、分泌和平滑肌收缩。TRPV2被鉴定为TRPV1的正向同源基因, 可被热 (>52 ℃)、各种配体 (大麻二酚、丙磺舒、2-氨基乙氧基二苯基硼酸酯和溶血磷脂酰胆碱) 和机械应力激活[18,19]。TRPV2广泛表达且与多种生物功能有关, 包括热感觉、神经元发育、渗透或机械感受、促炎过程等[20,21]。TRPV3是位于细胞膜上的一种对温度敏感 (31～39 ℃) 且受多种化学刺激的非选择性阳离子钙渗透通道, 与其他TRPV通道显示约30%～40%的氨基酸序列同源性[22]。TRPV3在背根神经节、鼻腔和口腔上皮细胞、肠道上皮细胞和皮肤角质形成细胞中大量表达, 其中在皮肤角质形成细胞中表达最为丰富[23]。TRPV4通道具有多样的激活机制, 既可对机械刺激 (热、肿胀、剪切力) 响应, 也可被多种化学刺激 (花生四烯酸及其代谢产物、内源性大麻素、ATP、钙调蛋白、4$\alpha$-PDD、GSK1016790A等) 所激活, 同时也可被钌红、链霉素、AB159908cc和RN-1734等选择性阻断[24]。TRPV4广泛表达于心脏、动脉及乳腺等组织, 不仅参与体温调节、渗透压调节、血管舒张等生理过程, 还涉及缺血再灌注损伤、心律失常、心肌肥大、纤维化等病理过程[25]。

**1.2 细胞内Ca$^{2+}$敏感的TRPV5和TRPV6** TRPV5和TRPV6是两个具有最高Ca$^{2+}$选择性的TRP通道, 其

PCa/PNa比值超过100, 对$Ca^{2+}$具有显著的主导和重吸收作用, 这两种通道在许多方面都有相似之处, 它们的氨基酸序列同源性很高 (75%), 功能特性与调节机制也相似。TRPV5和TRPV6作为独特的钙选择性TRPV通道, 对于维持钙稳态至关重要。TRPV5主要定位于肾脏的远曲小管和连接小管, 而TRPV6的分布则更为广泛, 存在于人体的消化系统和泌尿生殖系统中, 包括胃、小肠、胰腺、前列腺、子宫及胎盘[26,27]。与其他TRPV通道相比, TRPV5及其同源家族成员TRPV6并不具备热敏感性或配体依赖的激活特性, 它们在生理膜电位下呈显著开放状态, 并以钙依赖的方式受到钙调素(calmodulin, CaM) 的调节[28]。TRPV5负责介导$Ca^{2+}$流入细胞, 作为跨上皮转运$Ca^{2+}$的初始步骤, 其选择性过滤序列由4个天冬氨酸残基环组成, 构成细胞外的$Ca^{2+}$结合袋, 参与调节细胞内外$Ca^{2+}$水平[29]。TRPV5主要分布于肾脏, 对尿钙水平具有调控作用, 而在肾脏中, 远曲小管和集合管是钙重吸收和$Ca^{2+}$调节激素的重要作用部位。研究发现[30], TRPV5基因敲除的小鼠尿钙排泄量比正常组小鼠高出6倍。另一方面, 肠胃对$Ca^{2+}$的吸收主要由TRPV6控制, 胃肠道中TRPV6蛋白的减少会导致骨密度降低, 生育能力下降, 并可能引发低钙血症[31]; 另外, TRPV6在人体多个系统的肿瘤形成、发展、增殖以及组织间迁移过程中扮演着重要角色, 它与食管癌、前列腺癌、胃癌、结直肠癌、肝癌和乳腺癌等多种癌症具有较高的关联性。如TRPV6通过增加活化T细胞核因子2 (nuclear factor of activated T-cells, cytoplasmic 2, NFATC2) 磷酸化来提高NFATC2的转录活性, 进而上调含血小板反应蛋白基序的解聚素样金属蛋白酶6 (a disintegrin and metalloproteinase with thrombospondin motifs 6, ADAMTS6) 表达, 促进乳腺癌的转移[32]; 在结肠癌与恶性细胞增殖过程中, TRPV6蛋白过表达[33]。TRPV1～6离子通道对比见表1。

## 2 辛味中药现代研究进展

辨识与表征五味及其物质基础为中药五味理论的研究奠定了基石, 亦对于五味理论体系的标准化建立具有重要作用。因此, 运用现代研究方法深入阐释中药五味理论的科学内涵, 是实现中药药性理论研究的重要环节。辛味是中药五味理论中的重要内容之一, 它能散能行, 有祛风解表散寒、行气化湿、活血行血的

