中药多糖抗衰老作用机制研究进展

李旭，张雪燕，杨世培，修明慧*，和建政*
（甘肃中医药大学，兰州 730000）

［摘要］ 近年来，人口老龄化趋势不断加剧，养老负担及高发率的老年病对社会、经济的发展产生了一定的负面影响。衰老是一个涉及多器官、多因素与多种疾病发生有关的生物学过程，由于衰老的发生发展涉及多种信号通路，如营养感应信号通路、胞内应激信号通路等，成为抗衰老药物研究的热点与难点。中药活性成分-多糖类物质，具有抗肿瘤、降血糖、降血脂、抗氧化、抗病毒等多种生物学活性，且在抗衰老方面有显著优势，有望成为潜在的抗衰老药物。研究表明，中药多糖能通过多种作用机制发挥抗衰老功效，其抗衰老功效主要体现在通过饮食限制，促进长寿基因沉默信息调节因子 1（Sirt1），叉头转录因子（FoxO）表达，增加机体对胰岛素的敏感性，激活 Sirt1 去乙酰化酶或抑制胰岛素/胰岛素样生长因子 1（IIS/IGF-1）及雷帕霉素靶蛋白（mTOR）信号通路，有效抑制衰老；此外，还可通过抑制活性氧（ROS）产生及促炎介质释放，增加抗炎及抗氧化能力，发挥免疫调节功效，有效抑制炎症衰老；也可通过 p53 介导的途径抑制细胞凋亡并延缓衰老。虽然中药多糖抗衰老研究多，作用广泛，效果良好，但是缺乏对中药多糖抗衰老作用机制的系统性综述，因此，该文总结 PubMed 与中国知网数据库中相关文献，就中药多糖抗衰老作用机制进行系统阐述，以期为科研研究者和临床工作者提供借鉴及信息参考。

［关键词］ 抗衰老；中药多糖；营养感应信号通路；胞内应激信号通路
［中图分类号］ R2-0；R339.3+8；G353.11　　［文献标识码］ A　　［文章编号］ 1005-9903（2022）04-0271-12
［doi］ 10.13422/j.cnki.syfjx.20220438
［网络出版地址］ https://kns.cnki.net/kcms/detail/11.3495.R.20211214.1730.003.html
［网络出版日期］ 2021-12-15 10:14

Anti-aging Mechanism of Chinese Medicinal Polysaccharides：A Review

LI Xu，ZHANG Xue-yan，YANG Shi-pei，XIU Ming-hui*，HE Jian-zheng*
（*Gansu University of Chinese Medicine*， *Lanzhou* 730000， *China*）

［**Abstract**］ In the greying society，pension burden and high incidence of geriatric diseases have hindered social and economic development to a certain extent. Aging is a biological process involving multiple organs and factors，which leads to the occurrence of a variety of diseases. The occurrence of aging is related to a variety of signal pathways，such as nutrient sensing signal pathway and intracellular stress signal pathway，which attracts the interest of scholars in anti-aging drugs and poses a challenge to the development of such drugs. The anti-tumor，hypoglycemic，hypolipidemic，antioxidant，and antiviral activities of Chinese medicinal polysaccharides have been gradually confirmed，and they also have significant advantages in anti-aging. Thus，they are potential candidates for the development of anti-aging drugs. It has been verified that Chinese medicinal polysaccharides exert the anti-aging effect through a variety of mechanisms. To be specific，through dietary restriction，they promote the expression of longevity genes silencing information regulator 1（Sirt1）and forkhead box O（FoxO）transcription factor，enhance the sensitivity to insulin，activate Sirt1 deacetylase or inhibit insulin/IGF-1

［收稿日期］ 20210730（018）
［基金项目］ 甘肃中医药大学人才引进项目（2018YJRC-12）；敦煌医学与转化教育部重点实验室 2019 年度开放课题（DHYX19-04）；甘肃中医药大学研究生创新基金项目（2021CX65）；甘肃省“双一流”科研重点项目（GSSYLXM-05）
［第一作者］ 李旭，在读硕士，从事中医药现代化及中药药理学研究，E-mail：1391939862@163. com
［通信作者］ * 修明慧，博士，副教授，从事中医药现代化及神经类疾病的机制研究，E-mail：523977132@qq. com；
* 和建政，博士，副教授，从事中西医结合抗衰老和防治代谢疾病研究，E-mail：gszynkx@163. com

signaling (IIS) and mammalian target of rapamycin (mTOR) signal pathway, thereby exerting the anti-aging effect. In addition, they can inhibit the production of reactive oxygen species (ROS) and the release of pro-inflammatory mediators, enhance anti-inflammatory and antioxidant capacity, and regulate the immunity to inhibit inflammation and aging. Moreover, they can also inhibit apoptosis and delay aging through p53-mediated pathway. Despite the extensive research on anti-aging effect of Chinese medicinal polysaccharides, and the diverse effects and ideal efficacy of the polysaccharides, the anti-aging mechanism has not been systematically reviewed. Therefore, this paper summarizes the relevant literature in PubMed and CNKI and systematically expounds the aging-related signal pathways regulated by Chinese medicinal polysaccharides, which is expected to provide a reference for researchers and clinical workers.

