

刘翼骁,韩欣园,肖依彤,等. 甘草次酸及其衍生物在神经退行性疾病中的防治作用研究进展 [J]. 中国实验动物学报, 2024, 32(7): 923-932.

LIU Y X, HAN X Y, XIAO Y T, et al. Advancements in research on the preventive and curative roles of glycyrrhetic acid and its derivatives in neurodegenerative disease [J]. Acta Lab Anim Sci Sin, 2024, 32(7): 923-932.

Doi:10.3969/j.issn.1005-4847.2024.07.011

# 甘草次酸及其衍生物在神经退行性疾病中的防治作用研究进展

刘翼骁<sup>1</sup>,韩欣园<sup>1</sup>,肖依彤<sup>1</sup>,于昕卓<sup>1</sup>,叶田园<sup>2\*</sup>

(1. 山东中医药大学中医学院,济南 250355;2. 山东中医药大学中医药创新研究院,济南 250355)

**【摘要】** 随着全球人口老龄化加剧,神经退行性疾病发病率逐年上升,严重影响老年患者的生活质量,给社会带来沉重负担。甘草次酸是中药甘草的主要活性成分之一,具有抑制神经炎症、保护神经元等作用,对于甘草次酸及其衍生物在神经退行性疾病中的作用机制研究日益增多。本研究综述了甘草次酸及其衍生物在阿尔茨海默病、帕金森病、肌萎缩性脊髓侧索硬化症、多发性硬化和小脑萎缩的作用及其机制的研究,并对其未来在神经退行性疾病中的应用进行讨论与展望。

**【关键词】** 甘草次酸;衍生物;作用机制;神经退行性疾病

**【中图分类号】** Q95-33 **【文献标志码】** A **【文章编号】** 1005-4847 (2024) 07-0923-10

## Advancements in research on the preventive and curative roles of glycyrrhetic acid and its derivatives in neurodegenerative disease

LIU Yixiao<sup>1</sup>, HAN Xinyuan<sup>1</sup>, XIAO Yitong<sup>1</sup>, YU Xinzhuo<sup>1</sup>, YE Tianyuan<sup>2\*</sup>

(1. College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250355, China; 2. Innovative Institute of Chinese Medicine and Pharmacy, Shandong University of Traditional Chinese Medicine, Jinan 250355, China)

Corresponding author: YE Tianyuan. E-mail: yetianyuan2013@163.com

**【Abstract】** The annual incidence of neurodegenerative disease has been increasing with the aging of the global population, seriously affecting the quality of life of elderly patients and imposing a heavy burden on society. Glycyrrhetic acid, which inhibits neuroinflammation and protects neurons, is one of the main active ingredients of the traditional Chinese medicine *Glycyrrhiza glabra*. Increasing numbers of studies are focusing on the mechanism of action of glycyrrhetic acid and its derivatives in neurodegenerative disease. This review summarizes studies on the effects and mechanisms of action of glycyrrhetic acid and its derivatives in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and cerebellar atrophy. Additionally, the future applications of glycyrrhetic acid and its derivatives in neurodegenerative disorders are discussed.

**【Keywords】** glycyrrhetic acid; derivative; mechanism of action; neurodegenerative disease

Conflicts of Interest: The authors declare no conflict of interest.

[基金项目] 国家自然科学基金(82205078),山东省自然科学基金(ZR2021QH157),山东省中医药科技项目(2021Q079),山东省大学生创新创业训练计划项目(S202310441013,S202310441012)。

Funded by National Natural Science Foundation of China (82205078), Natural Science Foundation of Shandong Province (ZR2021QH157), Shandong Province Traditional Chinese Medicine Technology Project (2021Q079), the Student Innovation and Entrepreneurship Training Program Project of Shandong Province (S202310441013, S202310441012).

[作者简介] 刘翼骁,在读本科生,研究方向:中药药理与毒理学研究。Email:2302534289@qq.com

[通信作者] 叶田园,硕士生导师,研究方向:中药药理与毒理学研究。Email:yetianyuan2013@163.com

神经退行性疾病是由中枢神经系统神经元变性引发的不可逆的神经病变,包括阿尔茨海默病、帕金森病、肌萎缩性脊髓侧索硬化症、多发性硬化、小脑萎缩等,主要表现为认知障碍和记忆力明显下降,同时也会出现运动障碍<sup>[1]</sup>。随着世界老龄化进展加速,神经退行性疾病逐渐成为棘手的社会难题。

中医学认为阿尔茨海默病 (Alzheimer's disease, AD) 属“痴呆”范畴,肾精亏虚所致的脑髓失养与脑内浊毒的内生会使脑消髓减、神机失常,从而引发阿尔茨海默病。 $\beta$ -淀粉样蛋白 (amyloid- $\beta$ , A $\beta$ ) 是阿尔茨海默病的主要病理产物之一,属于脑内浊毒内生,会损伤脑髓、蒙蔽心窍<sup>[2]</sup>。帕金森病 (Parkinson's disease, PD) 属于“颤证”范畴,病位在脑,病性本虚标实,其以脾虚为本,络脉阻滞为标。患者脾失运化,致水湿停聚,气血运行不畅,脾主升清功能失常,且脾在体合肉,脾在液为涎<sup>[3]</sup>。临床上帕金森病患者表现为精神萎靡、四肢沉重、肌肉僵硬、流涎等,与中医理论相应<sup>[3]</sup>。肌萎缩性脊髓侧索硬化症 (amyotrophic lateral sclerosis, ALS) 初期,表现为肌肉颤动伴发疼痛,归为“瘛病”,中后期肌肉萎缩逐渐成为主要症状,归为“痿病”,多表现为脾肾亏虚,临床上可见肌肉萎缩无力、精神不振<sup>[4]</sup>。中医对于神经退行性疾病治疗多以补肾健脾、益气活血为主,补肾健脾以治疗肾精亏虚所致的脑髓失养与脾胃亏虚所致的精神萎靡、四肢无力,益气活血以“补其不足,损其有余”,补气血,祛瘀毒<sup>[5]</sup>。

当前能够明确治愈神经退行性疾病的药物尚未出现,某些药物服用后会产生一系列不良反应。中药凭借其多靶点、副作用较少的优势,逐渐被人们重视,大量中药活性成分的作用机制被逐渐挖掘。许多中药单体与复合物已被证实在促进神经

元生成和减轻神经炎症等方面发挥着有效作用,如川陈皮素能够下调 APP/PS1 小鼠中高迁移率族蛋白 B1 (high mobility group box 1 protein, HMGB-1) 和半胱氨酸蛋白酶-1 (Caspase-1) 表达,抑制神经炎症,提高小鼠空间学习和记忆能力<sup>[6]</sup>。鱼腥草酸钠可以通过抑制 NOD 样受体热蛋白结构域相关蛋白 3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3)/焦孔素 D (gasdermin D, GSDMD) 表达来减轻 A $\beta$  氧化应激造成的神经元损伤<sup>[7]</sup>。海藻糖可以通过诱导细胞自噬清除突变亨廷顿蛋白以及  $\alpha$ -突触核蛋白的自噬底物,并抑制 tau 蛋白的磷酸化<sup>[8]</sup>。越来越多的中药在神经退行性疾病的治疗中展现出巨大潜力。

甘草来源于豆科甘草属植物的干燥根以及根茎,为中医组方中的常见药,归心、肺、脾、胃经。具备益气解毒,调和诸药的功效,被誉为“国老”,其主要活性成分甘草次酸 (glycyrrhetic acid, GA) 是一种五环三萜类化合物,具有手性刚性骨架和多个反应位点,生物相容性较好,近年来备受关注<sup>[9]</sup>。甘草次酸及其衍生物 18 $\alpha$ -甘草次酸 (18 $\alpha$ -GA)、18 $\beta$ -甘草次酸 (18 $\beta$ -GA) (化学结构见图 1) 逐渐被证实具有抑制神经炎症、防止神经元损伤、抗氧化应激等作用,能够通过血脑屏障<sup>[10]</sup>,对于神经退行性疾病的预防和治疗展现出潜在的价值。本研究综述了近年来对于甘草次酸及其衍生物在神经退行性疾病中的作用及机制研究,以期对神经退行性疾病的防治提供新思路。