**Table 1** Comparison of transient receptor potential vanilloid (TRPV) ion channels

| TRPV channel | Activating factor | Distribution site | Biological function |
|---|---|---|---|
| TRPV1 | Physical factors: heat (43 °C), mechanical stimuli;<br>Chemical factors: protons, capsaicin, resin toxins and endogenous ligands-intra vanillin etc. | Neurons, substantia nigra, hippocampus, cerebellum, hypothalamus, immune cells, organ epithelial cells and keratin-forming cells | Neuronal excitation and secretion, smooth muscle contraction, release of airway inflammatory mediators, tumors, proliferation, angiogenesis and regulation of cell death |
| TRPV2 | Physical factors: heat (>52 °C), mechanical stress;<br>Chemical factors: cannabidiol, probenecid, 2-aminoethoxydiphenylborate and lysophosphatidylcholine, etc. | Over the whole body, highly expressed in lungs, lymph nodes, spleen, placenta and appendix | Thermal sensation, neuronal development, osmosis, mechanosensation, maintenance of cardiac structure, insulin secretion, pro-inflammatory processes and tumor formation |
| TRPV3 | Physical factors: heat (>33 °C), mechanical stress;<br>Chemical factors: unsaturated fatty acids, eugenol, carvacrol, menthol, mullein, forsythia glycoside B, osthole, and isochlorogenic acids A, B, etc. | Dorsal root ganglia, nasal and oral epithelial cells, intestinal epithelial cells, highly expressed in skin keratinocytes | Sensing temperature, maintaining skin barrier function, promoting hair growth, influencing nerve signaling, regulating vascular tone, influencing keratinocyte proliferation and differentiation |
| TRPV4 | Physical factors: heat (30 °C), swelling, shear forces;<br>Chemical factors: arachidonic acid and its metabolites, endogenous cannabinoids, ATP, calmodulin, ruthenium red, and streptomycin | Widely expressed in nerves, retina, lungs, gastrointestinal tract, heart, vascular arteries and mammary glands | Thermoregulation, vasodilation, osmotic pressure regulation, ischemia-reperfusion injury, cardiac hypertrophy, arrhythmia, fibrosis, and tumor cell proliferation, differentiation, migration, and apoptosis |
| TRPV5 | Intracellular and extracellular $Ca^{2+}$ concentration, arachidonic acid and its metabolites, calmodulin, vitamin D | Peripheral tissues, kidneys and in distal tubules and connecting tubules, osteocytes | Neuroendocrine regulation, calcium reabsorption, regulation of calcium homeostasis |
| TRPV6 | Intracellular and extracellular $Ca^{2+}$ concentration, estradiol, calmodulin, 1,25-dihydroxyvitamin D3 | Brain, bronchial, lung, and bone cells, highly expressed in tissues of the human digestive and genitourinary systems, such as the stomach, small intestine, pancreas, and prostate, uterus, placenta, etc. | Extracellular calcium transport, calcium ion reuptake, involvement in regulation of bone metabolism, maintenance of local low-calcium environment, tumor cell proliferation and apoptosis |

作用, 并且现代研究表明, 辛味中药与TRPV通道关系密切, 其中TRPV1离子通道能通过多种途径影响机体水液代谢[34]; 辛味中药还通过敏化TRP通道产生疼痛, 持续刺激时, 使得TRP通道对辛味的刺激不再敏感, 疼痛信号减弱或消退从而产生止痛效果, 其中辛味中药羌活、艾叶、蛇床子、甘遂、芫花、细辛、香薷的醇提物能够激活TRPV1[35]。

**2.1　辛味中药物质基础的现代研究**　中药五味学说是中药研究的核心内容, 五味有其物质基础, 即药物中的化学成分、不同化学成分组合, 亦有各自特有的味道及特有功效, 寻找其中的规律, 有利于阐明药物作用机制与指导临床合理用药[36]。诸多学者对辛味药的现代研究主要从物质基础角度探究辛味药物的科学内涵[37]。中医药现代化的关键, 应是中医药在物质基础与化学成分上的融会贯通[38], 因此, 可以选择中药五味与化学成分之间的关系作为突破口开展研究。

近年来, 学者们针对辛味药的化学成分进行了广泛的研究, 结果表明辛味药的主要成分包括挥发油、苷类、生物碱、萜类等, 并认为“辛味”相关的药性理论可能由这些特殊的化学成分所决定[39,40]。为了寻找辛味中药共有的“印迹模板”特征, 研究者们采用分子连接性指数和匹配频数总量统计矩法, 对广藿香等6种辛味中药的指纹图谱进行了分析[41], 发现各批辛味中药挥发油中的主要成分均为萜类, 其中代表性成分如巴伦西亚橘烯、$\beta$-榄香烯、石竹素, 均属于倍半萜类, 这表明辛味物质是基于异戊二烯代谢途径的倍半萜“印迹模板”修饰的产物。电子舌主要由传感器阵列、信号采集系统、模式识别系统组成, 由多种味觉电极组成的传感器阵列可以将味道成分等化学信号转化为电信号, 相当于味觉系统的受体细胞负责识别味道成分; 信号采集相当于人的神经感觉系统, 负责传导、收集响应信号; 模式识别相当于人脑, 运用一些机器学习等算法建模, 对样品的不同味道进行判别、区分[42]。以川芎为例, 作为辛味中药的代表药之一, 通过电子舌表征和化学成分的“谱味”相关性分析, 发现挥发油是川芎发挥辛味的有效部位, 其中, 藁本内酯、洋川芎内酯A与丁烯苯酞这三种苯酞类成分是川芎挥发油辛味的物质基础[43]。采用数据挖掘技术对具有辛味的唇形科中药开展化学成分特征规律研究, 利用支持向量机算法构建辛味药性判别预测模型, 发现倍半萜类化学成分、倍半萜类和单萜类化学成分、倍半萜类和简单苯丙素类化学成分3种组合与辛味药性的关联性最强[44]。

