PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2024, 51(1): 59~69
www.pibb.ac.cn

萝卜硫素的成药性及其在肿瘤和神经退行性疾病中的作用*

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摘要 萝卜硫素是一种来源于十字花科类蔬菜的天然活性物质，具有强大的抗氧化和抗癌能力。研究表明，萝卜硫素可通过调节Nrf2、NF-κB、HSF1-HSP信号通路和调控表观遗传，从而作用于II相解毒酶、HDAC和DNMT，影响癌症、神经退行性疾病等疾病的发生、发展。此外，由于萝卜硫素具有易吸收易代谢等特点，用纳米材料包裹萝卜硫素可提高其生物利用度和稳定性，更好发挥其疗效。近年来已有多项I/II期临床实验显示，萝卜硫素具有良好的成药性，这表明萝卜硫素在治疗癌症和神经退行性疾病方面有极高的药用潜力。本文主要针对萝卜硫素的药代动力学、作用靶点、安全性及其在肿瘤和神经退行性疾病中的研究进展进行综述，为萝卜硫素未来应用于肿瘤和神经退行性疾病的治疗提供参考。

关键词 萝卜硫素，药代动力学，信号通路，肿瘤，神经退行性疾病
中图分类号 R9，R33 **DOI**：10.16476/j.pibb.2022.0545

萝卜硫素（sulforaphane，SFN）是从十字花科类蔬菜中发现具有强生物活性的天然化合物，在西兰花中含量最高，其诱导II相解毒酶的活力是槲皮素的14倍，抗氧化能力是槲皮素的20倍、姜黄素的80倍，具有极高的营养价值和药用潜力，因此逐渐成为研究热点[1]。研究发现，SFN主要通过作用于核转录因子红系2相关因子2（nuclear factor erythroid 2 related factor 2，Nrf2）、核因子κB（nuclear factor κB，NF-κB）、热休克因子1（heat shock factor 1，HSF1）和表观遗传修饰[2]，显示出抗肿瘤[3]、抗炎[4]、改善糖尿病[5]和心血管疾病[6]等药理活性（图1），可用于癌症[3]、神经退行性疾病（neurodegenerative disease，NDD）[7]、炎症疾病[8]等的治疗。本文主要对萝卜硫素的药代动力学、分子靶点、安全性及其在肿瘤和神经退行性疾病中的研究进展进行综述。

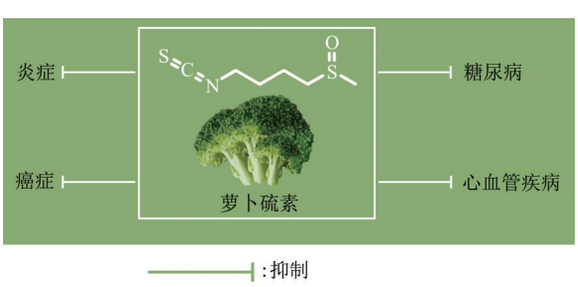

Fig. 1 Structural formula of sulforaphane and its pharmacological activity
图1 萝卜硫素的结构式及其药理活性

* 国家自然科学基金（21961003），江西省自然科学基金（20212ACB206001），江西省“千人计划”（jxsq2018106059），赣州市自然科学基金，中央引导地方科技发展专项基金（20231ZDF03071）和江西省教育厅科学研究项目（GJJ2201443）资助。
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收稿日期：2022-12-29，接受日期：2023-03-17

1　SFN的药代动力学

SFN作为一种亲脂性小分子很容易通过被动扩散被小肠吸收[9]。Clarke等[10]对小鼠灌胃5 μmol和20 μmol SFN，以比较肝脏、肾脏、小肠、结肠、肺、脑和前列腺中SFN及其代谢物在不同时刻的变化，发现SFN及其代谢物在小肠中的浓度最高，同时浓度在灌胃2 h后达峰，随后迅速下降。此外，当SFN被小肠吸收后，在谷胱甘肽巯基转移酶（glutathione S-transferase，GST）作用下，能够快速与谷胱甘肽（glutathione，GSH）形成SFN-GSH。Petri等[11]发现，小肠里大部分SFN-GSH是通过血液进入循环系统，剩下的SFN-GSH则通过膜结合蛋白从肠腔排泄。Gu等[12]表明，SFN-GSH是SFN在体内运输的主要代谢物。但由于其本身结构不稳定，加上血浆中的GSH含量很低，使SFN-GSH在血浆中易分解成SFN和GSH，游离出的SFN可与血清白蛋白结合，从而被转运到肝脏、肾脏等器官[13-14]。研究结果表明，无论是人口服还是大鼠灌胃SFN或者西兰花提取物，SFN会在12~24 h内通过疏基酸途径基本全部排泄[15-16]。在肝脏和肾脏中，SFN与GSH在GST作用下生成SFN-GSH，经疏基尿酸途径依次代谢成萝卜硫素-半胱氨酸-甘氨酸（SFN-Cys-Gly）、萝卜硫素-半胱氨酸（SFN-Cys）和萝卜硫素-N-乙酰半胱氨酸（SFN-NAC），最后经过胆汁和尿液排泄[17]（图2）。更多实验结果证明，SFN的代谢物主要是通过尿液排泄[12]，例如，Kassahun等[18]给大鼠灌胃50 mg/kg SFN，在24 h后检测尿液中SFN不同代谢物的含量，发现在尿液中SFN-NAC占灌胃剂量的60%。Zhang等[16]也证实，当人口服西兰花提取物时，其尿液中SFN的代谢物以SFN-NAC为主。总之，SFN在人体小肠部位所吸收，并迅速与GSH结合生成SFN-GSH，随后经疏基酸途径代谢为SFN-NAC，且主要通过尿液排泄。