## 1 甘草次酸的药物代谢动力学

### 1.1 人体内的药物代谢动力学

健康男性志愿者口服不同剂量的甘草次酸

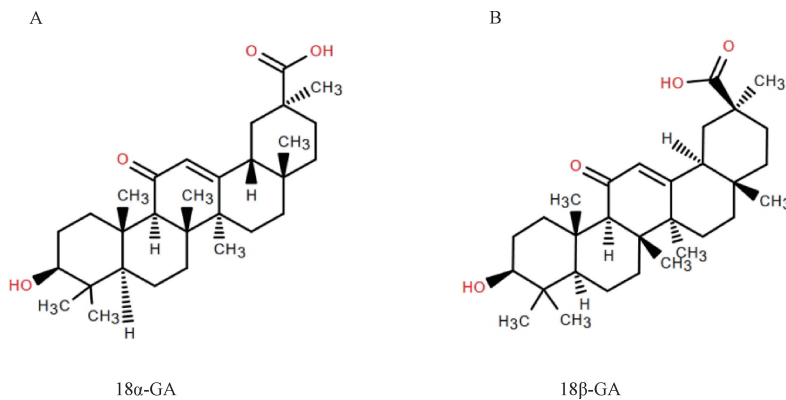


图 1 18 $\alpha$ -GA 和 18 $\beta$ -GA 的化学结构

Figure 1 Chemical structures of 18 $\alpha$ -GA and 18 $\beta$ -GA

(500、1000、1500 mg)后,采用高效液相色谱法测定血浆和尿液中甘草次酸的浓度,当甘草次酸剂量 > 500 mg 时,血药浓度-时间曲线呈双相衰减。1000 mg 组和 1500 mg 组第二消除相的平均半衰期分别为(11.5 ± 1.2)h 和(38.7 ± 10.5)h。血药浓度峰值和药时曲线下面积(area under curve, AUC)随甘草次酸剂量增加而增大。甘草次酸和甘草次酸葡萄糖醛酸苷在 24 h 内的尿排出量的含量不到给药剂量的 1%。其动力学特点是在组织中广泛分布,达峰时间长<sup>[11]</sup>,同时甘草次酸在人体内存在肠肝循环<sup>[12]</sup>。

### 1.2 大鼠体内的药物代谢动力学

通过反相高效液相色谱法分析大鼠血浆中甘草次酸,乙腈沉淀法处理血浆样品,甘草次酸血药浓度在 50 ~ 2000 ng/mL 时,线性关系良好( $r = 0.9997$ ),血药浓度-时间曲线与二室开放模型相符合。100、1000、2000 ng/mL 的甘草次酸回收率分别为(105.2 ± 2.23)%、(102.5 ± 2.95)%、(98.4 ± 2.32)%。分布相的生物半衰期为(0.153 ± 0.023)h,消除相的生物半衰期为(2.365 ± 0.866)h,  $C_{max} = (2.074 \pm 0.100) \text{ mg/L}$ ,  $CL = (0.715 \pm 0.082) \text{ L}/(\text{h} \cdot \text{kg})$ ,  $Vd = (2.427 \pm 0.872) \text{ L/kg}$ ,  $AUC_{0-6 \text{ h}} = (1.302 \pm 0.151) \text{ mg}/(\text{h} \cdot \text{L})$ 。表明甘草次酸在大鼠体内快速广泛分布<sup>[13]</sup>。甘草次酸在大鼠体内的分布容积为 100 ~ 1000 mL/kg,在大鼠血浆中先快速分布,后缓慢消除。甘草次酸主要以葡萄糖醛酸苷以及硫酸盐的形式被胆汁排出,在尿液中含量极少,未发现明显的肠肝循环<sup>[14]</sup>。

## 2 甘草次酸的毒性

大鼠口服甘草次酸(100 mg/kg) 16 d 后,血浆和尿液中甘草次酸的代谢产物 3-O-单葡萄糖醛酸基甘草次酸(glycyrrhetic acid 3-O-mono- $\beta$ -d-glucuronide, GAMG)水平显著升高,GAMG 通过有机阴离子转运体(organic anion transporters, OATs)主动转运到肾小管后,11 $\beta$ -羟基类固醇脱氢酶(11 $\beta$ -hydroxysteroid dehydrogenase, 11 $\beta$ -HSD)受到抑制,肾小管上皮细胞中的皮质醇累积,从而诱发假性醛固酮增多症<sup>[15]</sup>。小鼠单次静脉注射甘草次酸(每只 100  $\mu\text{L}$ )后发现 11 $\beta$ -HSD2 受到抑制,皮质酮水平增加,胸腺和脾中的淋巴细胞凋亡<sup>[16]</sup>。18 $\beta$ -GA (20  $\mu\text{mol/L}$ )能够诱导小鼠腹膜巨噬细胞中一氧化氮(nitrous oxide, NO)的产生,下调抗炎细胞因子白介

素-10(interleukin-10, IL-10)和白介素-4(interleukin-4, IL-4)的表达水平,上调促炎细胞因子白介素-12(interleukin-12, IL-12)、干扰素- $\gamma$ (interferon gamma, IFN- $\gamma$ )和肿瘤坏死因子- $\alpha$ (tumor necrosis factor- $\alpha$ , TNF- $\alpha$ )表达水平<sup>[17]</sup>,这可能会导致靶器官损伤。甘草次酸(10  $\mu\text{mol/L}$ )处理大鼠肝细胞线粒体后,会引起线粒体肿胀以及膜电位丧失,并引发细胞色素 C 释放,从而引发细胞凋亡<sup>[18]</sup>。

## 3 甘草次酸及其衍生物在神经退行性疾病中的作用

### 3.1 阿尔茨海默病(Alzheimer's disease, AD)

AD 是与年龄密切相关的最常见的神经退行性疾病之一,其发生与 A $\beta$  的沉积、tau 蛋白高度磷酸化形成的神经原纤维缠结、神经元丢失和神经炎症等密切相关<sup>[19]</sup>。

甘草次酸及其衍生物可以通过减弱神经毒性、减少神经元死亡发挥神经保护作用。3  $\times$  Tg-AD 小鼠是 AD 的常用模型<sup>[20]</sup>,谷胱甘肽(glutathione, GSH)耗竭会引发 3  $\times$  Tg-AD 小鼠神经元的死亡,上调核因子 NF-E2 相关因子(nuclear factor-erythroid 2-related factor 2, Nrf2)能够提高神经元抗氧化应激能力<sup>[21]</sup>。18 $\alpha$ -GA 可以恢复 3  $\times$  Tg-AD 神经元中较低的 Nrf2 和谷氨酰半胱氨酸连接酶(glutamate cysteine ligase, GCL)水平,通过上调 GCL 水平刺激 GSH 的合成,并促进 Nrf2 转移至细胞核,提高神经元在 A $\beta$  应激下的存活率,从而达到保护神经的目的<sup>[22]</sup>。7-酮胆固醇能诱导大鼠肾上腺嗜铬细胞瘤(rat adrenal pheochromocytoma, PC12)细胞核受损,线粒体跨膜电位丧失,胞质促凋亡蛋白(Bcl2-associated X, Bax)和细胞色素 C 水平升高, Caspase-3 活化和细胞死亡,18 $\beta$ -GA 能够降低线粒体促凋亡蛋白/B 细胞淋巴瘤 2(Bcl2-associated X/B-cell lymphoma-2, Bax/Bcl-2)比率<sup>[23]</sup>,抑制线粒体受损,抑制 Caspase-3 活化以减少细胞色素 C 释放,并能够通过抑制线粒体膜通透性的变化,保护 7-酮胆固醇诱导的神经元损伤<sup>[24]</sup>。同时,18 $\beta$ -GA 还可以激活 PC12 细胞中的磷脂酰肌醇-3-激酶/丝苏氨酸蛋白激酶(phosphatidylinositol 3-kinase/serine-threonine kinase, PI3K/AKT)信号通路<sup>[23]</sup>,使其免受 A $\beta$  诱导的神经毒性,减少 A $\beta$  的产生和沉积、tau 的过度磷酸化<sup>[25]</sup>。N-甲基-D-天冬氨酸受体(N-methyl-D-aspartic acid receptor, NMDAR)是谷氨酸触发的离