**2.2　辛味中药分子生物学的现代研究**　辛味中药以其独特的药理作用和临床应用在传统中医药学中占有重要地位, 近年来辛味中药的分子生物学研究取得显著进展, 揭示了其在分子水平的作用机制和药效物质基础。有研究者采用代谢组学比较了辛味中药麻黄茎和麻黄根的化学成分, 发现二者挥发性成分相差较大, 麻黄茎中川芎嗪和$\alpha$-松油醇的含量远高于麻黄根, 且麻黄茎具有较高的游离自由基清除活性[45]。通过整合代谢组学和转录组学分析了蓝光通过诱导辛味中药川芎中黄酮类化合物生物合成基因的表达, 通过上调关键转录因子HY5 (elongated hypocotyl5) 和MYB (v-myb avian myeloblastosis viral oncogene homolog), 进而显著提高黄酮和黄酮类化合物的积累[46]。也有研究者[47]采用蛋白组学探讨生长调节剂对红花幼苗盐胁迫反应的影响, 发现水杨酸和戊唑醇可以使盐响应蛋白主要参与光合作用、离子稳态、氧化胁迫反应及氮、蛋白质和碳水化合物代谢。通过对辛温药附子、干姜和花椒进行大鼠能量代谢和生物标志物相结合的蛋白质组学研究, 结果发现[48]这3味辛温药主要通过两条途径来影响机体的物质代谢和能量代谢: 一是通过调控代谢相关蛋白的表达来影响机体代谢过程, 加快肝糖原分解, 减少糖原合成, 增加体内热量的产生; 二是通过调控氨基酸代谢相关蛋白的表达, 促进生物体内类固醇代谢, 并能通过N-聚糖生物合成途径来提高对能量的利用, 通过胰岛素信号通路上调相关的蛋白糖原合酶, 使糖原合成增多, 耗能增多。

通过建立阳虚大鼠模型发现辛热药可以对阳虚状态的下丘脑−垂体−靶腺轴相关指标如甲状腺4、皮质醇、雌二醇等具有显著上调作用, 而苦寒药反之[49]。吴茱萸有效成分吴茱萸碱[50]可以通过诱导铁死亡和低氧诱导转录因子1$\alpha$ (hypoxia-inducible factor-1$\alpha$, HIF1$\alpha$) 组蛋白乳酸化受损来抑制信号素3A (semaphorin 3A, Sema3A) 介导的前列腺癌细胞血管生成和细胞程序性死亡−配体1 (programmed cell death ligand 1, PD-L1) 表达。研究[51]发现, 川芎中主要有效成分川芎嗪通过激活核因子E2相关因子2/血红素加氧酶1/趋化因子C-X-C-基元受体4通路 (Nrf2/HO-1/CXCR4) 调控神经干细胞迁移干预缺血再灌注大鼠, 进一步从体外C17.2小鼠神经干细胞系明确了川芎嗪可易化脑内神经干细胞修复性、趋化性及放射性迁移等不同迁移类别。辛味中药附子[52]中的双酯型生物碱可以降低hERG蛋白和基因表达水平, 抑制心肌细胞hERG通道开放率, 其中次乌头碱抑制作用最为显著且呈剂量依赖性, 也有学者发现乌头碱可通过抑制腺苷酸激活蛋白激酶 (adenosine 5'-monophosphate-activated protein kinase, AMPK) 信号通路和破坏线粒体动力学, 导致SH-SY5Y细胞的线粒体能量代谢功能障碍, 表现为ATP生成抑制和线粒体呼吸功能异常[53]。辛味中药的分子生物学

研究涉及有效成分鉴定、生物活性研究、作用靶点探索、代谢途径解析及量效关系评价等, 通过分子生物学研究可以揭示辛味中药复杂的作用机制, 为辛味中药临床应用提供科学依据。

**2.3 辛味中药临床应用的现代研究** 辛味中药在传统临床医学中的应用比例较大, 被广泛用于治疗诸多疾病。辛味中药“能散、能行”。“散”即发散表邪, 主要用于表证, 统计国家“十四五”规划《临床中药学》解表药27味, 其中药味为辛味的24味, 占88%, 属辛且入肺经的21味占比77%, 说明辛味药主入肺经, 且具有发散表邪、解除表证的作用[54], 如麻黄、桂枝发散肌表的风寒邪气, 薄荷、牛蒡子发散肌表的风热邪气,《灵枢·五味论》所言“辛入而与汗俱出”, 可知辛味药是通过发汗的方式祛除表邪。“行”的含义有二, 一是行气, 主要用于气滞证, 统计《临床中药学》教材中行气药为25味, 药味为辛味的中药18味, 占72%, 主入脾、胃、肝、肺经, 通过调理气机、疏通郁滞, 促使气机通畅, 从而治疗气滞证, 如陈皮、木香均能理气健脾, 治疗脾胃气滞证; 二是行血, 主要用于瘀血证, 统计活血化瘀药为37味, 其中药味为辛味的18味, 占48%, 主入心、肝经, 通过通利血脉, 促进血行, 从而达到活血化瘀的目的, 如川芎、延胡索等均治疗血瘀气滞诸痛证。

此外, 古籍《素问·藏气法时论》中记载[55]“肾主冬, 足少阴太阳主治, 其日壬癸, 肾苦燥, 急食辛以润之, 开腠理, 致津液, 通气也”。指出“辛以润燥”,“燥”即缺少津液, 但导致津液缺少的原因是多方面的, 如津液充足、经络阻塞、输布不畅, 或单纯的津亏阴少、化源不足, 或阳气虚衰、无力载津运行等都可出现燥证[56], 现代研究表明津液输布失常是胰岛素抵抗形成的重要因素[57], 而辛味药则能促进津液的正常输布, 有助于改善胰岛素抵抗, 如辛味中药葛根[58]、苍术[59]、茺蔚子[60]等都可改善胰岛素抵抗。糖尿病是以多饮、多食、多尿为主要临床表现的疾病, 中医将其归于消渴证的范畴[61], 整理古籍发现辛味药是通过“辛以行气”、“辛以润之”的功效调畅三焦[62], 以助气机畅达、祛除三焦燥邪从而治疗糖尿病, 辛味中药佩兰[63]、厚朴[64]、枳实[65]等被证实能有效改善糖尿病。辛味中药的现代研究流程图如图2所示。