[**Keywords**] anti-aging; Chinese medicinal polysaccharides; nutrient sensing signal pathway; intracellular stress signal pathway

衰老(aging)是一个涉及体内外多种因素(环境因素、精神因素、遗传因素等),与多种疾病发生有关的生物学过程。近年来,全球65岁人口逐年增加,老龄化趋势日趋严峻。研究表明,中药能延缓机体多系统与多器官的衰老,但由于衰老过程的复杂性和中药成分的多样性,中药抗衰老的作用机制尚未完全阐明。中药活性成分-多糖类物质具有安全、低毒、丰富的生物学活性等特性,包含抗肿瘤、降血糖、降血脂、抗氧化、抗病毒等多种生物学活性,且在抗衰老方面有显著优势。近年来,中药多糖抗衰老的机制取得一定的进展,基于此,以"中药多糖"和"抗衰老"作为关键词,在中国知网(CNKI)数据库进行文献检索,为避免纳入文献不全,又以研究较多的"黄芪多糖""当归多糖""石斛多糖""等与"抗衰老"作为关键词检索文献,同时追溯纳入研究的参考文献,以补充获取相关文献。为确保文献纳入充分,在PubMed数据库以"(anti-aging, signal pathway)""(Chinese medicine polysaccharide, aging/age)"作为检索式进行检索,检索中药多糖抗衰老相关文献,为保证纳入文献足够,之后又以"(*Astragalus* polysaccharides, aging/age)""(*Angelica sinensis* polysaccharide, aging/age)""(*Lycium barbarum* polysaccharide, aging/age)""(*Dendrobium* polysaccharide, aging/age)""(*Cyclocarya paliurus* polysaccharide, aging/age)"等作为检索式检索。通过中英文数据库检索文献,共找到690篇相关文献,排除包括①非中、英文文献;②无法获取全文的文献;③个案报道、理论探讨和会议论文等;④同一数据重复发表的文献;⑤信息不完整或有逻辑错误的数据;纳入中药多糖与抗衰老相关的文献86篇。结合文献研究,对中药多糖抗衰老作用机制进行了归纳,主要包括营养感应信号相关通路,胞内应激信号相关通路等,并对中药多糖存在问题提出解决方案,为其临床应用提供依据。

1 中药多糖组成和提取

1.1 中药多糖的组成 糖类化合物广泛存在于自然界的植物中[1],是构成生命的四大基本物质之一,对植物的生长发育极为重要,其中的多糖类化合物种类繁多,具有多种生物学活性。多糖是由醛糖或酮糖通过糖苷键连接而成的大分子多聚物,在许多中草药中含量丰富,具有广泛的药理作用[2]。中药多糖成分复杂,其基本糖单位有鼠李糖、阿拉伯糖、木糖、核糖、半乳糖、葡萄糖、甘露糖、果糖、岩藻糖、葡萄糖醛酸和半乳糖醛等[3]。中药多糖按照单糖种类组成分为均多糖和杂多糖,由同一种单糖组成的多糖为均多糖,由2种以上单糖组成的多糖为杂多糖,大部分中药多糖为杂多糖,多指使用现代科技方法从单味中药中提取的有效多糖组分[4]。

1.2 提取方法 中药多糖的提取方法众多,包括传统提取方法和新型提取方法。传统方法包括热水提取法[5]、酸碱提法[6]、酶提法[7]、超声辅助法[8]、微波辅助法[9-10]等。这些提取方法主要是将中药进行粉粹、过筛等处理后,用极性溶剂水、乙醇等提取,除去其中的蛋白质,并利用水浴加热、超声、振荡、微波、加酶、加酸碱等提高多糖产率。新型方法包括高压脉冲电场辅助法、动态高压微射流辅助法、加速溶剂萃取法和超临界流体萃取法等。与传统提取方法相比,新型提取方法可获得纯度较高的多糖组分,提取时间远少于热水提取法,多糖产率明显高于热水提取法。

2 中药多糖抗衰老的作用机制

中药多糖作为多种中药的主要活性成分,具有抗氧化、免疫调节、抗肿瘤、抗病毒、抗衰老等功效。

多种中药多糖具有抗衰老的活性,研究多集中于黄芪多糖(APS),枸杞多糖(LBP),当归多糖(ASP),石斛多糖(DOP)等,其中涉及信号通路主要是营养感应信号通路、胞内应激信号通路及其他相关信号通路,本文就中药多糖抗衰老的作用机制进行系统阐述,具体中药多糖抗衰老作用机制见表1。