子门控通道,在神经系统的兴奋性突触传递、可塑性和神经毒性中起关键作用<sup>[26]</sup>。NMDAR 可以结合 A $\beta$  并转导突触毒性<sup>[27]</sup>,而甘草次酸能够抑制 NMDAR 以发挥神经保护作用<sup>[28]</sup>。乙酰胆碱 (acetylcholine, ACh) 能够减少 A $\beta$  产生与集聚<sup>[29]</sup>,通过 Ellman 方法检测 18 $\beta$ -GA 对乙酰胆碱酯酶 (acetylcholinesterase, AChE) 的抑制作用,发现 18 $\beta$ -GA 可以通过抑制 AChE 从而维持 ACh 的水平和作用持续时间,从而减轻 AD<sup>[30]</sup>。

18 $\beta$ -GA 能够通过抑制炎症反应和 tau 磷酸化在 AD 中发挥作用。小胶质细胞的 p38 丝裂原活化蛋白激酶 (p38 mitogen-activated protein kinase, p38 MAPK) 信号激活会引发 AD 中的炎症,同时星形胶质细胞中的 c-Jun 氨基末端激酶 (c-Jun N-terminal kinase, JNK) 与 p38 MAPK 级联能导致炎症反应并引发兴奋毒性,神经元的 p38 MAPK 信号则会促使 tau 磷酸化<sup>[31]</sup>。研究表明,18 $\beta$ -GA 能够抑制 p38 MAPK、JNK 和 tau 磷酸化水平<sup>[32]</sup>。AD 的发生与神经炎症密切相关,病原体脂多糖 (lipopolysaccharide, LPS) 激活的巨噬细胞可以引发神经炎症。LPS 可诱导磷脂酰肌醇-3-激酶 (phosphatidylinositol 3-kinase, PI3K) 和核因子- $\kappa$ B (nuclear factor  $\kappa$ B, NF- $\kappa$ B) 活化,从而产生活性氧 (reactive oxygen species, ROS)、前列腺素 (prostaglandin, PG)、NO、TNF- $\alpha$ , 促进 AD 炎症反应<sup>[33]</sup>。18 $\beta$ -GA 能够抑制 NF- $\kappa$ B 和 PI3K 的活性,减少 LPS 诱导的 TNF- $\alpha$ 、白介素-6 (interleukin-6, IL-6) 和白介素-1 $\beta$  (interleukin-1 $\beta$ , IL-1 $\beta$ ) 的产生,抑制 LPS 诱导的 NO、前列腺素 E2 (prostaglandin E2, PGE2) 的生成和 ROS 堆积,从而通过抑制炎症反应改善 AD<sup>[34]</sup>。

A $\beta$  斑块集聚会诱导连接蛋白半通道开放,从而释放谷氨酸和三磷酸腺苷 (adenosine triphosphate, ATP),引发神经毒性,损伤神经元来加速 AD 进程<sup>[35]</sup>。在 A $\beta$  斑块周围反应性星形胶质细胞中的间隙连接蛋白 43 (connexin43, Cx43) 表达增加,Cx43 半通道活性也增加,18 $\alpha$ -GA 能够通过抑制连接蛋白半通道的开放来改善 AD 病理<sup>[36]</sup>。8-溴-环二磷酸腺苷核糖 (8-bromo-cadp-ribose, 8-Br-cADPR) 处理小鼠原代小胶质细胞后,ADP-核糖基环化酶/环 ADP 核糖 (cluster of differentiation 38/cyclic ADP ribose, CD38/cADPR) 通路被抑制,Cx43 半通道过度激活,小胶质细胞释放 ATP 增多,引发小胶质细胞的凋亡和炎症,18 $\alpha$ -GA 能够抑制其诱

导的 Cx43 半通道开放,并激活 CD38,减少 ATP 释放,从而减少小胶质细胞的凋亡<sup>[37]</sup>。另有研究表明,特异性敲除 Cx43 可显著改善 APP/PS1 双转基因小鼠的空间学习记忆能力和物体识别记忆能力<sup>[38]</sup>,因此推测 18 $\alpha$ -GA 可通过抑制 Cx43 半通道来改善认知障碍。

### 3.2 帕金森病 (Parkinson's disease, PD)

PD 为常见的神经退行性疾病之一,PD 患者可表现为肌肉强直、运动迟缓和步态失常等运动障碍以及抑郁、认知功能减退等非运动障碍。病理特征主要包括黑质多巴胺能神经元的缺失以及纹状体多巴胺含量减少<sup>[39]</sup>。

甘草次酸及其衍生物能够调节促炎因子释放,减少神经元缺失。小胶质细胞促炎因子的释放量与多巴胺神经元的存活率呈负相关<sup>[40]</sup>,根据微环境的不同,小胶质细胞会形成促炎或抗炎表型,这两种表型都对神经元起重要的调节作用<sup>[41]</sup>。1-甲基-4-苯基-1,2,3,6-四氢吡啶 (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP) 可以诱导促炎型小胶质细胞释放促炎因子,如 IL-1 $\beta$ 、IL-6 和 TNF- $\alpha$ ,诱发神经炎症引起神经元缺失,常用于构建 PD 动物模型<sup>[42]</sup>。小胶质细胞可通过上调 IL-4、IL-10 等抗炎因子表达发挥神经保护作用<sup>[43]</sup>。18 $\beta$ -GA 能够通过激活抗炎型小胶质细胞释放抗炎因子从而对 MPTP 诱导的小鼠显示出神经保护作用,随着 18 $\beta$ -GA 浓度的增加,抗炎因子 IL-4 和 IL-10 表达水平升高,促炎细胞因子 IL-6 和 IL-1 $\beta$  数量减少<sup>[44]</sup>,炎症反应引起的神经元受损也得到缓解。Cx43 半通道异常开放释放的 ATP 可诱导小胶质细胞活化,其中以促炎型小胶质细胞为主<sup>[45]</sup>。在 MPTP 诱导的雄性杂合 Cx30 KO 小鼠中,纹状体中 Cx43 表达增加<sup>[46]</sup>,星形胶质细胞 Cx43 半通道通透性也增加<sup>[47]</sup>,18 $\beta$ -GA 可以抑制 Cx43 半通道开放,减少促炎因子释放,以防止神经元变性<sup>[48]</sup>。Caspase 的激活为神经元凋亡的主要因素之一,Bcl-2 家族成员是调节其激活环节的关键<sup>[49]</sup>,Bcl-2 可降低线粒体外膜的通透性,抑制线粒体释放凋亡因子,在双酚 A (bisphenol A, BPA) 诱导后,大鼠脑细胞 Bax/Bcl-2 比率升高,18 $\beta$ -GA 给药可下调 Bax 和 Caspase-3 的表达,上调 Bcl-2 表达,从而抑制细胞色素 C 释放,减少神经元损伤与凋亡<sup>[32]</sup>。髓系细胞触发受体 2 (triggering receptor expressed on myeloid cells 2, TREM2) 作为炎症反应的关键调节因子,能够下调 TNF- $\alpha$  的表达<sup>[50]</sup>,Nrf2