## 3 辛味中药基于TRPV通道的药理作用

**3.1 辛味中药基于TRPV通道发挥抗炎作用** 激活TRPV通道后, 可以诱导钙类物质、螺旋体缩氨酸及钙素基因相关肽的释放, 这些感觉神经肽作用于呼吸道的部分效应细胞, 包括平滑肌细胞、胆碱神经节和黏液腺等, 进而触发细胞周围的轴突反射、支气管收缩、蛋白质渗出、炎症细胞的定向迁移等效应[66]。生姜中的辛辣化合物 (姜辣素、姜烯酚和姜酮等) 通过激活TRPV1通道发挥抗炎作用, 这些辛辣化合物与TRPV1通道中特定的氨基酸残基 (如T551和E571) 形成氢键, 从而激活通道, 导致钙离子的流入, 发挥抗炎作用[67]。研究发现, 从辛味中药辣椒中分离得到的辣椒素 (capsaicin, CAP) 可以使牙周炎模型小鼠的TRPV1表达升高, 白细胞介素 (interleukin, IL)-1$\beta$ 降低, 并且辣椒素可用于减轻牙周炎的疼痛和加速愈合过程[68]。此外, 给大鼠骨关节炎 (osteoarthritis, OA) 模型的关节腔内注射辣椒素, 能显著减轻骨关节炎表型, 包括关节肿胀、滑膜炎、软骨损伤和骨赘形成等[69,70], 具体机制如图3所示。TRPV4作为软骨生成的关键调节因子, 其功能变化也被认为是骨关节炎的危险因素, 它的表达和功能异常会引起细胞坏死和凋亡、软骨细胞外基质降解、滑膜炎症反应和痛觉过敏[71]。吴茱萸碱 (evodiamine, EVO) 是辛味中药吴茱萸“辛香走窜”的物质基础, 能够激活TRPV1受体来发挥抑制炎症反应

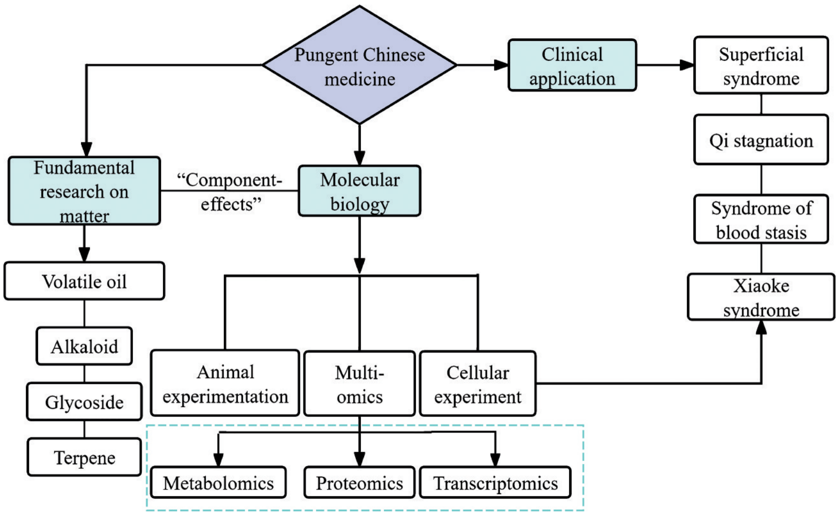

**Figure 2** Flowchart of modern research on pungent Chinese medicine

的作用, 其机制主要涉及抑制IL-4诱导的M2型巨噬细胞分泌的细胞因子转化生长因子-$\beta$ (transforming growth factor-$\beta$, TGF-$\beta$)[72], 吴茱萸碱还能通过TRPV1受体抑制Toll样受体4/核因子$\kappa$B (TLR4/NF-$\kappa$B)信号通路, 促进细胞的增殖和NO的合成, 进而减轻脂多糖引起的人脐静脉内皮细胞炎性损伤[73]。也有研究发现, 抑制TRPV1亦可发生抗炎作用, TRPV1拮抗剂辣椒平通过调控TRPV1使气道上皮细胞因子和前额叶皮质中辅助性T细胞2型相关细胞因子下调, 从而减轻气道炎症, 使气道重塑来发挥抗炎作用[74]。在卵清蛋白诱导的哮喘小鼠模型中, TRPV1在肺组织中的表达显著升高, 其肺泡灌洗液中Th2细胞相关细胞因子IL-3、IL-5和IL-13显著升高, 而使用TRPV1抑制剂治疗的哮喘小鼠IL-3、IL-5和IL-13显著降低[75]。

**3.2　辛味中药基于TRPV通道发挥镇痛作用**　TRPV1被认为是痛觉过敏的中枢传导器和控制疼痛的主要靶点, 因为它是许多痛觉通路会聚的中心点。在炎症条件下, TRPV1表现出高度的易激性, 一方面, 众多炎症介质及其受体信号的整合能够敏化并激活TRPV1, 如炎症期间受影响的组织会产生质子, 进而激活TRPV1, 导致TRPV1敏化并引发疼痛, 此外, 磷脂酶C活化的下游过程也会激活TRPV1, 从而将TRPV1与多种疼痛途径和过程紧密联系起来[76], 值得注意的是, 在炎症的刺激下, TRPV1还会降低疼痛产生的阈值, 进而引发痛觉过敏; 另一方面, 表达TRPV1的神经元不仅负责检测有害刺激, 它们的外周末梢还是多种神经肽的释放位点, 其中最主要的是P物质 (substance P) 和降钙素基因相关肽, 这些神经肽的释放会反过来触发神经源性炎症的生化级联反应, 导致血浆外渗、血管扩张和白细胞募集, 从而进一步放大炎症反应并加剧疼痛[77]。树脂毒素 (resiniferatoxin, RTX) 是从大戟属植物的乳胶中提取的辣椒素超能类似物, 是一种选择性的TRPV1激动剂, 持续或反复激活TRPV1通道导致其脱敏, 可以选择性地减少TRPV1初级痛觉信号传递, 全身或局部应用树脂毒素几乎可以完全消除痛感[78]。高浓度的辣椒素导致TRPV1表达的传入末梢消融介导的长期去功能化, 与树脂毒素相同, 反复激活TRPV1通道导致其功能下调, 减少痛觉信号的传递, 发挥镇痛作用。