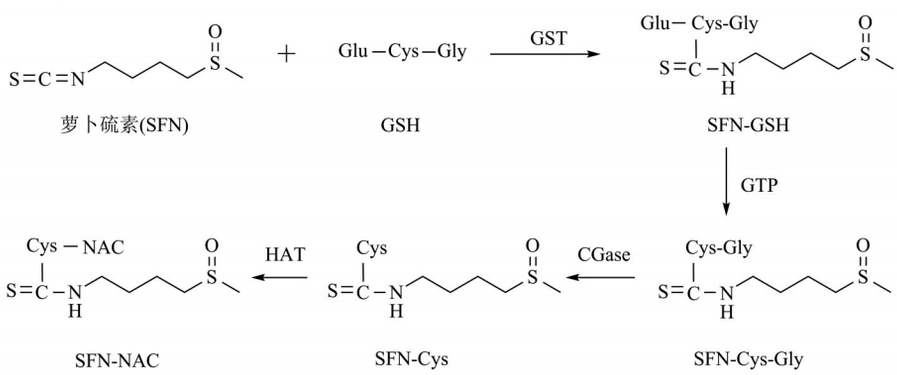

Fig. 2　Mercapturic acid pathway of sulforaphane *in vivo*

图2　萝卜硫素在体内的疏基酸代谢途径

GST：谷胱甘肽巯基转移酶；GTP：γ-谷氨酰转移酶；CGase：半胱氨酸甘氨酸酶；HAT：N-乙酰基转移酶。

在生物利用度方面，Hanlon等[19]对大鼠灌胃不同剂量的SFN，发现SFN的绝对生物利用度与其剂量有关，在5 mg/kg下SFN的绝对生物利用度仅为20%，1 mg/kg剂量下的绝对生物利用度为25%，但0.5 mg/kg剂量下的绝对生物利用度达到了82%，推测可能是血液中与SFN结合的蛋白质较少，游离形式的SFN更容易通过尿液排出体外，导致SFN的生物利用度随着剂量的增加而下降。Son等[20]对大鼠灌胃0.1、0.2、0.5 mg/kg SFN后发现其半衰期分别是（41.9±7.60）min、（197.7±16）min、（320±75.4）min，推测导致上述差异可能是血浆结合蛋白的原因。由于SFN具有半衰期短，稳定性差等特点，研究人员发现将SFN微胶囊化或者用纳米材料包裹可以提高其生物利用度和稳定性[21-22]。比如，Kheiri等[23]用聚己内酯-聚乙二醇-聚己内酯组成的纳米颗粒负载SFN发现，SFN在大鼠体内的半衰期由0.5 h延长到4 h，相对生物利用度则是相同剂量SFN的55.85倍。Wang等[24]也发现用小米和玉米提取的醇溶蛋白制作纳米颗粒可包裹SFN，其热稳定性和生物利用度得到了很大的提高，这表明在未来SFN与纳米材料相结合可更好提高其疗效。

2 SFN及其分子靶点

2.1 SFN作用于Nrf2信号通路

大量研究表明，SFN是Nrf2的天然强力诱导剂之一。Takaya等[25]发现，SFN主要靶向Kelch样ECH相关蛋白（kelch liked ECH-associated protein 1，Keap1）的半胱氨酸（Cys15）残基，通过硫醇基团与Keap1形成硫酰复合物，从而阻止Keap1与Cul3（Cullin 3）形成的复合物对Nrf2泛素化，使Nrf2能够进入细胞核。当Nrf2进入细胞核后会与sMaf（small Musculo-aponeurotic-factor）家族成员形成异二聚体Nrf2-sMaf，再与抗氧反应元件（antioxidant response element，ARE）结合，并调节抗氧化酶，比如醌脱氢酶1（quinone dehydrogenase 1，NAPDH）、血红素加氧酶1（heme oxygenase-1，HO-1）、GST等的转录和激活[26]。此外，Eren等[27]发现，SFN可通过激活细胞外信号调节激酶1和2（extracellular signal-regulated kinase 1 and 2，ERK1/2），使Nrf2进入核内从而达到抗氧化和抗炎的效果。Wang等[28]研究证实，SFN可通过分别激活ERK1/2和蛋白激酶B（protein kinase B，PKB）使Nrf2进入细胞核，从而激活II相解毒酶。Banerjee等[29]的实验结果表明，SFN还可以通过介导丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）亚族P38从而导致Nrf2进入细胞核（图3）。总之，SFN通过激活Nrf2信号通路可以激活一系列的II相解毒酶和抗氧化蛋白酶，从而维持机体内活性氧（ROS）的正常水平[4]。

2.2 SFN作用于NF-κB信号通路

当受到外界刺激时，经典NF-κB信号通路中的核因子κB抑制蛋白α（inhibitor alpha of NF-κB，IκBα）被其激酶迅速磷酸化和泛素化，随后NF-κB亚基（p65和p50）进入细胞核与DNA结合，从而激活下游促炎信号分子比如肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）、白介素（interleukin，IL）-1、IL-2和IL-6的表达[26]。Nallasamy等[30]在脂多糖（lipopolysaccharide，LPS）诱导的单核细胞实验中发现，TNF-α是NF-κB的有效激活剂，SFN可通过介导TNF-α从而抑制对IκBα的磷酸化导致NF-κB亚基进入细胞核受到抑制。同时，Moon等[31]的研究结果也表明，SFN可完全抑制TNF-α诱导的IκBα磷酸化，将p65和p50隔离在细胞质中。此外，NF-κB在进入细胞核内需要高比例的还原型GSH/氧化型GSH来激活，且核内的NF-κB与DNA结合需要大量的Cys的参与[32]。Heiss等[33]发现，SFN很容易与还原性GSH结合形成硫醇结合物，使还原型GSH的浓度水平降低，从而抑制NF-κB与核内其DNA的结合。Liu等[34]也表明，SFN在短时间内会降低GSH的浓度，从而抑制NF-κB活性。此外，研究人员发现Nrf2下游信号分子HO-1的浓度上升也会抑制NF-κB的活性[35]（图3）。Bellezza等[36]发现，HO-1会导致胆绿素降解为胆红素，从而降低NF-κB亚基在核内与其DNA结合。Seldon等[37]也发现，HO-1催化血红素裂解为Fe^{2+}，从而抑制NF-κB亚基在核内与DNA结合。Huang等[38]研究表明，SFN可以通过激活Nrf2/HO-1介导血管内皮细胞氧化从而抑制NF-κB的表达，进而预防动脉粥样硬化的发生。

2.3 SFN作用于HSF1-HSP信号通路

HSF1作为肿瘤和NDD的潜在药物靶点，近年来被广泛研究[39]。研究人员发现在非应激条件下，HSF1与热休克蛋白（heat shock protein，HSP）家族成员HSP40、HSP70、HSP90以及TRic复合物（tailless complex polypeptide 1 ring complex，TRic）结合在细胞质，在应激条件下，HSF1被磷酸化，与上述复合物分离，形成三聚体易位到细胞核中，与其DNA基序（HSF）结合，并激活HSP27、HSP70、HSP90的转录[40]（图3）。HSF1通过激活HSP参与细胞凋亡、DNA修复、代谢调节等，从而影响肿瘤和NDD的发生、发展[41-42]。Gan等[43]在体外实验发现，SFN以浓度和时间依赖的方式促进HSF1进入细胞核，激活HSP27磷酸化，并诱导蛋白酶活化，修复错误折叠的蛋白质。之后，Lellahi等[44]也在体外实验表明SFN可通过激活HSF1诱导非编码RNA NEAT1（nuclear enriched abundant transcript 1，NEAT1）的表达，激活HSP90、HSP70、HSP27，从而抑制有害蛋白质的聚集，保护正常细胞。

2.4 SFN作用于表观遗传修饰

研究发现，导致癌症的主要因素之一是表观遗传修饰发生改变，主要包括组蛋白去乙酰化酶（histone deacetyltransferases，HDAC）、DNA甲基转移酶（DNA methyltransferase，DNMT）的活性增加以及非编码的RNA表达[45]。Blaheta等[46]发现SFN是HDAC的天然抑制剂之一，Jiang等[47]研究表明，SFN可通过抑制HDAC导致组蛋白H3和

H4表达水平上升，使肿瘤抑制基因P21、P53和促凋亡蛋白Bax被重新激活从而导致肺癌细胞的凋亡。越来越多证据表明，SFN也是DNMT的潜在调节剂，许多癌症细胞周期相关因子P21、P16、D型细胞周期蛋白和部分miRNA的启动子呈现高甲基化与DNMT激活密切相关[48]。例如，在肺癌中miRNA家族成员miR-9-3的启动子呈现高甲基化，Gao等[49]发现，SFN通过抑制DNMT的活性降低miR-9-3的启动子CpG高甲基化，从而使miR-9-3被激活。Hsu等[50]也发现，SFN通过介导DNMT降低细胞周期D2蛋白启动子的DNA甲基化，从而抑制前列腺癌细胞的增殖（图3）。SFN可通过表观遗传修饰靶向Nrf2/Keap1，但其具体作用机制还未明确[51]。