能够启动 TREM2 的转录, 1-甲基-4-苯基吡啶 (N-methyl-4-phenylpyridinium, MPP) 是一种神经毒性化合物, 能够引发神经炎症, 杀死多巴胺能神经元<sup>[51]</sup>, 18 $\beta$ -GA 处理 MPP 诱导的小胶质细胞后, 抗炎型小胶质细胞活化, 细胞核中 Nrf2 的水平上调, TREM2 的表达也随 18 $\beta$ -GA 浓度升高而升高, 神经元缺失得到抑制<sup>[44]</sup>。综上, 18 $\beta$ -GA 可通过抑制 Cx43 半通道开放, 激活抗炎型小胶质细胞, 减少神经元受损。

18 $\beta$ -GA 可通过多条通路延缓 PD 进程。BDNF/TrkB 信号通路与中枢神经系统活动密切相关, 酪氨酸激酶受体 B (tyrosine kinase receptor B, TrkB) 为脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 的受体, 促进 BDNF 上调可防止黑质变性<sup>[52]</sup>。18 $\beta$ -GA 处理 Wistar 大鼠后, 发现其前额叶皮层和海马体中的 TrkB 与 BDNF 的表达均有所增加<sup>[53]</sup>。18 $\beta$ -GA 可以通过上调 PI3K-Akt 通路抑制 6-羟基多巴胺 (oxidopamine hydrobromide, 6-OHDA) 诱导的 PC12 细胞死亡<sup>[23]</sup>。另有研究发现, 18 $\beta$ -GA 还能够通过激活 PI3K-AKT 通路<sup>[23]</sup>, 促进多巴胺神经元生长<sup>[54]</sup>。以上研究表明, 18 $\beta$ -GA 可通过促进 BDNF 表达上调, 激活 PI3K-Akt 信号通路保护神经细胞。

### 3.3 肌萎缩性脊髓侧索硬化症

肌萎缩性脊髓侧索硬化症 (amyotrophic lateral sclerosis, ALS) 是一种由运动神经元变性引起的破坏性疾病。ALS 患者在脊髓星形胶质细胞中表现出 NF- $\kappa$ B 活性增加的趋势<sup>[55]</sup>, NF- $\kappa$ B 已被证明能够推动神经退行性疾病发展<sup>[56]</sup>, 其可控制 TNF- $\alpha$  等炎症细胞因子, 引起神经元死亡和脱髓鞘<sup>[57]</sup>。18 $\beta$ -GA 可以通过抑制 NF- $\kappa$ B 信号通路来缓解 BPA 诱导的 Wistar 白化大鼠的神经炎症, 显著下调 TNF- $\alpha$  表达, 抑制 NF- $\kappa$ B 信号通路, 减少神经元死亡与脱髓鞘<sup>[32]</sup>。同时在家族性病例中 ALS 是超氧化物歧化酶 1 基因 (recombinant superoxide dismutase 1, SOD1) 发生突变所致<sup>[58]</sup>。几乎所有突变都导致 SOD 活性显著丧失<sup>[59]</sup>。18 $\beta$ -GA 可提高成年正常小鼠侧脑室室下区 (subventricular zone, SVZ) 中神经干细胞 (neural stem cell, NSCs) 的 SOD1 表达, 减少细胞内 ROS 的堆积, 维持成年小鼠 SVZ 的 NSCs 增殖潜能<sup>[60]</sup>。

### 3.4 多发性硬化和小脑萎缩

多发性硬化 (multiple sclerosis, MS) 是中枢神经系统慢性炎症性脱髓鞘疾病的一种, 病理上可见中枢

神经系统白质的脱髓鞘、炎症细胞因子浸润等<sup>[61]</sup>, 包括肢体无力等症状。小脑萎缩 (cerebellar atrophy, CA) 是小脑的退行性病变, 也会出现脱髓鞘的现象<sup>[62]</sup>。氯丙嗪 (chlorpromazine, CPZ) 能够诱导细胞凋亡并引发中枢神经系统脱髓鞘<sup>[63]</sup>。18 $\beta$ -GA 能够上调髓鞘碱性蛋白 (myelin basic protein, MBP) 水平, 降低 CPZ 诱导的脱髓鞘损伤; 同时还能够使小胶质细胞极化由促炎型小胶质细胞向抗炎型小胶质细胞转移, 并改善小鼠的运动能力<sup>[64]</sup>。

## 4 甘草次酸治疗神经退行性疾病的主要机制

### 4.1 抗氧化应激

中枢神经系统含多种不饱和脂肪酸、耗氧量大, 抗氧化能力弱, 神经元容易受到氧化应激的影响<sup>[65]</sup>。当代谢失衡, ROS 累积到一定程度, 大于神经元细胞解毒能力时, 就会导致氧化应激, 造成神经元凋亡。氧化应激与 AD、PD 等和年龄关联紧密的神经退行性疾病息息相关<sup>[66]</sup>。GSH 是存在于人体的抗氧化剂, 可以拮抗各类炎症细胞因子的氧化, 在神经退行性疾病中发挥重要作用<sup>[67]</sup>。1-甲基-4-苯基吡啶离子 (N-methyl-4-phenylpyridinium iodide, MPP<sup>+</sup>) 处理可以抑制呼吸链, 引发线粒体功能障碍, 从而致使 ROS 堆积, 产生毒性与炎症<sup>[68]</sup>。18 $\beta$ -GA 能够有效预防 MPP<sup>+</sup> 诱导的 GSH 减少<sup>[69]</sup>, 减少氧化应激带来的损伤。

### 4.2 抑制细胞衰老和凋亡

上述提到的氧化应激能够通过线粒体激活 MAPK-JNK 途径, JNK 转运入细胞核后会激活 p53 转录, p53 能够引发细胞凋亡和自噬从而导致神经元损伤和死亡<sup>[70-71]</sup>, BPA 对生物体具有急性毒性<sup>[72]</sup>。BPA 诱导后, 大鼠脑组织中 JNK 水平上升, 而 18 $\beta$ -GA 与 BPA 联合给药后, p38 MAPK 和 JNK 的水平受到抑制, 脑细胞凋亡减少<sup>[32]</sup>。DNA 损伤可以通过诱导细胞衰老凋亡和组织功能障碍来促进个体衰老, 并引发与年龄相关的神经退行性疾病<sup>[73]</sup>, 18 $\beta$ -GA 可以通过激活细胞外调节蛋白激酶 (extracellular regulated protein kinases, ERK)/Nrf2 途径减轻丝裂霉素 C (mitomycin C, MMC) 诱导的 DNA 损伤<sup>[74]</sup>, 从而治疗神经退行性疾病。18 $\beta$ -GA 可以抑制 Caspase-3 的激活, 减少 MPP<sup>+</sup> 诱导的细胞凋亡<sup>[69]</sup>。泛素-蛋白酶体系统 (ubiquitin-proteasome system, UPS) 能够调控蛋白酶体功能, 蛋白酶体系统

表 1 各类模型中甘草次酸及其衍生物对于神经退行性疾病的作用机制研究

Table 1 Mechanism of action of glycyrrhetic acid and its derivatives in various models of neurodegenerative diseases