最新研究[79]表明, 在小鼠神经病理性疼痛模型中辣椒素诱导的Ca$^{2+}$/钙蛋白酶介导的轴突终末消融与钙蛋白酶结合, 产生持久的镇痛作用。已有研究证实生姜中的活性成分8-姜烯酚 (8-shogaol, 8S) 可以直接激活TRPV1, 诱导细胞内Ca$^{2+}$内流, 在体外和体内实验中, 8-姜烯酚诱导的TRPV1激活导致通道脱敏, 原因可能是TRPV1的降解或细胞中TRPV1的表达减少[80]; 6-姜烯酚 (6-shogaol, 6S) 与8-姜烯酚作用机制类似, 通过脱敏TRPV1通道减少脊髓中TRPV1和*N*-甲基-*D*-天冬氨酸2B (*N*-methyl-*D*-aspartic acid receptor 2B, NMDAR2B) 的表达来减轻糖尿病神经病理性疼痛的症状[81,82], 具体机制如图4所示。大鼠体内预先给予吴茱萸碱, 能有效抑制由足底注射辣椒素引发的热痛觉过敏现象, 这一作用机制涉及脱敏TRPV1, 从而抑制HEK293细胞中由辣椒素诱导的电流反应[83]。大麻素作为辛味中药大麻的主要活性成分之一, 能够部分阻断由神经生长因子诱导的传入痛觉感受器神经末梢TRPV1的敏化过程, 进而产生镇痛效果[84]。从辛味中药丁香中提取得到的丁香酚在高浓度下可以抑制辣椒素诱导的小鼠TRPV1的激活, 减少TRPV1内向电流, 从而减少疼痛信号的传导, 可作为靶向TRPV1的止痛药的先导化合物[85]。

**3.3　辛味中药基于TRPV通道发挥神经保护作用**　当感觉神经被激活后, 它不仅能够触发外周神经释放神经肽, 进而引发外周的神经源性炎症, 还具备向中枢神经系统传递信号的能力, 这些信号经过中枢解码后, 可导致防御性或厌恶性行为反射, 如喷嚏, 并可能进一步引发一系列精神行为症状, 包括认知缺陷、情绪波动、记忆力减退、焦虑及抑郁等。TRPV通道存在于中枢神经系统的广泛区域, 包括前述的海马、大脑皮层及中央杏仁核、丘脑、下丘脑、三叉神经脊束核等的广泛区域, 因此已经成为治疗神经精神障碍的新型靶点[86]。TRPV1和TRPV4已被证明在中枢神经系统中的调节

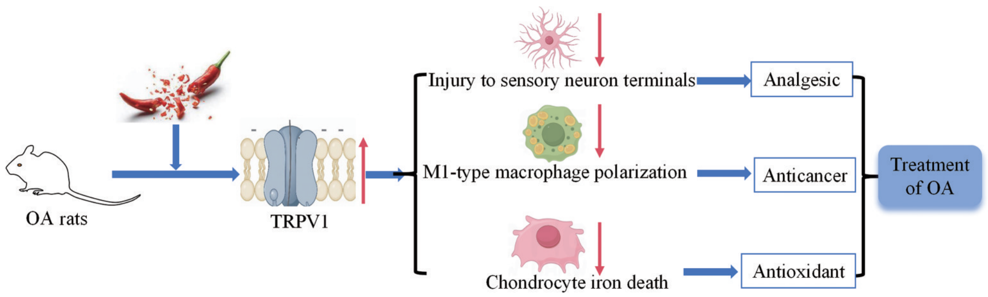

**Figure 3**　Mechanism of action of capsaicin in the treatment of osteoarthritis (OA) through activation of TRPV1

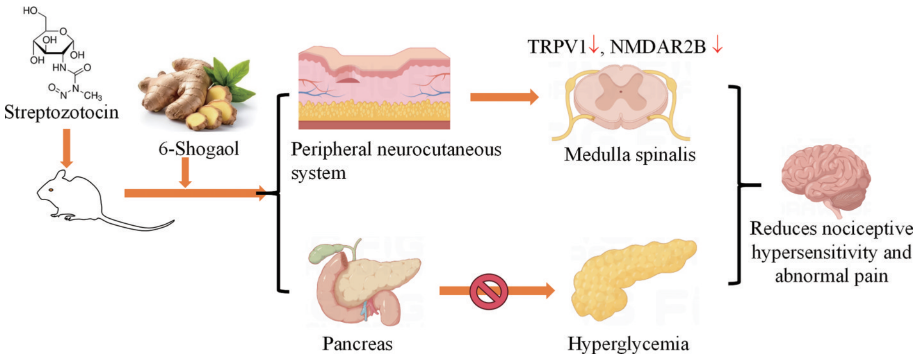

**Figure 4** Mechanism of action of 6-shogaol in alleviating diabetic neuralgia by inhibiting TRPV1. NMDAR2B: *N*-Methyl-*D*-aspartic acid receptor 2B