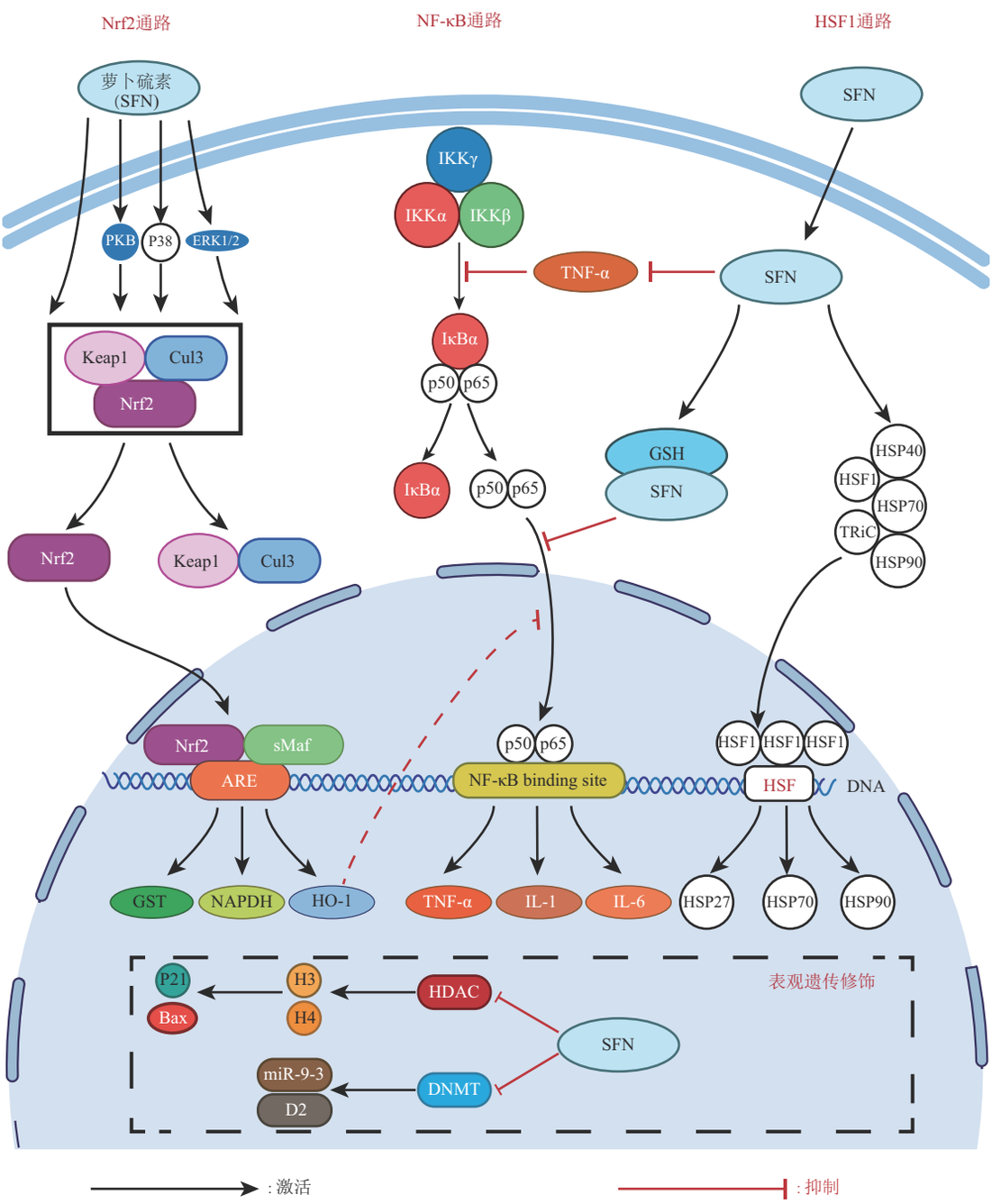

Fig. 3　Diagram of the mechanism of sulforaphane related signaling molecular targets

图3　萝卜硫素的相关信号分子靶点机制图

3　SFN药理活性研究

3.1　肿瘤

研究发现，SFN可以参与肺癌[52]、乳腺癌[53]、膀胱癌[54]等癌症的发生与发展（表1）。Yan等[52]发现，SFN会抑制非小细胞型肺癌细胞A549和SK-1微管蛋白的活性，导致脂肪酸的合成减少和线粒体自噬从而诱导细胞凋亡。Wang等[55]研究也表明，SFN可通过抑制Shh（sonic hedgehog）和PHC3（polycomb group molecule human polyhomeotic homolog 3）的表达，使非小细胞型肺癌细胞A549和H460活力下降同时抑制其增殖。而Iida等[56]还发现，SFN可通过介导铁死亡诱导小细胞肺癌细胞H69和H69AR凋亡，进而达到抗癌的效果。

SFN也有很好的治疗乳腺癌效果。Zhang等[53]发现，SFN会抑制乳腺癌细胞MDA-MB-231和MDA-MB-157的迁移和侵袭。在7.5~30 μmol/L SFN的剂量范围内，随着SFN的剂量增加，抑制效果更强。而且，SFN的两种同分异构体R-SFN和S-SFN对上述两种乳腺癌细胞的抑制效果几乎一样。Palliyaguru等[57]在体内实验中发现，SFN可以预防经17β-雌二醇处理的ACI大鼠乳腺肿瘤的形成，并且还可通过降低ACI大鼠体内游离的脂肪酸和甘油三脂去抑制肿瘤的形成。此外，Rong等[58]在体内实验中发现，SFN与阿霉素协同用药治疗乳腺癌优于单一用药，而Sharma等[59]在体外实验也发现，SFN、染料木黄酮和丁酸钠联合用药治疗乳腺癌效果是最好的，这些结果表明了SFN与临床上治疗乳腺癌药物联合用药的前景。

SFN具有一定的治疗膀胱癌的作用。Wang等[54]发现，在20~80 μmol/L剂量范围内，SFN以剂量依赖的方式抑制膀胱癌细胞T24和SW780的活力、转移和侵袭，同时也抑制脂肪非典型钙黏蛋白（FAT atypical cadherin 1，FAT1）表达使上述细胞发生凋亡。He等[60]也得到了相似的结果，SFN可通过诱导Nrf2进入细胞核引起GSH消耗，从而抑制T24增殖。Justin等[61]研究表明，SFN与依维莫司联合用药可抑制膀胱癌细胞RT112的耐药性。

SFN也可抑制前列腺癌、宫颈癌和胃肠道相关肿瘤细胞的增殖[3]。Rutz等[62]发现，与前列腺癌细胞PC-3和DU-145孵育24 h后，SFN会导致两株细胞在G2/M周期的数量减少，S期细胞数量增加。Wang等[63]发现，SFN在5~50 μmol/L给药范围和24~48 h孵育时长内能以时间和剂量依赖的方式抑制宫颈癌细胞SiHa、HeLa和C33A增殖。在胃肠道相关癌症方面，Wang等[64]等发现SFN对胃癌有预防作用；Zheng等[65]通过体外实验发现SFN在食管癌中有一定的抗癌效果；Hao等[66]发现SFN可以抑制结直肠癌细胞HT-29和SW480的增殖。