成分 Ingredient	模型 Model	作用机制 Mechanisms of action	参考文献 Reference
	GCL 抑制剂处理的 3 × Tg-AD 小鼠神经元 GCL inhibitor-treated neurons in 3 × Tg-AD mice	激活 Nrf2, 上调 GCL, 刺激 GSH 合成, 促进 Nrf2 入核, 提高神经元存活率 Activates Nrf2, upregulates GCL, stimulates GSH synthesis, promotes Nrf2 entry into the nucleus, improves neuronal survival	[22]
	DCFS 处理的星形胶质细胞 DCFS-treated astrocytes	通过抑制半通道, 限制谷氨酸的过量释放, 减少兴奋性毒性 Reducing excitotoxicity by inhibiting hemichannels, limiting excessive glutamate release	[80]
	HIV 处理的星形胶质细胞 HIV-treated astrocytes	作用于半通道和间隙连接, 减少细胞凋亡 Acts on hemichannels and gap junctions to reduce apoptosis	[85]
	PGN 处理的小胶质细胞 PGN-treated microglia	抑制连接蛋白 Cx43 表达, 抑制促炎信号传导 Inhibition of connexin Cx43 expression and inhibition of pro-inflammatory signalling	[82]
18 $\alpha$ -GA	8-Bromo-cADPR 处理的小胶质细胞 8-Bromo-cADPR-treated microglia	促进 CD38/cADPR 依赖性信号传导, 激活 CD38, 减轻 ATP 过量释放引发的小胶质细胞凋亡 Promotion of CD38/cADPR-dependent signalling, activation of CD38 attenuates microglial apoptosis triggered by excessive ATP release	[37]
	BALB/c 小鼠中的 NSCs NSCs in BALB/c mice	上调 Nrf2 蛋白水平, 促进 SOD1 表达, 减少 ROS 堆积, 维持 NSCs 增殖潜能 Up-regulation of Nrf2 protein level, promotes SOD1 expression, reduces ROS accumulation, maintains the proliferative potential of NSCs	[60]
	BPA 处理的 NSCs BPA-treated NSCs	激活 UPS, 增加蛋白酶体活性, 促进 NSCs 增殖和分化 Activation of UPS, increase in proteasome activity, promotion of NSCs proliferation and differentiation	[76]
	LPS 处理的 IEC-6 细胞 LPS-treated IEC-6 cells	抑制 Cx43 半通道开放, 减少促炎因子释放 Inhibition of Cx43 hemichannel opening, reduces pro-inflammatory factor release	[48]
	MMC 处理的人成纤维细胞 MMC-treated human fibroblasts	激活 ERK/Nrf2 途径, 减轻 DNA 损伤和氧化应激以减少细胞凋亡 Activation of ERK/Nrf2 pathway, attenuate DNA damage and oxidative stress to reduce apoptosis	[74]
	CUMS 处理的 Wistar 大鼠 CUMS-treated Wistar rats	激活 BDNF/TrkB 信号通路, 减轻神经炎症 Activation of BDNF/TrkB signalling pathway, reduce neuroinflammation	[53]
	BPA 处理的 Wistar 白化大鼠 BPA-treated Wistar albino rats	抑制 JAK1/STAT1 与 NF- $\kappa$ B 信号通路, 抑制细胞色素 C 释放, 减少神经元损伤 Inhibition of JAK1/STAT1 and NF- $\kappa$ B signalling pathway, inhibits cytochrome C release and reduces neuronal damage	[32]
	全脑缺血再灌注处理的 C57BL/J6 小鼠 Whole brain ischemia-reperfusion-treated C57BL/J6 mice	提高 SOD 活性, 发挥抗炎抗氧化作用 Enhances SOD activity, exerts anti-inflammatory and antioxidant effects	[86]
	CPZ 处理的 KM 小鼠 CPZ-treated KM mice	上调 MBP 表达, 降低脱髓磷脂损伤, 扭转小胶质细胞极化方向, 改善小鼠运动能力 Up-regulation of MBP expression, reduces demyelinating phospholipid damage, reverses the direction of microglia polarisation, improves locomotion in mice	[64]
18 $\beta$ -GA	MPP 处理的 PC12 细胞 MPP treated PC12 cells	限制 GSH 减少, 抑制 Caspase-3 激活, 减少细胞凋亡 Limiting GSH reduction, inhibiting Caspase-3 activation, reduces apoptosis	[69]
	6-OHDA 处理的 PC12 细胞 6-OHDA-treated PC12 cells	激活 PI3K/Akt 信号通路, 降低 Bax/Bcl-2 比率, 抑制 Caspase-3 活化, 减少细胞色素 C 释放, 减少细胞死亡 Activates PI3K/Akt signalling pathway, reduces Bax/Bcl-2 ratio, inhibits Caspase-3 activation, reduces cytochrome C release, reduces cell death	[23]
	LPS 处理的巨噬细胞 LPS-treated macrophages	抑制 NF- $\kappa$ B 信号通路传导与 PI3K 活性, 减少 TNF- $\alpha$ , IL-6 和 IL-1 $\beta$ 等促炎因子产生, 抑制 NO、PGE2 生成, 改善 ROS 堆积 Inhibits NF- $\kappa$ B signalling pathway transmission and PI3K activity, reduces the production of pro-inflammatory factors such as TNF- $\alpha$ , IL-6 and IL-1 $\beta$ , inhibits NO and PGE2 production, ameliorates ROS accumulation	[34]
	MPP 处理的小胶质细胞 MPP-treated microglia	上调细胞核中 Nrf2 水平, 启动 TREM2 转录, 活化抗炎型小胶质细胞 Up-regulation of Nrf2 levels in the nucleus, initiates TREM2 transcription, activation of anti-inflammatory microglia	[44]

故障可能导致泛素阳性聚合体在神经元细胞的包涵体中积聚,从而引发神经元的功能紊乱,导致细胞应激和凋亡。越来越多的研究表明蛋白酶体失效在多种神经退行性疾病的发病机制中起着重要作用<sup>[75]</sup>。BPA 通过抑制蛋白酶体介导神经毒性<sup>[76]</sup>,能够抑制 NSCs 的增殖分化,损害髓鞘形成,并导致线粒体碎片化过多<sup>[77]</sup>。18 $\alpha$ -GA 能够激活 UPS,使蛋白酶体活性增加,抑制 BPA 介导的神经毒性,促进 NSCS 增殖和分化,并发挥神经保护作用<sup>[76]</sup>。

#### 4.3 调节星形胶质细胞与连接蛋白

星形胶质细胞与在其内部高度表达的连接蛋白在神经退行性疾病的发展中发挥着重要作用,近年来对其在神经退行性疾病中的机制研究日益增多<sup>[78]</sup>。谷氨酸是大脑中主要的兴奋性神经递质。星形胶质细胞谷氨酸转运蛋白能够通过摄取细胞外谷氨酸来防止神经元因谷氨酸兴奋性中毒而死亡<sup>[79]</sup>。18 $\alpha$ -GA 能够通过星形胶质细胞来抑制半通道,限制谷氨酸的过量释放<sup>[80]</sup>,减少谷氨酸诱导的细胞死亡<sup>[81]</sup>。金黄色葡萄球菌衍生的肽聚糖 (peptidoglycan, PGN) 会诱导 Cx43 表达的显著增加,促进促炎信号传导,通过间隙连接阻断剂 18 $\alpha$ -GA 可以逆转 PGN 诱导的小胶质细胞损伤<sup>[82]</sup>。人类免疫缺陷病毒-1 (human immunodeficiency virus-1, HIV-1) 感染会损害中枢神经系统,导致认知障碍甚至严重的神经功能障碍<sup>[83]</sup>,其可以抑制含连接蛋白的通道,如缝隙连接和半通道,促进细胞色素 C 以及促炎因子大量释放,并引发细胞凋亡<sup>[84]</sup>。18 $\alpha$ -GA 可通过抑制缝隙连接和半通道防止 HIV-1 对中枢神经系统的损伤<sup>[85]</sup>。

## 5 讨论

甘草次酸作用于神经元后,能够激活 Nrf2 并上调 GCL 水平,促进 GSH 合成并促进 Nrf2 移位进入细胞核,提高神经元在 A $\beta$  应激下的存活率。在上调 Nrf2 水平的同时,甘草次酸能够促进 TREM2 转录,激活抗炎型小胶质细胞释放抗炎因子,抑制 MAPK-JNK 途径,减少促炎细胞因子生成,减轻神经炎症,保护神经元。在小胶质细胞中,甘草次酸能够抑制连接蛋白 Cx43 表达,促进 CD38/cADPR 依赖性信号传导,减少 ATP 释放,降低 Bax/Bcl-2 比率,减少细胞色素 C 释放,同时能够上调 MBP 表达,降低脱髓磷脂损伤,改善小胶质细胞极化方向,