突触可塑性、介导神经行为和调节神经炎症方面发挥重要作用[87]。TRPV1是重要的小胶质细胞功能调节因子, TRPV1的激活触发钙离子内流以启动丝裂原激活蛋白激酶 (mitogen-activated protein kinase, MAPK) 信号家族, 而MAPK信号家族在神经元可塑性、中枢敏化和认知能力方面的作用已得到了证实[88]。在大鼠下丘脑神经元中, TRPV5与加压素、催产素、雌激素受体以及可卡因和安非他明调节转录共表达[86], TRPV6与雌激素受体$\alpha$共表达, 并且发现是小鼠脑中动情周期的关键调节剂[89]。

在大鼠的大脑局部缺血模型中, 辣椒素展现出神经保护效应, 这一效应与神经元TRPV1的参与以及NMDA受体表达的下调密切相关[90]。此外, 辣椒素还能在帕金森病模型大鼠中激活TRPV1蛋白, 通过调节氧化应激水平保护多巴胺能神经元, 进而改善大鼠的运动功能并缓解帕金森病的症状[91], 进一步的研究表明, 辣椒素通过调节自噬途径和氧化应激途径, 特异性地作用于TRPV1, 下调肌动蛋白$\gamma$1 [gamma($\gamma$)-actin 1, Actg1] 的表达并上调谷胱甘肽*S*-转移酶$\alpha$2 (glutathione *S*-transferase alpha 2, Gsta2), 从而减轻由6-羟基多巴胺诱导的帕金森病模型中细胞的凋亡, 实现神经保护的作用[92], 具体机制如图5所示。6-姜烯酚通过调控凋亡蛋白、PI3K/Akt/mTOR/s6K信号通路以及HIF-1$\alpha$/HO-1的表达来增强七弗醚介导的针对缺血/再灌注诱导的脑损伤的神经保护作用[93]; 8-姜烯酚预处理可有效降低胞内$Ca^{2+}$水平、胞外乳酸脱氢酶含量, 提高细胞存活率, 具有神经保护作用[94]。大麻二酚 (cannabidiol, CBD) 是辛味中药大麻中的非精神治疗活性成分, 大麻二酚可以通过激活TRPV2来诱导人脑内皮细胞的增殖、迁移和小管形成, 增加跨内皮电阻, 因此, TRPV2可以作为调节血脑屏障的一个潜在靶点[95]。$\beta$-细辛醚是辛味中药细辛的挥发油成分之一, $\beta$-细辛醚以剂量依赖性地抑制谷氨酸诱导的$Ca^{2+}$超载, 抑制TRPV4的表达, 对兴奋性毒性具有较强的神经保护作用[96]。

**3.4 辛味中药基于TRPV通道发挥抗癌作用** 离子通道功能障碍与肿瘤细胞的增殖、抵抗凋亡、侵袭及迁移等特征密切相关。TRPV通道的激活会受到细胞内信号、翻译后修饰以及脂质和蛋白质相互作用的影响, 一旦被激活, TRPV通道可能会改变膜电位或细胞内$Ca^{2+}$浓度, 从而影响细胞活力, 它们与癌症的发生发展密切相关[97]。大麻二酚具有直接激活TRPV1受体的能力, 在乳腺癌细胞系中, 大麻二酚可以通过激活TRPV1受体, 诱导$Ca^{2+}$内流, 进而触发内质网应激反应, 从而提高细胞内ROS水平并破坏蛋白质折叠, 成

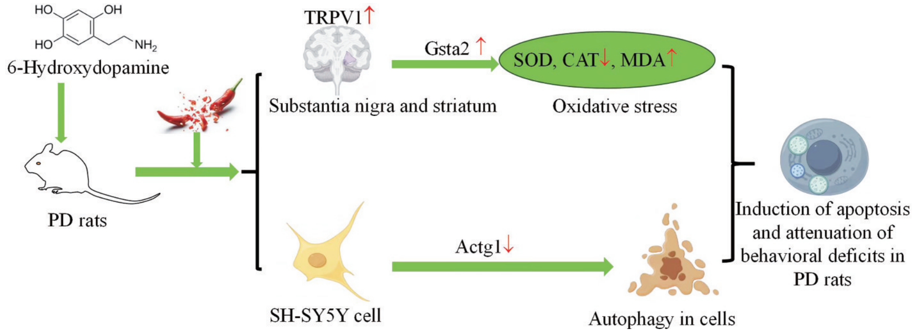

**Figure 5** Mechanism of action of capsaicin in ameliorating PD through activation of TRPV1. PD: Parkinson's disease; Gsta2: Glutathione *S*-transferase alpha 2; Actg1: Gamma ($\gamma$)-actin 1; SOD: Superoxide dismutase; CAT: Catalase; MDA: Malondialdehyde

为导致肿瘤细胞死亡加剧的一个有力途径[98]。多形性胶质瘤 (glioblastoma multiforme, GBM) 是人类最致命的脑肿瘤之一, TRPV2表达的下降或完全丧失与GBM的进展有关, 大麻二酚可抑制人脑胶质瘤细胞系的活力并且增加细胞内钙离子、TRPV2的表达和化疗药物的摄取, 同时促进自噬和细胞凋亡[99,100], 具体机制如图6所示。研究发现TRPV2在口腔鳞状细胞癌 (oral squamous cell carcinoma, OSCC) 中呈现高表达, 并与预后不良相关, 其可通过PI3K/Akt等信号通路以及调控巨噬细胞免疫浸润水平参与OSCC的发生和发展过程[101]; 另一方面, TRPV3的高度表达与胰腺癌、骨癌、乳腺癌的疼痛发生密切相关[102]。值得注意的是, 甘草酸能通过激活TRPV4诱导线粒体自噬, 进而有效抑制脑胶质瘤的生长[103]。金雀异黄素 (5,7,4'-三羟基异黄酮, 亦称金雀异黄酮或染料木素), 作为多种辛味中草药的天然活性成分, 广泛存在于葛根、大豆、金雀花、槐角、广豆根等豆科植物中, 大量的体内、体外实验与临床试验结果均表明, 金雀异黄素能通过调控肿瘤细胞的细胞周期、细胞凋亡、血管生成、细胞侵袭和细胞转移, 进而发挥显著的抗肿瘤作用[104], 金雀异黄素还能与TRPV6通道的孔隙结合[105], 当二者结合时, 金雀异黄素发挥双重作用: 一方面, 它能够阻断离子通道, 阻止钙离子的流入, 从而降低细胞内的钙离子浓度; 另一方面, 它能够作为门控修饰剂, 影响离子通道的开闭, 并且导致通道结构在S4-S5和S6-TRP螺旋区域发生一系列对称性的结构调整。