Table 1　Research results of sulforaphane in cancer within the last 3 years

表1　近3年内萝卜硫素在癌症的研究成果

癌种	实验模型	实验结果	参考文献
肺癌	A549、SK-1、H460 H69、H69AR	抑制微管蛋白、脂肪酸合成和线粒体自噬；抑制Shh和PHC3蛋白表达；诱导铁死亡，引发细胞凋亡	［52，55-56］
乳腺癌	MDA-MB-231、MDA-MB-157、4T1、MCF-7、Hs578T、MDA-MB-231	抑制细胞的迁移、侵袭、乳腺球的形成；抑制PGE2、HDAC、DNMT酶的活性和β连环蛋白、NF-κB、MMP-9、miR-19的表达	［53，58-59，67-69］
	皮下注射4T1、MDA-MB-23细胞的裸鼠；17β-雌二醇处理的ACI大鼠	抑制小鼠肿瘤的体积、体重；预防大鼠肿瘤的形成	［57，70］
膀胱癌	T24、SW780、RT4、RT112、TCC-SUP、UMUC3	抑制FAT-1的表达、ATP-产生、细胞的增殖、迁移、耐药性；激活Nrf2的表达、降低CSH的浓度；降低细胞活力，诱导细胞凋亡	［54，60，71-72］
结直肠癌	HT-29、HCT116、SW480、Oct-4	激活Nrf2、ERK、ZO-1，miR-15b-5p；抑制β连环蛋白，细胞增殖和生长	［66，73-74］
	皮下注射HCT116细胞的裸鼠	抑制小鼠肿瘤的体积、体重，剂量越大，效果更好	［75］
食管癌	ECA-109、TE-1、EC9706、Het-1A	激活Nrf2、诱导细胞自噬，破坏GSH/GSSG平衡；引起细胞衰老，抑制细胞生长	［65，76］
	皮下注射ECA-109细胞的裸鼠	抑制小鼠肿瘤的体积、体重	［65］

续表1

癌种	实验模型	实验结果	参考文献
宫颈癌	SiHa、HeLa、C33A 皮下注射SiHa细胞的裸鼠	促进LATS2表达，抑制细胞增殖 抑制小鼠肿瘤的体积、体重	［63］
胃癌	BGC-823、MGC-803、A498、Caki1、786O	诱导P53、P21的表达；在G2/M期停滞，引起细胞在S期凋亡	［64，77］
肝癌	HepG2	诱导细胞DNA损伤、有丝分裂停滞，引发细胞凋亡、抑制细胞增殖	［78］
前列腺癌	PC3、DU145	抑制细胞增殖和生长	［62］
皮肤癌	SCC-13、HaCaT	抑制YAP1/TEAD、细胞球状体的形成，抑制细胞转移和侵袭	［79］

3.2　神经退行性疾病

NDD在全世界的患病率和死亡率不断增加，是危害人类身体健康的重大问题之一。NDD主要包括阿尔茨海默病（Alzheimer’s disease，AD）、帕金森病（Parkinson’s disease，PD）、亨廷顿病（Huntington diseases，HD）、多发性硬化症（multiple sclerosis，MS）等[80]。NDD作为一种常见的疾病，现今很少或者没有有效的治疗手段。越来越多的研究人员发现SFN作为亲脂小分子，易穿过血脑屏障，从而保护中枢神经元，在治疗NDD方面有着很大的潜力[7]（表2）。

AD的主要病理特征是β淀粉样蛋白（β amyloid protein，Aβ）积聚形成细胞外神经炎性斑块和异常磷酸化的Tau蛋白错误折叠、聚集形成的神经纤维缠结，从而引起过量ROS生成和神经元死亡，导致记忆力减退和认知功能下降[81-82]。Villavicencio-Tejo等[83]的体外实验结果表明，SFN可以抑制异常磷酸化Tau蛋白聚集所引起的线粒体功能障碍和ROS的增加，引起（标记GFP、GFP-T4和GFP-T4C3的Tau构建体）CN 1.4细胞线粒体产生的ATP增加以及II相解毒酶表达的增加。Tang等[84]通过体内实验发现，每日注射24 μmol/L SFN的AD大鼠，在经过7 d治疗后，其认知功能、记忆功能以及抑郁症得到了一定的改善。导致上述结果的原因是SFN通过Nrf2信号通路使AD大鼠脑组织的炎症因子IL-1β和TNF-α浓度下降、II相解毒酶GSH浓度的升高。

PD的主要病理特征是黑质纹状体中的多巴胺能（dopaminergic，DA）神经元退化或者功能丧失[85]。研究发现，氧化应激会使大脑中ROS增加，引发线粒体功能障碍和黑质中的关键蛋白氧化，最终导致DA神经元细胞发生死亡[86]。SFN可降低ROS的浓度，从而对PD有一定的治疗效果。例如，Jazwa等[87]对DA损伤的小鼠腹腔注射240 μmol/L SFN后发现，SFN可以穿过血脑屏障，激活基底节的Nrf2从而抑制DA神经元的变性和死亡。与对照组相比，DA神经元损伤经SFN治疗3 d后减少了30%，治疗6 d后减少了60%，其星形胶质细胞和小胶质细胞也相应减少。Morroni等[88]研究表明，SFN可以抑制退化DA神经元产生的有毒物质6-羟基多巴胺。他们先将6-羟基多巴胺注射到小鼠的纹状体内，再腹腔注射24 μmol/L SFN 4周后发现，与对照组相对比，经SFN治疗的小鼠有两个明显改善的特征：a. 完整的DA神经元增加，因6-羟基多巴胺导致小鼠大脑黑质GSH减少的现象得到了逆转；b. PD小鼠的运动协调和旋转等行为障碍有很大的改善。

SFN在治疗HD、MS等疾病方面也有不错的疗效，Jang等[89]发现，SFN可以抑制HD小鼠的小胶质细胞活性、促炎因子的表达以及神经细胞的凋亡，达到治疗HD的效果。Yoo等[90]也发现，SFN可减少ROS和炎症细胞的产生从而对MS小鼠有一定的保护功能。此外，Gillespie等[91]发现，SFN可以抑制LPS诱导的小鼠脑微血管血栓形成的时间，同时也会抑制血小板的聚集和活化，加快止血时间，防止脑血栓的形成。Li等[92]在缺血性脑卒中小鼠模型实验中发现，在经过SFN治疗后，小鼠的学习、记忆功能显著提高，且因脑卒中引起的神经元细胞损伤和死亡也得到明显改善。

Table 2　Research results of sulforaphane in neurodegenerative disease within the last 3 years