表1 中药多糖抗衰老的作用机制

Table 1 Anti-aging mechanisms of Chinese medicine polysaccharide

多糖种类	模型	相关表型	信号通路	参考文献
APS	果蝇	寿命延长,运动能力改善,改善氧化损伤	胰岛素(IIS)途径↓,雷帕霉素靶蛋白(mTOR)途径↓,抗氧化应激	[11]
	线虫	延长寿命	IIS途径↓;未折叠蛋白反应(UPR)↓	[12-13]
	大鼠/猪肺泡巨噬细胞	改善免疫应激	腺苷酸活化蛋白激酶(AMPK)/沉默信息调节因子1(Sirt1)途径↑	[14]
	RPE细胞	减轻2型糖尿病(T2DM)的胰岛素抵抗	Sirt1途径↑	[15]
	小鼠	改善线粒体功能障碍、减轻氧化应激	Sirt1//过氧化物酶体增殖物激活受体γ共激活因子-1α(PGC-1α)途径↑	[16]
	小鼠	清除活性氧(ROS),抑制线粒体肿胀、提高抗氧化能力	改善能量代谢	[17]
	骨髓基质细胞	抑制细胞凋亡、衰老、增殖及多能性降低	抑制细胞凋亡	[18]
	阿尔茨海默病(AD)小鼠	减轻氧化应激、细胞凋亡与Aβ蛋白沉积	核因子E_2相关因子2(Nrf2)途径↑	[19]
	小鼠	炎性因子与ROS产生减少	p38/有丝分裂原活化蛋白激酶(MAPK)和Toll样受体4(TLR4))/核转录因子-κB(NF-κB)↓	[20-23]
	家蚕	寿命延长,运动能力改善	重链结合蛋白(Bip)/蛋白激酶R样ER激酶(PERK)途径↓	[24]
	6-OHDA细胞	降低6-OHDA神经毒性	调节凋亡途径及胆碱能系统	[25]
ASP	小鼠	抑制氧化应激损伤,下调衰老相关β-半乳糖苷酶(SA-β-Gal)表达	c-Jun氨基末端激酶(JNK)/Nrf2/抗氧化反应元件(ARE)抗氧化信号通路↑	[26]
	神经干细胞(NSC)	促进细胞增殖,增强抗氧化能力	p53/p21信号通路↓	[27]
	小鼠/造血干、祖细胞(HSC/HPCs)	减轻氧化应激,防止DNA损伤	p53/p21,p16^{INK4a}/Rb↓;Wnt/糖原合成酶激酶-3β(GSK-3β)信号通路↑	[28]
APS,ASP	细胞	抑制过氧化氢(H_2O_2)诱导的细胞周期阻滞	抑制p53/p21和p16/pRb通路	[29]
LBP	线虫	生殖潜能增强,抗应激能力提高,延长寿命	IIS信号通路↓	[30]
	果蝇	延长寿命	mTOR信号通路↓	[31]
	H9c2细胞/大鼠	提高H9c2细胞的存活率	AMPK信号通路↑;MAPK激酶(MEK)/细胞外调节蛋白激酶(ERK)信号通路↑;p53/p21信号通路↓	[32]
	高氧肺损伤(ALI)小鼠	抗氧化酶活性增强	Nrf2信号通路↑	[33]
	小鼠	炎性因子与ROS产生减少	NF-κB↓	[34]
	更年期记忆障碍小鼠	减轻神经炎症和海马神经元损伤	TLR4/NF-κB↓	[35]
	IPEC-J2细胞	提高细胞存活率,减轻内质网应激(ERS)	减轻ERS;UPR信号通路↓	[36]
	MLTC-1细胞	抑制细胞凋亡,减轻ERS	减轻ERS;UPR信号通路↓	[37]
	斑马鱼	抑制细胞凋亡	p53信号通路↓	[38]
	原代皮层神经元细胞	降低同型半胱氨酸(Hcy)诱导的原代皮层神经元细胞死亡和凋亡	MAPK↓	[39]
黄连多糖(CCP)	AD转基因线虫	降低Aβ的毒性,延长AD线虫的寿命	β淀粉样蛋白(Aβ)	[40]