### 3.5　辛味中药基于TRPV通道发挥抗皮肤瘙痒作用

TRPV通道广泛表达于皮肤组织, 包括角质形成细胞和外周感觉神经纤维, 由于遗传、炎症和环境损害造成的皮肤屏障损害会增加表皮的水分损失, 并通过激活无髓鞘C纤维来增强瘙痒感觉, 最初的激活通常会刺激瘙痒−抓挠循环, 这会加剧表皮损伤, 从而继续导致瘙痒, 参与皮肤相关性瘙痒的TRPV通道是TRPV1、TRPV3和TRPV4[106]。多项体内外研究均证实了TRPV1在特应性皮炎病理生理学机制中的重要作用及关键效应, 因此以TRPV1为靶标的药物研发取得了迅速发展, TRPV1拮抗剂不仅能够抑制由TRPV1、PAR-2及组胺介导的瘙痒搔抓行为, 还通过加速皮肤屏障的恢复, 有效抑制特应性皮炎样症状[107]。

诸多研究表明TRPV3有助于检测瘙痒信号[108,109], 在人和小鼠体内, TRPV3的功能获得性突变表现为严重瘙痒、角化过度和总免疫球蛋白E (immunoglobulin E, IgE) 水平升高[110]; 也会导致表皮金黄色葡萄球菌定植增加, 血清IL-4水平升高, $CD4^+$ T细胞浸润增加, 干扰皮肤屏障的内稳态, 抑制真皮中的毛发生长[111]; TRPV3通道的激活还可触发多种因子的释放, 包括前列腺素E2 (prostaglandin E2, PGE2)、ATP、NO和神经生长因子 (nerve growth factor, NGF), 加重皮肤瘙痒[112]。从辛味中药牛至中提取的天然单萜香芹酚是一种已知的TRPV3激动剂[113], 可引起小鼠的抓挠行为, 而敲除TRPV3或给予TRPV3抑制剂可缓解小鼠的皮肤瘙痒[114]。连翘苷B可以抑制TRPV3通道来减轻急性和慢性瘙痒, 降低由功能增强的TRPV3突变或通道激动剂香芹酚引起的细胞毒性[115]。辛味中药蛇床子的主要药效物质基础蛇床子素已被证实是一种TRPV3抑制剂, 它可以逆转2,4-二硝基氟苯 (2,4-dinitrofluorobenzene, DNFB) 诱导的特应性皮炎 (atopic dermatitis, AD) 模型与耳肿胀模型, 并能够抑制小鼠原代角质形成细胞中TRPV3及炎症因子肿瘤坏死因子$\alpha$ (tumor necrosis factor-$\alpha$, TNF-$\alpha$)、IL-6和IL-1$\beta$ mRNA表达的增加[116], 从而来减轻皮肤损伤、水肿和严重瘙痒, 具体机制如图7所示。还有研究认为, 巨噬细胞中TRPV4的缺失抑制了小鼠模型中的过敏性和非过敏性瘙痒[117], 因此TRPV4对皮肤瘙痒具有间接作用, 在皮肤角质形成细胞中发挥最前沿的信号分子作用。

## 4　总结和展望

近年来, 随着对辛味中药药理作用的深入研究, 越

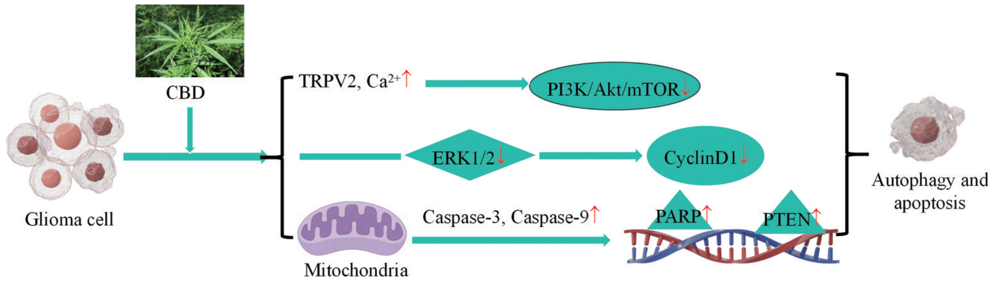

**Figure 6**　Mechanism of anticancer action of cannabidiol through activation of TRPV2. PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; mTOR: Mammalian target of rapamycin; ERK1/2: Extracellular regulatory protein kinase 1/2; Caspase-3: Cysteine-aspartate protease 3; Caspase-9: Cysteine-aspartate protease 9; PARP: Poly adenosinediphosphate-ribose polymerase; PTEN: Phosphatase and tensin homolog deleted on chromosome ten