抑制促炎信号传导,减少小胶质细胞凋亡。在星形胶质细胞中,甘草次酸能够抑制 p38MAPK 和 JNK 水平,降低 tau 磷酸化水平,抑制 NF- $\kappa$ B 信号通路,显著下调 TNF- $\alpha$  表达,抑制半通道,降低谷氨酸的过量释放引起的神经毒性,减少神经炎症(见表 1)。

综上,甘草次酸可通过 Nrf2、Cx43、MBP 等多靶点和 MAPK-JNK、NF- $\kappa$ B、PI3K-AKT 等多条信号通路,保护神经元、星形胶质细胞、小胶质细胞等神经细胞。由于神经退行性疾病发病机制复杂,传统的单靶点药物较难发挥疗效,甘草次酸及其衍生物能够通过多靶点、多信号通路在神经退行性疾病中发挥作用。不过,要将甘草次酸及其衍生物推广到临床应用还需要进一步的体内外实验研究。

#### 参 考 文 献 (References)

- [1] WILSON D M 3rd, COOKSON M R, VAN DEN BOSCH L, et al. Hallmarks of neurodegenerative diseases [J]. *Cell*, 2023, 186(4): 693-714.
- [2] 王晋平,莫雪妮,古联,等. 基于认知障碍症状分期分度标准探讨阿尔茨海默病论治新思路 [J]. *中华中医药杂志*, 2023, 38(11): 5360-5364.  
WANG J P, MO X N, GU L, et al. Exploration on the new idea of treating Alzheimer's disease based on the grading standard of cognitive impairment symptoms [J]. *Chin J Tradit Chin Med Pharm*, 2023, 38(11): 5360-5364.
- [3] 潘才钰,盛和静. 培元解痉汤结合调神畅志安眠法针刺治疗帕金森病伴失眠疗效观察 [J]. *中华中医药学刊*, 2023, 41(12): 207-210.  
PAN C Y, SHENG H J. Clinical effect of Peiyuan jiejing decoction combined with acupuncture for regulating spirit, invigorating mind and calming sleep on Parkinson's disease with insomnia [J]. *Chin Arch Tradit Chin Med*, 2023, 41(12): 207-210.
- [4] 王柳丁,樊雪鸣,申伟,等. 张允岭从“脾肾并重”论治肌萎缩侧索硬化症经验 [J]. *中医杂志*, 2023, 64(20): 2067-2070.  
WANG L D, FAN X M, SHEN W, et al. ZHANG Yunling's experience in the treatment of amyotrophic lateral sclerosis from emphasis on both spleen and kidney [J]. *J Tradit Chin Med*, 2023, 64(20): 2067-2070.
- [5] 应春苗,刘飞翔,潘小龙,等. 中药延缓神经血管单元衰老治疗神经退行性疾病的研究进展 [J]. *中国中药杂志*, 2023, 48(15): 4060-4071.  
YING C M, LIU F X, PAN X L, et al. Research progress on traditional Chinese medicine in treatment of neurodegenerative diseases by delaying neurovascular unit aging [J]. *Chin J Chin Mater Med*, 2023, 48(15): 4060-4071.
- [6] CHAI W, ZHANG J, XIANG Z, et al. Potential of nobletin against Alzheimer's disease through inhibiting neuroinflammation [J]. *Metab Brain Dis*, 2022, 37(4): 1145-1154.

- [ 7 ] ZHAO Y, TIAN Y, FENG T. Sodium houttuynonate ameliorates  $\beta$ -amyloid<sub>1-42</sub>-induced memory impairment and neuroinflammation through inhibiting the NLRP3/GSDMD pathway in Alzheimer's disease [J]. *Mediators Inflamm*, 2021, 2021: 8817698.
- [ 8 ] WANG S F, WU M Y, CAI C Z, et al. Autophagy modulators from traditional Chinese medicine: Mechanisms and therapeutic potentials for cancer and neurodegenerative diseases [J]. *J Ethnopharmacol*, 2016, 194: 861-876.
- [ 9 ] JIN L, DAI L, JI M, et al. Mitochondria-targeted triphenylphosphonium conjugated glycyrrhetic acid derivatives as potent anticancer drugs [J]. *Bioorg Chem*, 2019, 85: 179-190.
- [ 10 ] SUN Y, DAI C, YIN M, et al. Hepatocellular carcinoma-targeted effect of configurations and groups of glycyrrhetic acid by evaluation of its derivative-modified liposomes [J]. *Int J Nanomedicine*, 2018, 13: 1621-1632.
- [ 11 ] KRÄHENBÜHL S, HASLER F, FREY B M, et al. Kinetics and dynamics of orally administered 18  $\beta$ -glycyrrhetic acid in humans [J]. *J Clin Endocrinol Metab*, 1994, 78(3): 581-585.
- [ 12 ] CARLAT L E, MARGRAF H W, WEATHERS H H, et al. Human metabolism of orally ingested glycyrrhetic acid and monoammonium glycyrrhizinate [J]. *Proc Soc Exp Biol Med*, 1959, 102: 245-248.
- [ 13 ] 陆洋, 李娟, 杜卓颖. 甘草次酸在大鼠体内药动学的 RP-HPLC 研究 [J]. *中国中药杂志*, 2008, 33(11): 1294-1296. LU Y, LI J, DU S Y. Study on pharmacokinetics of glycyrrhetic acid in rats by RP-HPLC [J]. *Chin J Chin Mater Med*, 2008, 33(11): 1294-1296.
- [ 14 ] KRÄHENBÜHL S, HASLER F, KRAPF R. Analysis and pharmacokinetics of glycyrrhizic acid and glycyrrhetic acid in humans and experimental animals [J]. *Steroids*, 1994, 59(2): 121-126.
- [ 15 ] MAKINO T, OKAJIMA K, UEBAYASHI R, et al. 3-Monoglucuronyl-glycyrrhetic acid is a substrate of organic anion transporters expressed in tubular epithelial cells and plays important roles in licorice-induced pseudoaldosteronism by inhibiting 11 $\beta$ -hydroxysteroid dehydrogenase 2 [J]. *J Pharmacol Exp Ther*, 2012, 342(2): 297-304.
- [ 16 ] HORIGOME H, HOMMA M, HIRANO T, et al. Glycyrrhetic acid induced apoptosis in murine splenocytes [J]. *Biol Pharm Bull*, 2001, 24(1): 54-58.
- [ 17 ] UKIL A, BISWAS A, DAS T, et al. 18 Beta-glycyrrhetic acid triggers curative Th1 response and nitric oxide up-regulation in experimental visceral leishmaniasis associated with the activation of NF- $\kappa$ B [J]. *J Immunol*, 2005, 175(2): 1161-1169.
- [ 18 ] SALVI M, FIORE C, ARMANINI D, et al. Glycyrrhetic acid-induced permeability transition in rat liver mitochondria [J]. *Biochem Pharmacol*, 2003, 66(12): 2375-2379.
- [ 19 ] GUO T, ZHANG D, ZENG Y, et al. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease [J]. *Mol Neurodegener*, 2020, 15(1): 40.
- [ 20 ] STOVER K R, CAMPBELL M A, VAN WINSSEN C M, et al. Analysis of motor function in 6-month-old male and female 3xTg-AD mice [J]. *Behav Brain Res*, 2015, 281: 16-23.
- [ 21 ] KANNINEN K, HEIKKINEN R, MALM T, et al. Intrahippocampal injection of a lentiviral vector expressing Nrf2 improves spatial learning in a mouse model of Alzheimer's disease [J]. *Proc Natl Acad Sci U S A*, 2009, 106(38): 16505-16510.
- [ 22 ] GHOSH D, LEVAULT K R, BREWER G J. Dual-energy precursor and nuclear erythroid-related factor 2 activator treatment additively improve redox glutathione levels and neuron survival in aging and Alzheimer mouse neurons upstream of reactive oxygen species [J]. *Neurobiol Aging*, 2014, 35(1): 179-190.
- [ 23 ] KAO T C, SHYU M H, YEN G C. Neuroprotective effects of glycyrrhizic acid and 18  $\beta$ -glycyrrhetic acid in PC12 cells via modulation of the PI3K/Akt pathway [J]. *J Agric Food Chem*, 2009, 57(2): 754-761.
- [ 24 ] KIM D E, YOUN Y C, KIM Y K, et al. Glycyrrhizin prevents 7-ketocholesterol toxicity against differentiated PC12 cells by suppressing mitochondrial membrane permeability change [J]. *Neurochem Res*, 2009, 34(8): 1433-1442.
- [ 25 ] KITAGISHI Y, NAKANISHI A, OGURA Y, et al. Dietary regulation of PI3K/AKT/GSK-3 $\beta$  pathway in Alzheimer's disease [J]. *Alzheimers Res Ther*, 2014, 6(3): 35.
- [ 26 ] CULL-CANDY S, BRICKLEY S, FARRANT M. NMDA receptor subunits: diversity, development and disease [J]. *Curr Opin Neurobiol*, 2001, 11(3): 327-335.
- [ 27 ] DE FELICE F G, VELASCO P T, LAMBERT M P, et al. Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine [J]. *J Biol Chem*, 2007, 282(15): 11590-11601.
- [ 28 ] YOSHIDA Y, FUJIGAKI H, KATO K, et al. Selective and competitive inhibition of kynurenine aminotransferase 2 by glycyrrhizic acid and its analogues [J]. *Sci Rep*, 2019, 9(1): 10243.
- [ 29 ] LANE R M, KIVIPELTO M, GREIG N H. Acetylcholinesterase and its inhibition in Alzheimer disease [J]. *Clin Neuropharmacol*, 2004, 27(3): 141-149.
- [ 30 ] ABDEL BAR F M, ELIMAM D M, MIRA A S, et al. Derivatization, molecular docking and *in vitro* acetylcholinesterase inhibitory activity of glycyrrhizin as a selective anti-Alzheimer agent [J]. *Nat Prod Res*, 2019, 33(18): 2591-2599.
- [ 31 ] MUNOZ L, AMMIT A J. Targeting p38 MAPK pathway for the treatment of Alzheimer's disease [J]. *Neuropharmacology*, 2010, 58(3): 561-568.
- [ 32 ] CAGLAYAN C, KANDEMIR F M, AYNA A, et al. Neuroprotective effects of 18 $\beta$ -glycyrrhetic acid against bisphenol A-induced neurotoxicity in rats; involvement of neuronal apoptosis, endoplasmic reticulum stress and JAK1/STAT1 signaling pathway [J]. *Metab Brain Dis*, 2022, 37(6): 1931-1940.