续表 1

多糖种类	模型	相关表型	信号通路	参考文献
DOP	线虫/衰老小鼠/果蝇	抗氧化能力增强	抗氧化应激	[41-43]
	小鼠	缓解更年期雌鼠症状,增强抗氧化能力	NF-κB 及 p53/B 细胞淋巴瘤(Bcl)途径信号通路↓	[44]
青钱柳多糖(CPP)	A549,H520 细胞	抑制肺癌细胞生长	mTOR/蛋白激酶 B(Akt)/磷脂酰肌醇 3-激酶(PI3K)途径↓	[45]
白芨多糖(BSP)	线虫	寿命延长,运动能力改善	IIS 信号通路↓	[46]
地黄多糖	线虫	寿命延长	IIS 信号通路↓	[47]
酸枣多糖	大鼠/Caco-2 细胞	缓解炎症	AMPK 依赖的 Sirt1 信号通路↑	[48]
党参多糖	PC12 细胞	减轻 Aβ 毒性	Sirt1/PGC-1α↑	[49]
银耳多糖	人皮肤成纤维细胞	提高细胞存活率,抑制氧化应激及细胞凋亡	Sirt1 途径↑;p53/Bcl-2 介导的信号通路↓	[50]
虫草多糖	果蝇	寿命延长,机体抗氧化能力增强	抗氧化应激	[51]
百合多糖	线虫	线虫寿命延长,抗氧化酶活性增强	抗氧化应激	[52]
蛹虫草多糖	大鼠	抑制线粒体肿胀和提高抗氧化酶活性	线粒体改善	[53]
羊栖菜多糖	线虫	抗氧化能力增强	Nrf2 信号通路↑	[54]
冬虫夏草多糖	大鼠	免疫功能明显增强	免疫调节	[55]
灵芝多糖	大鼠	氧化酶活性增强	钙稳态信号通路	[56]
柴胡多糖	RAW264.7 细胞	衰老相关基因的表达受到抑制	抑制 NF-κB 信号通路	[57]
玉郎伞多糖	小鼠	抗氧化应激损伤与保护机体免疫功能	抗氧化应激、免疫调节	[58]
山茱萸多糖	小鼠	抑制细胞凋亡	抑制细胞凋亡	[59]
山药多糖	神经细胞	抑制凋亡	抑制细胞凋亡	[60]
菟丝子多糖	大鼠	抑制凋亡,延缓衰老	抑制细胞凋亡	[61]
黄精多糖(PSP)	大鼠	减轻氧化应激	Klotho-FGF23 内分泌轴	[62]

注:↑.激活;↓.抑制。

2.1 营养感应信号通路　营养感应途径主要包括生长激素—IIS/胰岛素样生长因子-1(IGF-1)信号通路,mTOR 信号通路,AMPK 信号通路,Sirt1 信号通路。

2.1.1 IIS/IGF-1 信号通路　IIS 信号通路是影响酵母、线虫、果蝇及哺乳动物衰老及衰老相关疾病的经典信号通路之一,主要参与调控细胞周期、生长、发育、寿命与应激等多种生物学过程[63-65]。生物体 IIS 信号通路主要包括:PI3K 相关蛋白激酶(PIKK),IIS/IGF-1 受体(IGF-1R)及胰岛素受体底物[66]。IIS 信号通路主要通过参与调节营养摄取与信号转导的过程调控衰老与寿命,其发挥抗衰老的机制在于减弱胰岛素信号的传导,增强胰岛素的敏感性和减少血浆胰岛素样生长因子。PIKK,IIS/IGF-1R 及胰岛素受体底物等基因发生突变或抑制情况下,IIS 信号通路受到抑制,模式生物酵母、果蝇、线虫及小鼠的寿命均延长[67-71]。

课题组前期研究发现,APS 抗衰老的作用机制与负调控 IIS 信号通路相关。APS 通过增加果蝇体内 IIS 信号通路下游叉头转录因子(FoxO)的表达并降低胰岛素样肽-2,3,5(Dilp-2,3,5)的表达,负调控 IIS 信号通路,延长果蝇寿命[11]。APS 能增加线虫 IIS 信号通路下游基因 FoxO 表达而延长寿命,发挥抗衰老作用[12]。BSP 能调控 IIS/IGF 信号通路关键基因 AGE-1(PI3K 同系物),宿主细胞因子-1(HCF-1)及 DAF-16(FoxO 同系物)的 mRNA 水平,抑制 IIS 信号通路,延长线虫寿命,改善运动能力,发挥抗衰老活性[46]。IIS 信号通路下游因子 DAF-2(IGF-1R 同系物)的表达,会受地黄多糖影响而表达下调,进而抑制其下游 AGE-1 的激活,使转录因子 DAF-16 的磷酸化受阻,促使 DAF-16 进入细胞核发挥转录调控功能,抑制 IIS 信号通路延长线虫的寿命[47]。

线虫经LBP干预后,体内IIS信号通路下游DAF-16的表达增加,延长线虫寿命;而沉默DAF-16基因后,发现LBP对线虫的延寿作用消失,因此LBP通过DAF-16依赖的IIS信号通路发挥抗衰老作用[30]。