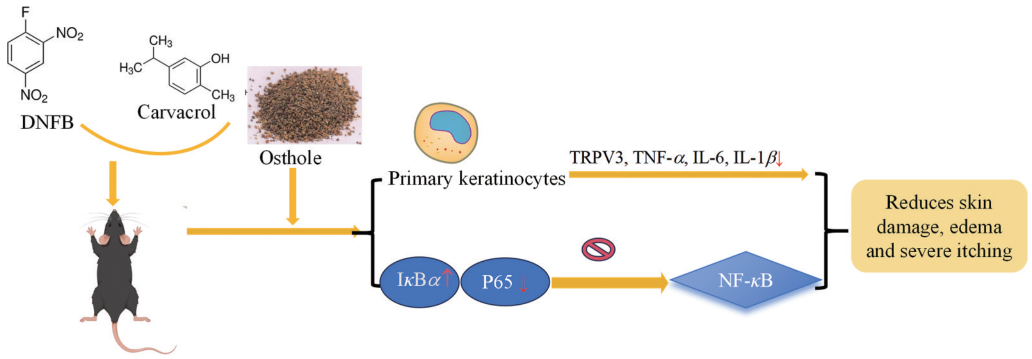

**Figure 7** Mechanism of action of serpentin inhibiting TRPV3 in the treatment of atopic dermatitis. DNFB: 2, 4-Dinitrofluorobenzene; TNF-*α*: Tumor necrosis factor-*α*; IL: Interleukin; NF-*κ*B: Nuclear factor-*κ*B; I*κ*B*α*: Inhibitor of NF-*κ*B*α*; P65: RelA

来越多的证据表明TRPV通道在辛味中药的作用机制中扮演着重要角色。TRPV通道作为一类重要的通透钙离子通道, 参与多种生理和病理过程, 如温度感知、渗透刺激、疼痛传导、糖尿病、炎症、心血管、中枢神经和泌尿系统疾病等。辛味中药“能行”、“能散”, 在传统中医药中被广泛应用于治疗表证、气滞证、瘀血证等病证, 而与这些病证相关的症状和TRPV通道的激活或抑制密切相关。如表2所示, 辛味中药中许多活性成分通过与TRPV受体相结合从而发挥药理作用。通过运用药效团虚拟筛选技术与文献挖掘相结合的方法, 发现[118]在TRPV1激动剂药效团模型所筛选出的中药活性成分中, 有60.11%的成分属于辛味中药。辛味中药中的有效成分能够通过激活TRPV通道产生温热感并缓解疼痛。作为温度感受器的TRP家族离子通道与中药药性中的辛热、辛凉特性存在关联。TRPV1是一种热激活通道的辣椒素受体, 能够被辛热中药辣椒中的辣椒素、吴茱萸中的吴茱萸碱等激活[119], 而TRPM8是一种冷激活通道的薄荷醇受体, 能够被辛凉中药薄荷的主要成分薄荷醇激活[120]。纵观前期学者对TRPV通道与辛味中药的研究主要从动物模型探究辛味中药对机体能量代谢、体温调节等方面的影响, 通过热电偶检测等技术监测相关生理参数的变化; 利用细胞培养、基因转染等细胞与分子生物学技术构建TRPV通道表达体系, 从而研究辛味中药成分对TRPV通道的影响。当然, 学者们也通过显微成像等技术观察通道蛋白的表达和激活情况; 药效团虚拟筛选技术能够筛选作用于TRPV通道的辛味中药成分, 以发现新的辛味中药或药效成分, 从而探索更多中药成分对TRPV通道的影响及其作用机制, 上述研究为中药药性的科学诠释提供了更多的依据和思路。

综上所述, 基于TRPV通道的辛味中药药理作用研究主要围绕辛味中药可以通过激活或调节TRPV通道来产生温热感、缓解疼痛、抗炎、抗癌、止痒、神经保护和心血管保护等药理作用开展了相关工作。后期学者们还可通过类器官培养、外泌体、空间代谢组学等技术进一步揭示辛味中药中的有效成分与TRPV通道间的相互作用机制, 以期为辛味中药的临床应用提供更充分的科学依据。

**作者贡献**: 王佳佳负责综述中相关文献查阅和撰写工作; 杨志军、牛鹏贤、田一虹、吉庆云完成文献查阅工作和作图; 段国建、李硕、杨秀娟完成文章修改、校对和审核。

**利益冲突**: 所有作者均声明不存在利益冲突。

**Table 2** Active molecules of pungent Chinese medicines

| Pungent Chinese medicine | Active ingredient | English abbreviation | Flavor and taste | Pharmacological effect | Site of action |
|---|---|---|---|---|---|
| Capsicum | Capsaicin | CAP | Pungent, hot | Anti-inflammatory, analgesia, neuroprotection | TRPV1 |
| Euodiae Fructus | Evodiamine | EVO | Pungent, bitter, hot | Anti-inflammatory | TRPV1 |
| Euphorbia | Resiniferatoxin | RTX | Pungent, bitter, cold | Analgesia | TRPV1 |
| Ginger | 6-Shogaol | 6S | Pungent, slightly warm | Anti-inflammatory, analgesia | TRPV1 |
| Ginger | 8-Shogaol | 8S | Pungent, slightly warm | Anti-inflammatory, analgesia | TRPV1 |
| Cloves | Eugenol | - | Pungent, warm | Analgesia | TRPV1 |
| Hemp | Cannabidiol | CBD | Pungent, warm | Neuroprotection, anti-cancer | TRPV1, TRPV2 |
| Asarum | *β*-Asarone | - | Pungent, warm | Neuroprotection | TRPV4 |
| Pueraria lobata root | Genistein | - | Pungent, sweet, cool | Anti-cancer | TRPV6 |
| Oregano | Carvacrol | - | Pungent, slightly bitter, cool | Relief of itching | TRPV3 |
| Cnidium monnieri | Osthole | - | Pungent, bitter, warm | Relief of itching | TRPV3 |

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