表2　近3年内萝卜硫素在神经退行性疾病的研究成果

病种	实验模型	实验结果	参考文献
阿尔茨海默病	标记GFP、GFP-T4和GFP-T4C3的Tau构建体CN 1.4细胞	抑制Tau诱导的ROS产生、ATP-的消耗，激活Nrf2	［83］
	淀粉样寡聚体处理的小胶质细胞	轻微减弱了小胶质细胞的吞噬活性	［93］
	神经母细胞瘤细胞N2a/APP；海马区注射淀粉样寡聚体的Wistar大鼠	抑制了Aβ和ROS的产生，激活Nrf2和II解毒酶；改善AD大鼠的学习、认知、记忆功能	［94］
	小胶质细胞系BV-2	抑制Aβ诱导小胶质细胞产生的毒性、神经元的损伤、NLRP3的表达，以及ROS的积累	［95］
	脑室内注射淀粉样寡聚体的SD大鼠	改善AD大鼠的认知功能、记忆功能以及抑郁症	［84］
缺血性脑卒中	小鼠脑微血管内皮细胞bEnd.3	诱导Nrf2/HO-1，降低ROS浓度	［92，96］
	缺血性脑卒中小鼠模型	改善小鼠的学习、记忆能力	

4　SFN的安全性

Liu等[97]在体外实验中发现，SFN浓度在20~80 μmol/L范围内，以剂量依赖方式降低人肝细胞HHL5和肝癌细胞HepG2的活力，当SFN的浓度大于80 μmol/L时，两种细胞活力都趋近于0。Socała等[98]在关于SFN的小鼠毒性实验中，单次腹腔注射超过200 mg/kg SFN，发现有一半的小鼠在24 h内死亡，在150 mg/kg剂量下，部分小鼠会出现眼上睑下垂，而在100 mg/kg剂量以下，未见小鼠不良反应。同时，多项临床研究表明，长期口服SFN在剂量范围为9~36 mg内，未见不良反应[17，99]，Poulton等[100]在I期临床实验也表明，人每日口服高剂量SFN（80 mg），至少在一周内未见任何健康问题。总之，在动物实验和人体实验都表明了SFN具有很好的安全性。

5　展　　望

SFN作为一种由西兰花提取得到具有强大生物活性的天然产物，近年来成为研究热点。此前，本课题组改善了现有SFN的提取工艺，建立了更易工业化的高纯度SFN工艺，为SFN的大量获得奠定了基础。虽然SFN易吸收，低浓度生物利用度高，但结构不够稳定，易代谢排泄，使得其临床应用受限。为此，将SFN包裹于纳米颗粒，可一定程度地改善其热稳定性和生物利用度。在药效学和安全性方面，近年来关于SFN在癌症、NDD的研究不断增多，且都表明SFN在预防和治疗上述疾病有着巨大潜力，多项I/II期临床实验表明SFN有着良好的疗效和安全性。此外，研究表明癌症和NDD等疾病的发展与体内ROS的浓度水平改变有着密切的联系，SFN可诱导ROS的产生来引发癌细胞凋亡，SFN又可通过抑制ROS来预防或治疗NDD，而Nrf2/Keap-1、NF-κB以及表观遗传修饰这3个途径都可改变ROS的浓度，因此，有必要深入了解SFN如何作用于这3种途径以及这3种途径之间的相互关系，从而实现SFN在预防或改善NDD、肿瘤和其他疾病方面的作用。

参　考　文　献

[1] Mahn A, Castillo A. Potential of sulforaphane as a natural immune system enhancer: a review. Molecules, 2021, **26**(3): 752

[2] Su X, Jiang X, Meng L, *et al*. Anticancer activity of sulforaphane: the epigenetic mechanisms and the Nrf2 signaling pathway. Oxid Med Cell Longev, 2018, **2018**: 5438179

[3] Kaiser A E, Baniasadi M, Giansiracusa D, *et al*. Sulforaphane: a broccoli bioactive phytocompound with cancer preventive potential. Cancers, 2021, **13**(19): 4796

[4] Calabrese E J, Kozumbo W J. The phytoprotective agent sulforaphane prevents inflammatory degenerative diseases and age-related pathologies *via* Nrf2-mediated hormesis. Pharmacol Res, 2021, **163**: 105283

[5] Zhang Y, Wu Q, Liu J, *et al*. Sulforaphane alleviates high fat diet-induced insulin resistance *via* AMPK/Nrf2/GPx4 axis. Biomed Pharmacother, 2022, **152**: 113273

[6] Bose C, Alves I, Singh P, *et al*. Sulforaphane prevents age-associated cardiac and muscular dysfunction through Nrf2 signaling. Aging Cell, 2020, **19**(11): e13261

[7] Schepici G, Bramanti P, Mazzon E. Efficacy of sulforaphane in neurodegenerative diseases. Int J Mol Sci, 2020, **21**(22): 8637

[8] Wei L Y, Zhang J K, Zheng L, *et al*. The functional role of sulforaphane in intestinal inflammation: a review. Food Funct, 2022, **13**(2): 514-529

[9] Santin-Marquez R, Alarcon-Aguilar A, Lopez-Diazguerrero N E, *et al*. Sulforaphane - role in aging and neurodegeneration. Geroscience, 2019, **41**(5): 655-670

[10] Clarke J D, Hsu A, Williams D E, *et al*. Metabolism and tissue distribution of sulforaphane in Nrf2 knockout and wild-type mice. Pharm Res, 2011, **28**(12): 3171-3179

[11] Petri N, Tannergren C, Holst B, *et al*. Absorption/metabolism of sulforaphane and quercetin, and regulation of phase II enzymes, in human jejunum *in vivo*. Drug Metab Dispos, 2003, **31**(6): 805-813

[12] Gu H F, Mao X Y, Du M. Metabolism, absorption, and anti-cancer effects of sulforaphane: an update. Crit Rev Food Sci Nutr, 2022, **62**(13): 3437-3452

[13] Oliviero T, Verkerk R, Dekker M. Isothiocyanates from brassica vegetables-effects of processing, cooking, mastication, and digestion. Mol Nutr Food Res, 2018, **62**(18): e1701069

[14] Bouranis J A, Beaver L M, Ho E. Metabolic fate of dietary glucosinolates and their metabolites: a role for the microbiome. Front Nutr, 2021, **8**: 748433

[15] Mangla B, Alam O, Rub R A, *et al*. Development and validation of a high throughput bioanalytical UPLC-MS/MS method for simultaneous determination of tamoxifen and sulphoraphane in rat plasma: application to an oral pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci, 2020, **1152**: 122260

[16] Zhang Z, Garzotto M, Davis E W, 2nd, *et al*. Sulforaphane bioavailability and chemopreventive activity in men presenting for biopsy of the prostate gland: a randomized controlled trial. Nutr Cancer, 2020, **72**(1): 74-87

[17] Mangla B, Javed S, Sultan M H, *et al*. Sulforaphane: a review of its therapeutic potentials, advances in its nanodelivery, recent patents, and clinical trials. Phytother Res, 2021, **35**(10): 5440-5458

[18] Kassahun K, Davis M, Hu P, *et al*. Biotransformation of the naturally occurring isothiocyanate sulforaphane in the rat: identification of phase I metabolites and glutathione conjugates. Chem Res Toxicol, 1997, **10**(11): 1228-1233

[19] Hanlon N, Coldham N, Gielbert A, *et al*. Absolute bioavailability and dose-dependent pharmacokinetic behaviour of dietary doses of the chemopreventive isothiocyanate sulforaphane in rat. Br J Nutr, 2008, **99**(3): 559-564