2.1.2 TOR信号通路 mTOR是调控机体生长、增殖、代谢及衰老的中心调控器及胞内能量传感器[72-74]。近年来,学者发现mTOR信号通路与衰老的诸多过程有关,其对衰老与寿命的研究日益广泛[75]。在营养丰富的条件下,mTOR信号通路通过激活核糖体S6蛋白激酶(S6K)与抑制真核细胞翻译起始因子4E结合蛋白(4EBP),增加mTOR蛋白的表达,缩短寿命;饮食限制或营养缺乏情况下,蛋白合成减少,机体寿命延长[76-77]。

课题组前期研究发现,APS能通过影响mTOR信号通路下游4EBP与S6K的表达,负调控mTOR信号通路,延长果蝇寿命[11]。LBP通过下调mTOR信号通路中S6K的表达,减少mTOR蛋白的表达,负调控mTOR信号通路,延长果蝇寿命[31]。虫草多糖(CSP)处理炎症细胞后,Akt,mTOR及PI3K的表达和磷酸化水平降低,增加丝氨酸/苏氨酸蛋白激酶-失调51样激酶1(ULK1)和AMPKα的表达和磷酸化水平,认为CSP通过抑制mTOR介导的PI3K/Akt/mTOR信号传导并激活AMPK/mTOR/ULK1通路,发挥抗炎活性[78]。CPP可通过抑制mTOR/Akt/PI3K信号通路,显著抑制低氧诱导的人非小细胞肺癌细胞A549和H520的生长,从而发挥抗肿瘤作用,起到延缓衰老的作用[45]。

2.1.3 AMPK信号通路 AMPK是一种单磷酸腺苷(AMP)依赖性的蛋白激酶,是广泛存在于多种真核细胞中的营养与能量传感器,具有维持细胞能量稳态的功能[79-80]。AMPK信号通路调控衰老与寿命的机制与其控制细胞稳态、应激、细胞生存及自噬等过程有关[81]。当机体出现应激时,体内二磷酸腺苷(ADP)/AMP:三磷酸腺苷(ATP)比例增高,上游激活因子-肝激酶B1(LK81)表达上调,Ca^{2+}/钙蛋白依赖性蛋白激酶激酶β(CaMKKβ)表达显著上调,激活AMPK信号通路[82]。激活的AMPK信号通路通过促进ATP的产生,有效预防衰老,延长线虫、果蝇及小鼠寿命[83-85]。特异性降低AMPK活性使机体对饥饿的敏感性增强、脂质异常积累,寿命缩短[86]。可知,与年龄相关的改变与AMPK途径密切有关。

LBP能提高缺氧损伤H9C2细胞的存活率,主要是通过下调微小核糖核酸-122(miR-122)表达,上调LKB1和CaMKKβ表达,激活AMPK信号通路来实现[32]。LIU等[14]通过体内外实验发现APS对免疫应激的保护作用,APS干预后,细胞毒性、细胞凋亡及促炎因子的表达受到抑制,免疫应激大鼠体内AMPK/Sirt1表达水平增加,NF-κB活性受到抑制,而下调或抑制Sirt1基因后,APS的功能会被消除,APS能通过激活AMPK/Sirt1信号通路,减轻免疫应激。酸枣多糖能改善大鼠结肠炎症状,降低炎症因子水平表达,缓解炎症;酸枣多糖上调Caco-2细胞体内AMPK活性,而使用AMPK特异性抑制剂能消除酸枣多糖对结肠炎的保护作用,因此酸枣多糖通过激活AMPK信号通路发挥抗炎作用[48]。

2.1.4 Sirt1/FoxO信号通路 Sirt1是一种极度保守的烟酰胺腺嘌呤二核苷酸(NAD^+)依赖的脱乙酰化酶[87-88]。Sirt1作为一种经典的长寿基因[89],与衰老的诸多过程密切相关。研究发现,Sirt1的延寿效应是通过调节不同细胞过程,如通过对肿瘤相关蛋白53(p53)的去乙酰化作用,抑制细胞凋亡,通过对FoxO1的去乙酰化,增强超氧化物歧化酶(SOD)等抗氧化酶活性[90];在脑中特异性过表达Sirt1的转基因BRASTO小鼠的寿命延长[89]。