- [33] YEN G C, DUH P D, HUANG D W, et al. Protective effect of pine (*Pinus morrissonicola* Hay.) needle on LDL oxidation and its anti-inflammatory action by modulation of iNOS and COX-2 expression in LPS-stimulated RAW 264.7 macrophages [J]. Food Chem Toxicol, 2008, 46(1): 175-185.
- [34] WANG C Y, KAO T C, LO W H, et al. Glycyrrhizic acid and 18 $\beta$ -glycyrrhetic acid modulate lipopolysaccharide-induced inflammatory response by suppression of NF- $\kappa$ B through PI3K p110 $\delta$  and p110 $\gamma$  inhibitions [J]. J Agric Food Chem, 2011, 59(14): 7726-7733.
- [35] ORELLANA J A, SHOJI K F, ABUDARA V, et al. Amyloid  $\beta$ -induced death in neurons involves glial and neuronal hemichannels [J]. J Neurosci, 2011, 31(13): 4962-4977.
- [36] YI C, MEI X, EZAN P, et al. Astroglial connexin43 contributes to neuronal suffering in a mouse model of Alzheimer's disease [J]. Cell Death Differ, 2016, 23(10): 1691-1701.
- [37] MA Y, CAO W, WANG L, et al. Basal CD38/cyclic ADP-ribose-dependent signaling mediates ATP release and survival of microglia by modulating connexin 43 hemichannels [J]. Glia, 2014, 62(6): 943-955.
- [38] REN R, ZHANG L, WANG M. Specific deletion connexin 43 in astrocyte ameliorates cognitive dysfunction in APP/PS1 mice [J]. Life Sci, 2018, 208: 175-191.
- [39] CABREIRA V, MASSANO J. Parkinson's disease: clinical review and update [J]. Acta Med Port, 2019, 32(10): 661-670.
- [40] OUCHI Y, YOSHIKAWA E, SEKINE Y, et al. Microglial activation and dopamine terminal loss in early Parkinson's disease [J]. Ann Neurol, 2005, 57(2): 168-175.
- [41] TANG Y, LE W. Differential roles of M1 and M2 microglia in neurodegenerative diseases [J]. Mol Neurobiol, 2016, 53(2): 1181-1194.
- [42] PORRAS G, LI Q, BEZARD E. Modeling Parkinson's disease in primates: the MPTP model [J]. Cold Spring Harb Perspect Med, 2012, 2(3): a009308.
- [43] HAN Y, ZHANG L, WANG Q, et al. Minocycline inhibits microglial activation and alleviates depressive-like behaviors in male adolescent mice subjected to maternal separation [J]. Psychoneuroendocrinology, 2019, 107: 37-45.
- [44] LUO H, ZHANG C, HE L, et al. 18 $\beta$ -glycyrrhetic acid ameliorates MPTP-induced neurotoxicity in mice through activation of microglial anti-inflammatory phenotype [J]. Psychopharmacology, 2023, 240(9): 1947-1961.
- [45] YIN X, FENG L, MA D, et al. Roles of astrocytic connexin-43, hemichannels, and gap junctions in oxygen-glucose deprivation/reperfusion injury induced neuroinflammation and the possible regulatory mechanisms of salvianolic acid B and carbenoxolone [J]. J Neuroinflammation, 2018, 15(1): 97.
- [46] FUJITA A, YAMAGUCHI H, YAMASAKI R, et al. Connexin 30 deficiency attenuates A2 astrocyte responses and induces severe neurodegeneration in a 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine hydrochloride Parkinson's disease animal model [J]. J Neuroinflammation, 2018, 15(1): 227.
- [47] MAATOUK L, YI C, CARRILLO-DE SAUVAGE M A, et al. Glucocorticoid receptor in astrocytes regulates midbrain dopamine neurodegeneration through connexin hemichannel activity [J]. Cell Death Differ, 2019, 26(3): 580-596.
- [48] ZOU Z, LIU B, ZENG L, et al. Cx43 inhibition attenuates sepsis-induced intestinal injury via downregulating ROS transfer and the activation of the JNK1/Sirt1/FoxO3a signaling pathway [J]. Mediators Inflamm, 2019, 2019: 7854389.
- [49] EKERT P G, SILKE J, VAUX D L. Caspase inhibitors [J]. Cell Death Differ, 1999, 6(11): 1081-1086.
- [50] KANAZAWA M, NINOMIYA I, HATAKEYAMA M, et al. Microglia and monocytes/macrophages polarization reveal novel therapeutic mechanism against stroke [J]. Int J Mol Sci, 2017, 18(10): 2135.
- [51] CAO Q, ZOU Q, ZHAO X, et al. Regulation of BDNF transcription by Nrf2 and MeCP2 ameliorates MPTP-induced neurotoxicity [J]. Cell Death Discov, 2022, 8(1): 267.
- [52] CAO Q, LUO S, YAO W, et al. Suppression of abnormal  $\alpha$ -synuclein expression by activation of BDNF transcription ameliorates Parkinson's disease-like pathology [J]. Mol Ther Nucleic Acids, 2022, 29: 1-15.
- [53] GUPTA G L, SHARMA L, SHARMA M. 18 $\beta$ -glycyrrhetic acid ameliorates neuroinflammation linked depressive behavior instigated by chronic unpredictable mild stress via triggering BDNF/TrkB signaling pathway in rats [J]. Neurochem Res, 2023, 48(2): 551-569.
- [54] WANG R, YANG S, NIE T, et al. Transcription factors: potential cell death markers in Parkinson's disease [J]. Neurosci Bull, 2017, 33(5): 552-560.
- [55] OUALI ALAMI N, SCHURR C, OLDE HEUVEL F, et al. NF- $\kappa$ B activation in astrocytes drives a stage-specific beneficial neuroimmunological response in ALS [J]. EMBO J, 2018, 37(16): e98697.
- [56] AZAM S, JAKARIA M, KIM I S, et al. Regulation of toll-like receptor (TLR) signaling pathway by polyphenols in the treatment of age-linked neurodegenerative diseases: focus on TLR4 signaling [J]. Front Immunol, 2019, 10: 1000.
- [57] COLOMBO E, FARINA C. Astrocytes: key regulators of neuroinflammation [J]. Trends Immunol, 2016, 37(9): 608-620.
- [58] BROWN R H Jr, ROBBERECHT W. Amyotrophic lateral sclerosis: pathogenesis [J]. Semin Neurol, 2001, 21(2): 131-139.
- [59] SACCON R A, BUNTON-STASYSHYN R K A, FISHER E M C, et al. Is SOD1 loss of function involved in amyotrophic lateral sclerosis? [J]. Brain, 2013, 136(8): 2342-2358.
- [60] 刘雪芹, 牛晓洁, 王必慧, 等. 18 $\alpha$ -甘草次酸通过抗氧化作用促进成年小鼠室管膜下区神经干细胞增殖 [J]. 解剖学报, 2022, 53(1): 11-18.
- LIU X Q, NIU X J, WANG B H, et al. 18 $\alpha$ -glycyrrhetic acid promoting neural stem cells proliferation through antioxidant in