[20] Son E S, Fei X, Yoon J H, *et al*. Comparison of pharmacokinetics and anti-pulmonary fibrosis-related effects of sulforaphane and sulforaphane N-acetylcysteine. Pharmaceutics, 2021, **13**(7): 958

[21] Wu Y, Lv C, Zou L, *et al*. Approaches for enhancing the stability and formation of sulforaphane. Food Chem, 2021, **345**: 128771

[22] Wang Q, Bao Y. Nanodelivery of natural isothiocyanates as a cancer therapeutic. Free Radic Biol Med, 2021, **167**: 125-140

[23] Kheiri Manjili H, Sharafi A, Ttari E, *et al*. Pharmacokinetics and *in vitro* and *in vivo* delivery of sulforaphane by PCL-PEG-PCL copolymeric-based micelles. Artif Cells Nanomed Biotechnol, 2017, **45**(8): 1728-1739

[24] Wang L, Rose D, Rao P, *et al*. Development of prolamin-based composite nanoparticles for controlled release of sulforaphane. J Agric Food Chem, 2020, **68**(46): 13083-13092

[25] Takaya K, Suzuki T, Motohashi H, *et al*. Validation of the multiple sensor mechanism of the Keap1-Nrf2 system. Free Radic Biol Med, 2012, **53**(4): 817-827

[26] Ruhee R T, Suzuki K. The integrative role of sulforaphane in preventing inflammation, oxidative stress and fatigue: a review of a potential protective phytochemical. Antioxidants, 2020, **9**(6): 521

[27] Eren E, Tufekci K U, Isci K B, *et al*. Sulforaphane inhibits lipopolysaccharide-induced inflammation, cytotoxicity, oxidative stress, and miR-155 expression and switches to mox phenotype through activating extracellular signal-regulated kinase 1/2-nuclear factor erythroid 2-related factor 2/antioxidant response element pathway in murine microglial cells. Front Immunol, 2018, **9**: 36

[28] Wang A S, Xu Y, Zhang Z W, *et al*. Sulforaphane protects MLE-12 lung epithelial cells against oxidative damage caused by ambient air particulate matter. Food Funct, 2017, **8**(12): 4555-4562

[29] Banerjee N, Wang H, Wang G, *et al*. Redox-sensitive Nrf2 and MAPK signaling pathways contribute to trichloroethene-mediated autoimmune disease progression. Toxicology, 2021, **457**: 152804

[30] Nallasamy P, Si H, Babu P V, *et al*. Sulforaphane reduces vascular inflammation in mice and prevents TNF-α-induced monocyte adhesion to primary endothelial cells through interfering with the NF-κB pathway. J Nutr Biochem, 2014, **25**(8): 824-833

[31] Moon D O, Kim M O, Kang S H, *et al*. Sulforaphane suppresses TNF-α-mediated activation of NF-kappaB and induces apoptosis through activation of reactive oxygen species-dependent caspase-3. Cancer Lett, 2009, **274**(1): 132-142

[32] Kim B R, Hu R, Keum Y S, *et al*. Effects of glutathione on antioxidant response element-mediated gene expression and apoptosis elicited by sulforaphane. Cancer Res, 2003, **63**(21): 7520-7525

[33] Heiss E, Herhaus C, Klimo K, *et al*. Nuclear factor kappa B is a molecular target for sulforaphane-mediated anti-inflammatory mechanisms. J Biol Chem, 2001, **276**(34): 32008-32015

[34] Liu Y C, Hsieh C W, Weng Y C, *et al*. Sulforaphane inhibition of monocyte adhesion *via* the suppression of ICAM-1 and NF-kappaB is dependent upon glutathione depletion in endothelial cells. Vascul Pharmacol, 2008, **48**(1): 54-61

[35] Ahmed S M, Luo L, Namani A, *et al*. Nrf2 signaling pathway: pivotal roles in inflammation. Biochim Biophys Acta Mol Basis Dis, 2017, **1863**(2): 585-597

[36] Bellezza I, Tucci A, Galli F, *et al*. Inhibition of NF-κB nuclear translocation *via* HO-1 activation underlies α-tocopheryl succinate toxicity. J Nutr Biochem, 2012, **23**(12): 1583-1591

[37] Seldon M P, Silva G, Pejanovic N, *et al*. Heme oxygenase-1 inhibits the expression of adhesion molecules associated with endothelial cell activation *via* inhibition of NF-kappaB RelA phosphorylation at serine 276. J Immunol, 2007, **179**(11): 7840-7851

[38] Huang C S, Lin A H, Liu C T, *et al*. Isothiocyanates protect against oxidized LDL-induced endothelial dysfunction by upregulating Nrf2-dependent antioxidation and suppressing NF-κB activation.

Mol Nutr Food Res, 2013, **57**(11): 1918-1930

[39] Wang G, Cao P, Fan Y, *et al*. Emerging roles of HSF1 in cancer: cellular and molecular episodes. Biochim Biophys Acta Rev Cancer, 2020, **1874**(1): 188390

[40] Kurop M K, Huyen C M, Kelly J H, *et al*. The heat shock response and small molecule regulators. Eur J Med Chem, 2021, **226**: 113846

[41] Prince T L, Lang B J, Guerrero-Gimenez M E, *et al*. HSF1: primary factor in molecular chaperone expression and a major contributor to cancer morbidity. Cells, 2020, **9**(4): 1046

[42] Zhang B, Fan Y, Cao P, *et al*. Multifaceted roles of HSF1 in cell death: a state-of-the-art review. Biochim Biophys Acta Rev Cancer, 2021, **1876**(2): 188591

[43] Gan N, Wu Y C, Brunet M, *et al*. Sulforaphane activates heat shock response and enhances proteasome activity through up-regulation of Hsp27. J Biol Chem, 2010, **285**(46): 35528-35536

[44] Lellahi S M, Rosenlund I A, Hedberg A, *et al*. The long noncoding RNA NEAT1 and nuclear paraspeckles are up-regulated by the transcription factor HSF1 in the heat shock response. J Biol Chem, 2018, **293**(49): 18965-18976

[45] Lee J E, Kim M Y. Cancer epigenetics: past, present and future. Semin Cancer Biol, 2022, **83**: 4-14

[46] Juengel E, Erb H H H, Haferkamp A, *et al*. Relevance of the natural HDAC inhibitor sulforaphane as a chemopreventive agent in urologic tumors. Cancer Lett, 2018, **435**: 121-126

[47] Jiang L L, Zhou S J, Zhang X M, *et al*. Sulforaphane suppresses *in vitro* and *in vivo* lung tumorigenesis through downregulation of HDAC activity. Biomed Pharmacother, 2016, **78**: 74-80

[48] Daniel M, Tollefsbol T O. Epigenetic linkage of aging, cancer and nutrition. J Exp Biol, 2015, **218**(Pt 1): 59-70

[49] Gao L, Cheng D, Yang J, *et al*. Sulforaphane epigenetically demethylates the CpG sites of the miR-9-3 promoter and reactivates miR-9-3 expression in human lung cancer A549 cells. J Nutr Biochem, 2018, **56**: 109-115

[50] Hsu A, Wong C P, Yu Z, *et al*. Promoter de-methylation of cyclin D2 by sulforaphane in prostate cancer cells. Clin Epigenetics, 2011, **3**(1): 3