LBP能显著延长线虫的寿命、增强生殖潜能和提高对外界环境的应激能力,其作用机制主要与Sirt2.1和FoxO信号通路相关[30]。党参多糖显著增加NAD^+,NAD^+/还原型辅酶I(NADH)比例,Sirt3,Sirt1和与NAD^+相关的PGC-1α的表达,从而部分恢复ATP,改善了β淀粉样蛋白1-40($A\beta_{1-40}$)对PC12细胞的毒性作用[49]。APS预处理呈浓度依赖性的逆转代谢记忆对视网膜色素上皮(RPE)细胞的损伤作用,其作用机制主要涉及逆转微小核糖核酸(miR-204)的表达,激活Sirt1,增强p53的去乙酰化作用,抑制ERS及其后的凋亡,以减轻T2DM的胰岛素抵抗,减缓代谢功能受损[15]。APS处理氧化应激小鼠及细胞后,Sirt1和PGC-1α蛋白表达水平增加,激活Sirt1信号通路,改善氧化应激及线粒体功能障碍,潜在发挥抗衰老功效[16]。银耳多糖处理人皮肤成纤维细胞能促进Sirt1蛋白表达,激活Sirt1信号通路,潜在发挥抗皮肤衰老的作用[50]。

2.2 胞内应激信号通路 机体细胞反复暴露于不利环境或内源性应激下,会出现一系列应激损伤。为避免应激过度所致损伤并维持应激损伤条件下细胞的正常形态及功能,细胞会通过多种应激反应调控其基础生理活动。研究表明,多种细胞应激反应与衰老直接相关,其中有Nrf2信号通路,NF-κB信号通路,UPR信号通路,p53/细胞周期依赖性蛋白

激酶抑制因子1A(p21)与p16/成视网膜母细胞瘤蛋白(pRb)信号通路等。

2.2.1 Nrf2信号通路 ROS是调控衰老与衰老相关疾病致病的关键因素[91-92]。随年龄增长,机体氧化还原平衡发生紊乱,ROS产生过量,机体自身分泌SOD,过氧化氢酶(CAT),血红素加氧酶-1(HO-1),谷胱甘肽过氧化物酶(GSH-Px)等抗氧化因子对抗氧化应激,而这些抗氧化因子拥有共同启动子元件,即ARE。机体受到氧化应激刺激时,氧化应激蛋白JNK表达增加,识别与Kelch样环氧氯丙烷相关蛋白1(Keap1)解偶联的Nrf2,Nrf2释放进入细胞核,与ARE相互作用,激活Nrf2/ARE信号通路,调节抗氧化因子的表达,从而保护机体免受氧化应激引起或加剧的紊乱[93]。研究证实激活Nrf2信号通路能延长模式生物果蝇、线虫及小鼠的寿命[94-96]。

多种中药多糖均具有增强机体抗氧化的能力,改善氧化应激功能,如PSP,肉苁蓉多糖能通过抑制氧化应激来减轻*D*-半乳糖(*D*-gal)诱导的衰老相关表型,发挥抗氧化作用[97-98];虫草多糖、百合多糖及DOP延长线虫或果蝇寿命的作用机制也主要与增加机体抗氧化能力,上调抗氧化相关基因CAT,SOD和MTH等的表达水平相关[41-43,51-53];APS与LBP能通过清除ROS,调节机体抗氧化因子的表达,保护线粒体,最终改善线粒体功能障碍,发挥线粒体保护作用及延缓衰老[17-18]。APS能通过激活Nrf2信号通路减轻AD小鼠的氧化应激、细胞凋亡和Aβ沉积,发挥神经保护作用[19]。羊栖菜多糖延缓线虫衰老的一项研究表明,其主要通过p21和JNK依赖性途径介导的Nrf2信号通路,上调核Nrf2易位,激活Nrf2信号通路,加强抗氧化防御延缓衰老进程[54]。ASP通过抑制氧化应激损伤,下调SA-β-Gal表达,发挥抗衰老作用[26-27],其作用机制与激活Nrf2/ARE抗氧化信号通路有关[26]。LBP改善ALI小鼠体内肺水肿等病变,增强HO-1,GSH-Px和Nrf2活性;当敲除Nrf2后,LBP对ALI的保护作用消失,故LBP通过激活Nrf2信号通路保护ALI[33]。

综上所述,中药多糖能激活Nrf2信号通路,调节抗氧化因子的表达,保护机体免受氧化应激引起或加剧的紊乱,增强机体抗氧化能力,延缓衰老。

2.2.2 NF-κB信号通路 机体免疫能力随年龄增长而降低,与免疫调节相关的信号通路有MAPK,NF-κB,Wnt/β-连环蛋白(β-catenin)等。NF-κB是机体负责调控细胞黏附、增殖、炎症、氧化还原状态及凋亡等因子表达的关键转录因子[99]。正常情况下,NF-κB以无活性的异二聚体形式存在,随年龄增加,机体免疫系统被激活,诱发慢性炎症,NF-κB通过磷酸化IκB激活NF-κB信号通路[100-101]。持续激活NF-κB通路不仅与衰老有关,还能促进衰老[102]。在果蝇和小鼠中,抑制NF-κB活性能延长寿命[103]。