- the subventricular zone of adult mice [J]. *Acta Anat Sin*, 2022, 53(1): 11–18.
- [61] KUMAR V. Toll-like receptors in the pathogenesis of neuroinflammation [J]. *J Neuroimmunol*, 2019, 332: 16–30.
- [62] PORETTI A, WOLF N I, BOLTSCHAUER E. Differential diagnosis of cerebellar atrophy in childhood: an update [J]. *Neuropediatrics*, 2015, 46(6): 359–370.
- [63] FALANGOLA M F, GUILFOYLE D N, TABESH A, et al. Histological correlation of diffusional kurtosis and white matter modeling metrics in cuprizone-induced corpus callosum demyelination [J]. *NMR Biomed*, 2014, 27(8): 948–957.
- [64] TIAN H, CHENG Y, ZHANG Y, et al. 18 $\beta$ -Glycyrrhetic acid alleviates demyelination by modulating the microglial M1/M2 phenotype in a mouse model of cuprizone-induced demyelination [J]. *Neurosci Lett*, 2021, 755: 135871.
- [65] SIES H, BELOUSOV V V, CHANDEL N S, et al. Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology [J]. *Nat Rev Mol Cell Biol*, 2022, 23(7): 499–515.
- [66] FERNANDEZ A, MEECHAN D W, KARPINSKI B A, et al. Mitochondrial dysfunction leads to cortical under-connectivity and cognitive impairment [J]. *Neuron*, 2019, 102(6): 1127–1142.
- [67] SMITH G A, LIN T H, SHEEHAN A E, et al. Glutathione S-transferase regulates mitochondrial populations in axons through increased glutathione oxidation [J]. *Neuron*, 2019, 103(1): 52–65.
- [68] JENNER P. Oxidative stress in Parkinson's disease [J]. *Ann Neurol*, 2003, 53(3): S26–S36.
- [69] YIM S B, PARK S E, LEE C S. Protective effect of glycyrrhizin on 1-methyl-4-phenylpyridinium-induced mitochondrial damage and cell death in differentiated PC12 cells [J]. *J Pharmacol Exp Ther*, 2007, 321(2): 816–822.
- [70] MAALOUF M, SULLIVAN P G, DAVIS L, et al. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation [J]. *Neuroscience*, 2007, 145(1): 256–264.
- [71] HE Z Q, HUAN P F, WANG L, et al. Paeoniflorin ameliorates cognitive impairment in Parkinson's disease via JNK/p53 signaling [J]. *Metab Brain Dis*, 2022, 37(4): 1057–1070.
- [72] LIU X, SHI H, XIE B, et al. Microplastics as both a sink and a source of bisphenol A in the marine environment [J]. *Environ Sci Technol*, 2019, 53(17): 10188–10196.
- [73] ZHAO Y, SIMON M, SELUANOV A, et al. DNA damage and repair in age-related inflammation [J]. *Nat Rev Immunol*, 2023, 23(2): 75–89.
- [74] LEFAKI M, PAPAEGENIOU N, TUR J A, et al. The dietary triterpenoid 18 $\alpha$ -Glycyrrhetic acid protects from MMC-induced genotoxicity through the ERK/Nrf2 pathway [J]. *Redox Biol*, 2020, 28: 101317.
- [75] FERNÁNDEZ-CRUZ I, REYNAUD E. Proteasome subunits involved in neurodegenerative diseases [J]. *Arch Med Res*, 2021, 52(1): 1–14.
- [76] SINGH S J, TANDON A, PHOOLMALA, et al. Bisphenol-A (BPA) impairs hippocampal neurogenesis via inhibiting regulation of the ubiquitin proteasomal system [J]. *Mol Neurobiol*, 2023, 60(6): 3277–3298.
- [77] AGARWAL S, YADAV A, TIWARI S K, et al. Correction: Dynamin-related protein 1 inhibition mitigates bisphenol A-mediated alterations in mitochondrial dynamics and neural stem cell proliferation and differentiation [J]. *J Biol Chem*, 2020, 295(9): 2887.
- [78] HUANG X, SU Y, WANG N, et al. Astroglial connexins in neurodegenerative diseases [J]. *Front Mol Neurosci*, 2021, 14: 657514.
- [79] ERIKSON K M, ASCHNER M. Manganese neurotoxicity and glutamate-GABA interaction [J]. *Neurochem Int*, 2003, 43(4/5): 475–480.
- [80] YE Z C, WYETH M S, BALTAN-TEKKOK S, et al. Functional hemichannels in astrocytes: a novel mechanism of glutamate release [J]. *J Neurosci*, 2003, 23(9): 3588–3596.
- [81] KAWAKAMI Z, IKARASHI Y, KASE Y. Isoliquiritigenin is a novel NMDA receptor antagonist in kampo medicine yokukansan [J]. *Cell Mol Neurobiol*, 2011, 31(8): 1203–1212.
- [82] GARG S, SYED M M, KIELIAN T. *Staphylococcus aureus*-derived peptidoglycan induces Cx43 expression and functional gap junction intercellular communication in microglia [J]. *J Neurochem*, 2005, 95(2): 475–483.
- [83] HEATON R K, CLIFFORD D B, FRANKLIN D R Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study [J]. *Neurology*, 2010, 75(23): 2087–2096.
- [84] EUGENIN E A, BERMAN J W. Cytochrome C dysregulation induced by HIV infection of astrocytes results in bystander apoptosis of uninfected astrocytes by an IP3 and calcium-dependent mechanism [J]. *J Neurochem*, 2013, 127(5): 644–651.
- [85] MALIK S, THEIS M, EUGENIN E A. Connexin 43 containing gap junction channels facilitate HIV bystander toxicity: implications in NeuroHIV [J]. *Front Mol Neurosci*, 2017, 10: 404.
- [86] OZTANIR M N, CIFTCI O, CETIN A, et al. The beneficial effects of 18 $\beta$ -glycyrrhetic acid following oxidative and neuronal damage in brain tissue caused by global cerebral ischemia/reperfusion in a C57BL/J6 mouse model [J]. *Neurol Sci*, 2014, 35(8): 1221–1228.