[51] Zhang S, Duan S, Xie Z, *et al*. Epigenetic therapeutics targeting NRF2/KEAP1 signaling in cancer oxidative stress. Front Pharmacol, 2022, **13**: 924817

[52] Yan Y, Zhou Y, Li J, *et al*. Sulforaphane downregulated fatty acid synthase and inhibited microtubule-mediated mitophagy leading to apoptosis. Cell Death Dis, 2021, **12**(10): 917

[53] Zhang Y, Lu Q, Li N, *et al*. Sulforaphane suppresses metastasis of triple-negative breast cancer cells by targeting the RAF/MEK/ERK pathway. NPJ Breast Cancer, 2022, **8**(1): 40

[54] Wang F, Liu P, An H, *et al*. Sulforaphane suppresses the viability and metastasis, and promotes the apoptosis of bladder cancer cells by inhibiting the expression of FAT-1. Int J Mol Med, 2020, **46**(3): 1085-1095

[55] Wang F, Sun Y, Huang X, *et al*. Sulforaphane inhibits self-renewal of lung cancer stem cells through the modulation of sonic hedgehog signaling pathway and polyhomeotic homolog 3. AMB Express, 2021, **11**(1): 121

[56] Iida Y, Okamoto-Katsuyama M, Maruoka S, *et al*. Effective ferroptotic small-cell lung cancer cell death from SLC7A11 inhibition by sulforaphane. Oncol Lett, 2021, **21**(1): 71

[57] Palliyaguru D L, Yang L, Chartoumpekis D V, *et al*. Sulforaphane diminishes the formation of mammary tumors in rats exposed to 17β-estradiol. Nutrients, 2020, **12**(8): 2282

[58] Rong Y, Huang L, Yi K, *et al*. Co-administration of sulforaphane and doxorubicin attenuates breast cancer growth by preventing the accumulation of myeloid-derived suppressor cells. Cancer Lett, 2020, **493**: 189-196

[59] Sharma M, Tollefsbol T O. Combinatorial epigenetic mechanisms of sulforaphane, genistein and sodium butyrate in breast cancer inhibition. Exp Cell Res, 2022, **416**(1): 113160

[60] He C, Buongiorno L P, Wang W, *et al*. The inhibitory effect of sulforaphane on bladder cancer cell depends on GSH depletion-induced by Nrf2 translocation. Molecules, 2021, **26**(16): 4919

[61] Justin S, Rutz J, Maxeiner S, *et al*. Chronic sulforaphane administration inhibits resistance to the mTOR-inhibitor everolimus in bladder cancer cells. Int J Mol Sci, 2020, **21**(11): 4026

[62] Rutz J, Thaler S, Maxeiner S, *et al*. Sulforaphane reduces prostate cancer cell growth and proliferation *in vitro* by modulating the Cdk-Cyclin axis and expression of the CD44 variants 4, 5, and 7. Int J Mol Sci, 2020, **21**(22): 8724

[63] Wang S, Wang Y, Liu X, *et al*. SFN enhanced the radiosensitivity of cervical cancer cells *via* activating LATS2 and blocking Rad51/MDC1 recruitment to DNA damage site. Cancers, 2022, **14**(8): 1872

[64] Wang Y, Wu H, Dong N, *et al*. Sulforaphane induces S-phase arrest and apoptosis *via* p53-dependent manner in gastric cancer cells. Sci Rep, 2021, **11**(1): 2504

[65] Zheng K, Ma J, Wang Y, *et al*. Sulforaphane inhibits autophagy and induces exosome-mediated paracrine senescence *via* regulating mTOR/TFE3. Mol Nutr Food Res, 2020, **64**(14): e1901231

[66] Hao Q, Wang M, Sun N X, *et al*. Sulforaphane suppresses carcinogenesis of colorectal cancer through the ERK/Nrf2-UDP glucuronosyltransferase 1A metabolic axis activation. Oncol Rep, 2020, **43**(4): 1067-1080

[67] Bagheri M, Fazli M, Saeednia S, *et al*. Sulforaphane modulates cell migration and expression of β-catenin and epithelial mesenchymal transition markers in breast cancer cells. Iran J Public Health, 2020, **49**(1): 77-85

[68] Cao W, Lu X, Zhong C, *et al*. Sulforaphane suppresses MCF-7 breast cancer cells growth *via* miR-19/PTEN axis to antagonize the effect of butyl benzyl phthalate. Nutr Cancer, 2022, **21**: 1-12

[69] Zhou T, Zhou M, Tong C, *et al*. Cauliflower bioactive compound sulforaphane inhibits breast cancer development by suppressing NF-κB /MMP-9 signaling pathway expression. Cell Mol Biol, 2022, **68**(4): 134-143

[70] Gu H F, Ren F, Mao X Y, *et al*. Mineralized and GSH-responsive hyaluronic acid based nano-carriers for potentiating repressive effects of sulforaphane on breast cancer stem cells-like properties.

Carbohydr Polym, 2021, **269**: 118294

[71] Xie H, Rutz J, Maxeiner S, *et al*. Plant-derived sulforaphane suppresses growth and proliferation of drug-sensitive and drug-resistant bladder cancer cell lines *in vitro*. Cancers, 2022, **14**(19): 4862

[72] Huang L, He C, Zheng S, *et al*. AKT1/HK2 Axis-mediated glucose metabolism: a novel therapeutic target of sulforaphane in bladder cancer. Mol Nutr Food Res, 2022, **66**(3): e2100738

[73] Gasparello J, Gambari L, Papi C, *et al*. High levels of apoptosis are induced in the human colon cancer HT-29 cell line by co-administration of sulforaphane and a peptide nucleic acid targeting miR-15b-5p. Nucleic Acid Ther, 2020, **30**(3): 164-174

[74] Chen Y, Tang L, Ye X, *et al*. Regulation of ZO-1 on β-catenin mediates sulforaphane suppressed colorectal cancer stem cell properties in colorectal cancer. Food Funct, 2022, **13**(23): 12363-12370

[75] Chen Y, Wang M H, Wu J Y, *et al*. ΔNp63α mediates sulforaphane suppressed colorectal cancer stem cell properties through transcriptional regulation of Nanog/Oct4/Sox2. J Nutr Biochem, 2022, **107**: 109067

[76] Lu Z, Ren Y, Yang L, *et al*. Inhibiting autophagy enhances sulforaphane-induced apoptosis *via* targeting Nrf2 in esophageal squamous cell carcinoma. Acta Pharm Sin B, 2021, **11**(5): 1246-1260

[77] Tsaur I, Thomas A, Taskiran E, *et al*. Concomitant use of sulforaphane enhances antitumor efficacy of sunitinib in renal cell carcinoma *in vitro*. Cancers, 2022, **14**(19): 4643

[78] Dos Santos P, Machado A R T, De Grandis R A, *et al*. Transcriptome and DNA methylation changes modulated by sulforaphane induce cell cycle arrest, apoptosis, DNA damage, and suppression of proliferation in human liver cancer cells. Food Chem Toxicol, 2020, **136**: 111047

[79] Chen X, Adhikary G, Ma E, *et al*. Sulforaphane inhibits CD44v6/YAP1/TEAD signaling to suppress the cancer phenotype. Mol Carcinog, 2023, **62**(2):236-248