多种中药多糖具有免疫调节功效,如冬虫夏草多糖、灵芝多糖能显著增强衰老大鼠的免疫功能[55-56]。APS通过调节微小核糖核酸-92a(miR-92a)/Krüppel样因子4(KLF4)轴,抑制脂多糖(LPS)诱导的p38/MAPK和TLR4/NF-κB信号途径的过度激活来抑制炎性因子与ROS产生,从而发挥免疫调节功效,有效抑制炎症衰老[20-23]。LBP通过抑制TLR4,IL-6等标志物的过度表达,增加IκB活性,抑制NF-κB信号通路,发挥神经保护和抗炎作用[34]。同时,LBP通过下调与TLR4/NF-κB信号通路相关的mRNA及蛋白质的表达水平,减轻更年期小鼠记忆障碍,从而减轻神经炎症和海马神经元损伤,发挥抗衰老作用[35]。柴胡多糖、羊栖菜多糖及DOP具有增强机体免疫的功能,其主要通过调节NF-κB,活化蛋白-1(AP-1),IκBα蛋白水平的表达,抑制NF-κB信号通路,抑制衰老相关基因的表达,有效抑制炎症衰老及其造成的损伤[44,57,104-106]。

2.2.3 UPR信号通路 ER是机体负责调控细胞内蛋白分泌、转运、折叠及钙稳态等过程的重要细胞器[107]。衰老过程中,ER中未折叠与错误折叠蛋白大量积聚[108]。细胞通过激活UPR信号通路对ER中过度积聚的错误折叠蛋白做出反应[109]。UPR信号通路主要由活化转录因子6(ATF6),PERK和肌醇需要酶1(IRE1)三种ER跨膜蛋白所介导。衰老过程中,UPR信号通路激活,编码伴侣蛋白基因-GRP78的表达增加[24],缩短果蝇寿命[110-111]。此外,UPR信号通路相关靶基因的缺失能显著延长寿命[112]。综上,UPR信号通路与寿命直接相关。

研究发现经APS干预后,线虫体内微小核糖核酸(miR-124)表达水平降低,进而降低ATF6的表达,延长寿命[13]。APS干预后,家蚕体内BmPERK与免疫球蛋白BmBip表达水平显著降低,且能恢复家蚕体内发生紊乱的ER稳态,因此APS延长寿命的分子机制与Bip/PERK信号通路恢复内质网稳态有关[24]。LBP通过减轻细胞ERS与UPR,保护细胞免受ERS诱导的凋亡,潜在发挥抗衰老作用[36]。同时,LBP通过调节ERS介导的信号通路保护MLTC-1细胞免受顺铂(DDP)的侵袭,其主要表现为磷酸化(p)-PERK,磷酸化真核细胞起始因子2α

(p-elF2α)和ATF4的下调,保护细胞免受ERS诱导的细胞凋亡[37]。因此,中药多糖抗衰老的作用机制涉及调控ERS相关信号通路。

2.2.4 p53/p21与p16/pRb信号通路 p53作为一种细胞转录因子主要参与调控细胞周期,DNA修复,凋亡及细胞应激反应。当细胞受到外界刺激时,p53蛋白表达水平会发生应激性上调,随之激活p21蛋白,抑制p21蛋白的磷酸化,并下调pRb/转录因子E2F(E2F)轴,导致正常细胞周期受阻,引起细胞衰老[113-115]。过表达p53基因的突变小鼠寿命会缩短[116]。p16^{INK4a}是调控细胞衰老的另一重要生物标记物[117],衰老过程中,p16表达上调,使pRb处于持久低磷酸化,下调pRb/E2F轴,导致正常细胞周期受阻,发生细胞衰老。敲除p16^{INK4a}基因表达的转基因小鼠寿命会延长,并改善与年龄相关的疾病症状[118]。因此,p53/p21,p16^{INK4a}/pRb蛋白的表达与衰老直接相关。

ASP处理后,衰老小鼠体内NSC及HSC/HPCs的衰老相关基因p53,p21及p16^{INK4a}/Rb的表达下调,促进神经发生和维持干细胞活性,延缓衰老[27-28]。APS与ASP联用对H_2O_2诱导的细胞周期阻滞具有抑制作用,并通过抑制p53/p21和p16/pRb通路,抑制细胞凋亡,对氧化应激诱导的衰老具有保护作用,具有延缓衰老和改善衰老相关疾病症状的潜力[29]。银耳多糖能降低H_2O_2对人皮肤成纤维细胞的氧化损伤,其作用机制涉及下调p53/p21信号通路中p16,p21,p53和半胱氨酸天冬氨酸蛋白水解酶-3(Caspase-3)水平,抑制细胞凋亡,延缓皮肤衰老[50]。DOP通过抑制p53/Bcl-2介导的信号通路来减轻衰老引起的损伤[44]。LBP能提高缺氧损伤的H9c2细胞的存活率,并一定程度抑制衰老斑马鱼体内p53,p21,Bax及p16的表达,通过p53介导的途径促进细胞迁移、抑制细胞凋亡并延缓衰老[32,38]。山茱萸多糖、山药多糖、玉郎伞多糖可影响线粒体功能及凋亡相关基因的表达,潜在延缓衰老[58-60]。菟丝子多糖通过降低衰老大鼠心肌细胞细胞色素C(CytC),Ca^{2+}含量,Caspase-3活性及Bcl-2相关X蛋白(Bax)表达,增加Bcl-2/Bax值,抑制心肌细胞凋亡,延缓衰老[61]。

2.3 其他 衰老是多种神经退行性疾病的危险因素,延缓衰老可降低神经退行性疾病的发病几率。研究发现,多种中药多糖具有神经保护作用,如CCP能上调AD转基因线虫体内热休克蛋白(HSP)基因的表达从而抑制Aβ蛋白的沉积,同时CCP能延长线虫寿命,但其抗衰老和神经保护机制仍需进一步阐明[40];APS能通过调节凋亡途径及胆碱能系统发挥神经保护作用[25];LBP抑制同型半胱氨酸(Hcy)诱导的原代皮层神经元细胞的死亡和凋亡,抑制MAPK信号通路下游p-JNK和磷酸化细胞外调节蛋白激酶(p-ERK)的升高,可能通过MAPK信号通路发挥神经保护作用[39]。

HSCs/HPCs参与机体造血和免疫调节,研究发现,随年龄增加,机体HSC/HPCs功能逐渐减弱,因此,保持干细胞年轻化为延缓衰老提供了新思路。ASP能下调衰老小鼠体内GSK-3β的基因表达,上调β-catenin表达,Wnt信号通路发生过度激活,在一定程度上延缓了*D*-gal诱导的干细胞衰老[28]。Klotho基因是一种经典的抗衰老基因,其与成纤维细胞生长因子-23(FGF-23)有一个共同的受体,调控衰老。PSP能上调衰老大鼠体内Klotho mRNA及其蛋白的表达水平,下调FGF-23蛋白的表达,因此PSP可能通过调节Klotho-FGF23内分泌轴,减轻氧化应激,平衡钙磷代谢发挥作用,延缓大鼠肾脏衰老[62]。

总之,中药多糖抗衰老的作用机制涉及多靶点、多通路协同发挥作用。

3 讨论与展望

随着人口老龄化趋势的不断加剧,养老负担及高发率的老年病对社会与经济的发展产生了一定负面影响。因此,亟需寻找既能延寿又能提高老年患者生活质量的药物。中药复杂的活性成分中,中药多糖以其安全、低毒、丰富的生物学活性备受关注,其在衰老及衰老相关疾病的治疗中具有一定的优势和良好的应用前景。本文综述了中药多糖抗衰老的相关信号通路,通过抗氧化应激,抗炎,ERS,营养限制等多途径奏效。中药多糖可通过调控营养感应信号途径,如负调控IIS信号通路,减少mTOR蛋白生成,抑制mTOR信号通路;激活AMPK信号通路,促进体内ATP产生;过表达Sirt1/FoxO信号通路中的长寿基因Sirt1,从而延缓衰老。此外,还可通过激活Nrf2/ARE信号通路调节抗氧化因子的表达,抑制NF-κB信号通路来抑制炎性因子与ROS产生;抑制UPR信号通路,减轻ERS,或抑制p53/p21和Bax相关基因的表达,通过p53介导的途径抑制细胞凋亡等多种胞内应激信号通路发挥抗衰老功效。

上述研究证实,中药多糖在抗衰老及改善衰老相关疾病方面具有很好的疗效,本文总结其作用机

制,探讨了中药多糖抗衰老的信号通路,一定程度拓宽了研究者对中药多糖的认识,但现有研究仅限于一些体内外实验,缺乏临床药效佐证,且中药多糖抗衰老的作用机制尚不完全明确。而衰老动物模型虽一定程度接近人类衰老状态,但仍无法复制人体衰老的真实病因及病机,故开展相应的临床试验是评价中药多糖抗衰老活性的关键。因此,开发中药多糖成为临床抗衰老用药,仍需进一步进行体内外实验及临床试验。随着新技术不断发展,中药多糖研究势必会进入一个崭新阶段,其抗衰老的研究会越发深入,基于中药多糖药理学活性新型药物的研发会具有巨大的挖掘价值。

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