[80] Esmaeili Y, Yarjanli Z, Pakniya F, *et al*. Targeting autophagy, oxidative stress, and ER stress for neurodegenerative disease treatment. J Control Release, 2022, **345**: 147-175

[81] Bhatt S, Puli L, Patil C R. Role of reactive oxygen species in the progression of Alzheimer's disease. Drug Discov Today, 2021, **26**(3): 794-803

[82] Busche M A, Hyman B T. Synergy between amyloid-β and tau in Alzheimer's disease. Nat Neurosci, 2020, **23**(10): 1183-1193

[83] Villavicencio-Tejo F, Olesen M A, Aránguiz A, *et al*. Activation of the Nrf2 pathway prevents mitochondrial dysfunction induced by caspase-3 cleaved Tau: implications for Alzheimer's disease. Antioxidants, 2022, **11**(3): 515

[84] Tang L, Ren X, Han Y, *et al*. Sulforaphane attenuates apoptosis of hippocampal neurons induced by high glucose *via* regulating endoplasmic reticulum. Neurochem Int, 2020, **136**: 104728

[85] Bose A, Petsko G A, Studer L. Induced pluripotent stem cells: a tool for modeling Parkinson's disease. Trends Neurosci, 2022, **45**(8): 608-620

[86] Xiao B, Kuruvilla J, Tan E K. Mitophagy and reactive oxygen species interplay in Parkinson's disease. NPJ Parkinsons Dis, 2022, **8**(1): 135

[87] Jazwa A, Rojo A I, Innamorato N G, *et al*. Pharmacological targeting of the transcription factor Nrf2 at the basal ganglia provides disease modifying therapy for experimental parkinsonism. Antioxid Redox Signal, 2011, **14**(12): 2347-2360

[88] Morroni F, Tarozzi A, Sita G, *et al*. Neuroprotective effect of sulforaphane in 6-hydroxydopamine-lesioned mouse model of Parkinson's disease. Neurotoxicology, 2013, **36**: 63-71

[89] Jang M, Cho I H. Sulforaphane ameliorates 3-nitropropionic acid-induced striatal toxicity by activating the Keap1-Nrf2-ARE pathway and inhibiting the MAPKs and NF-κB pathways. Mol Neurobiol, 2016, **53**(4): 2619-2635

[90] Yoo I H, Kim M J, Kim J, *et al*. The anti-inflammatory effect of sulforaphane in mice with experimental autoimmune encephalomyelitis. J Korean Med Sci, 2019, **34**(28): e197

[91] Gillespie S, Holloway P M, Becker F, *et al*. The isothiocyanate sulforaphane modulates platelet function and protects against cerebral thrombotic dysfunction. Br J Pharmacol, 2018, **175**(16): 3333-3346

[92] Li Q, Fadoul G, Ikonomovic M, *et al*. Sulforaphane promotes white matter plasticity and improves long-term neurological outcomes after ischemic stroke via the Nrf2 pathway. Free Radic Biol Med, 2022, **193**(Pt 1): 292-303

[93] Chilakala R R, Manchikalapudi A L, Kumar A, *et al*. Sulforaphane attenuates Aβ oligomers mediated decrease in phagocytic activity of microglial cells. Neuroscience, 2020, **429**: 225-234

[94] Zhang S, Zhao J, Bai Z, *et al*. Sulforaphane inhibits the production of Aβ partially through the activation of Nrf2-regulated oxidative stress. Food Funct, 2021, **12**(22): 11482-11490

[95] Yang Y, Zhang J, Yang C, *et al*. Sulforaphane attenuates microglia-mediated neuronal damage by down-regulating the ROS/autophagy/NLRP3 signal axis in fibrillar Aβ-activated microglia. Brain Res, 2023, **1801**: 148206

[96] Warpsinski G, Smith M J, Srivastava S, *et al*. Nrf2-regulated redox signaling in brain endothelial cells adapted to physiological oxygen levels: consequences for sulforaphane mediated protection against hypoxia-reoxygenation. Redox Biol, 2020, **37**: 101708

[97] Liu P, Wang W, Tang J, *et al*. Antioxidant effects of sulforaphane in human HepG2 cells and immortalised hepatocytes. Food Chem Toxicol, 2019, **128**: 129-136

[98] Socała K, Nieoczym D, Kowalczuk-Vasilev E, *et al*. Increased seizure susceptibility and other toxicity symptoms following acute sulforaphane treatment in mice. Toxicol Appl Pharmacol, 2017, **326**: 43-53

[99] Yagishita Y, Fahey J W, Dinkova-Kostova A T, *et al*. Broccoli or sulforaphane: is it the source or dose that matters?. Molecules, 2019, **24**(19): 3593

[100] Poulton E J, Levy L, Lampe J W, *et al*. Sulforaphane is not an effective antagonist of the human pregnane X-receptor *in vivo*. Toxicol Appl Pharmacol, 2013, **266**(1): 122-131

The Pharmaceutical Properties of Sulforaphane and Its Role in Tumor and Neurodegenerative Diseases*

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Abstract Sulforaphane is a naturally occurring active substance derived from cruciferous vegetables with potent antioxidant and anticancer properties. Researches have shown that sulforaphane has good bioavailability and can be absorbed by the small intestine through passive transport, followed by excretion in the form of urine *via* the hydrophobic acid pathway. In addition, since sulforaphane is easy to be absorbed and metabolized, wrapping sulforaphane with nanomaterials can improve its bioavailability and stability, prolong its action time in human body, and better utilize its therapeutic effect. In terms of mechanism of action, sulforaphane can activate Nrf2 and HSF1 signaling pathways, induce the expression of phase II detoxification enzymes HO-1, NADPH, GST and HSP, thus regulating the concentration of oxidative stress ROS *in vivo*; inhibit NF-κB signaling pathway, thus suppressing the expression of inflammatory factors TNF-α, IL-1 and IL-6; regulate epigenetic modifications, thus inhibiting HDAC and DNMT, and increasing the concentration of histone H3 and H4. By regulating the expression levels of the above factors, sulforaphane can affect the occurrence and development of cancer, neurodegenerative diseases and other diseases. In recent years, several phase I/II clinical trials have shown that sulforaphane has good drug-generating properties. For example, researchers have found that patients with skin cancer have not shown any health problems and their corresponding functional problems have improved greatly after long-term use of sulforaphane. This suggests that in the future sulforaphane has a very high medicinal potential for the treatment of cancer and neurodegenerative diseases. In this paper, we review the pharmacokinetics, target of action and safety of sulforaphane and its research progress in tumor and neurodegenerative diseases to provide a reference for the future application of sulforaphane in the treatment of tumor and neurodegenerative diseases.

Key words sulforaphane, pharmacokinetic, signal pathway, tumor, neurodegenerative disease
DOI：10.16476/j.pibb.2022.0545

* This work was supported by grants from The National Natural Science Foundation of China (21961003), Natural Science Foundation of Jiangxi Province (20212ACB206001), “Thousand People Program” in Jiangxi Province (jxsq2018106059), Ganzhou Natural Science Foundation, The Central Guidance on Local Science and Technology Development Fund (20231ZDF03071), and The Science and Technology Research Project of Education Department in Jiangxi Province (GJJ2201443).

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Received：December 29，2022 Accepted：March 17，2023