黄精多糖结构特征及其生物活性研究进展

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摘 要:中药黄精为百合科黄精属植物黄精(*Polygonatum sibiricum* Delar. ex Redoute)、滇黄精(*Polygonatum kingianum* Coll. et Hemsl)与多花黄精(*Polygonatum cyrtonema* Hua)的干燥根茎,具有悠久的药用历史。黄精多糖是黄精中最重要的活性化合物之一,具有抗氧化、调节免疫、抗肿瘤、抗骨质疏松、降血糖、降血脂和抗动脉粥样硬化等多种生物活性,已经成为黄精开发应用研究的热点。本文综述了近年来国内外对黄精多糖的结构特征、生物活性及其相关机制的研究进展,以期为黄精多糖的深入研究与开发提供理论参考。

关键词:黄精;多糖;结构特征;生物活性;作用机制
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Progress on the structural characteristic and biological activity of Polygonati Rhizoma polysaccharides

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Abstract: The Chinese herb Polygonati Rhizoma, which is the dried rhizome of *Polygonatum sibiricum* Delar. ex Redoute, *Polygonatum kingianum* Coll. et Hemsl and *Polygonatum cyrtonema* Hua in genus *Polygonatum*, family Liliaceae, has a long history of medicinal use. The Polygonati Rhizoma polysaccharide is one of the most important active compounds in Polygonati Rhizoma, which has various biological activities such as antioxidant, immune modulation, anti-tumor, anti-osteoporosis, hypoglycemic, hypolipidemic and anti-atherosclerosis effects, etc. It has become a hot spot for the development and application research of Polygonati Rhizoma. In this article, the recent domestic and foreign literatures on the structural characteristics, biological activities and action mechanisms of Polygonati Rhizoma polysaccharides were summarized, which provide some reference for the in-depth research and development of Polygonati Rhizoma.

Key words: Polygonati Rhizoma; polysaccharide; structural characteristics; biological activity; mechanism of action

黄精 Polygonati Rhizoma 为药食同源的中药,《中国药典》2020 年版规定黄精 *Polygonatum sibiricum* Delar. ex Redoute、滇黄精 *Polygonatum kingianum* Coll. et Hemsl 和多花黄精 *Polygonatum cyrtonema* Hua 的干燥根茎为黄精的正品。一般是在春、秋两季采挖,除去须根,洗净,至于沸水中略烫或蒸至透心,干燥即得[1]。根据其性状的不同,也可分为“大黄精”“鸡头黄精”“姜型黄精”。黄精始载于《名医别录》,具有补气养阴、健脾、润肺、益肾的功效,临床上常用于脾胃虚弱、体倦乏力、口干食少、肺虚燥咳、精血不足、内热消渴等病症的治疗[2]。现代药理研究表明,黄精具有广泛的生物活性,可用于预防和治疗多种疾病。黄精中含有多种化学成分,主要包括多糖、生物碱、甾体皂甙、氨基酸等[3]。其

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中,黄精多糖被认为是黄精中最重要的活性化合物之一,具有抗氧化、调节免疫、抗肿瘤、抗骨质疏松、降血糖、降血脂和抗动脉粥样硬化等多种生物活性。

本文对近年来国内外对黄精多糖的研究进行归纳与总结,综述了黄精多糖结构特征、生物活性及其作用机制研究进展,以期为黄精多糖的深入研究与开发提供理论参考。

1 黄精多糖的提取与分离纯化

水提醇沉法为黄精多糖最常用的提取方法[4]。提取的黄精多糖经浓缩、分级醇沉、脱蛋白、脱色以及透析等步骤得粗多糖;粗多糖再采用离子交换柱色谱以及凝胶柱色谱分离等技术,进一步分离纯化可得到均一多糖,如图 1 所示。与此同时,在黄精多糖的提取过程中可适当加入稀碱液,破坏植物细胞细胞壁,提高黄精多糖产率[5]。此外,近年来报道从黄精中提取多糖还有其他几种新型辅助提取方法,如超声波辅助酶法[6]、微波辅助提取法[7,8]等,在一定程度上提高了黄精多糖的提取率。上述黄精多糖的提取纯化方法为黄精多糖的进一步研究提供了强大的助力。

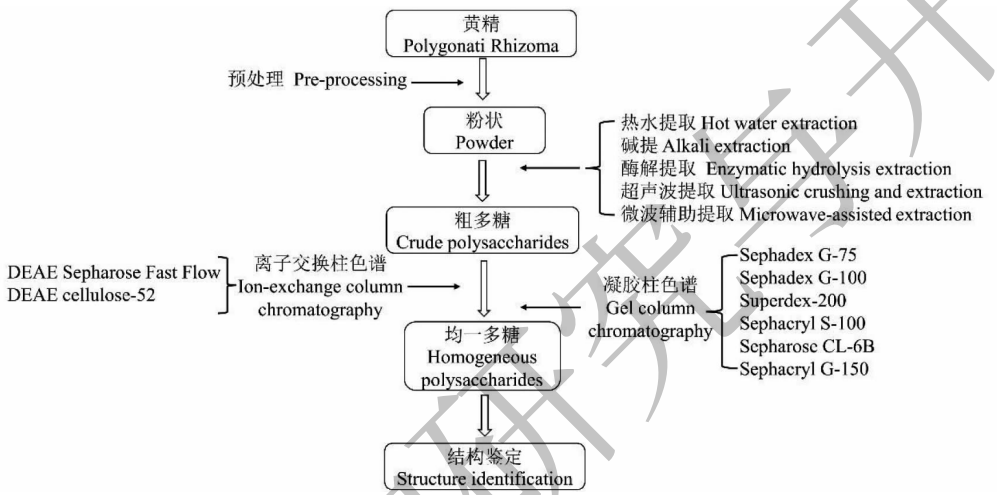

图 1 黄精多糖的提取和纯化流程

Fig. 1 Flowchart for extraction and purification of Polygonati Rhizoma polysaccharides

2 黄精多糖的结构特征

多糖的生物活性主要取决于其化学结构,多糖的结构表征对多糖的深入研究具有重大意义。与此同时,多糖的结构复杂,对于其结构表征通常包括相对分子质量测定、单糖组成分析、糖链结构的分析等。黄精多糖的结构信息如表 1 所示。

表 1 黄精多糖结构信息

Table 1 Structural information of the Polygonati Rhizoma polysaccharides

组分 Component	相对分子质量 Relative molecular mass	单糖组成 Monosaccharide composition	构型及糖苷键 Conformation and glycosidic bond	参考文献 Ref.
黄精 *Polygonatum sibiricum* Delar. ex Redoute				
PSP	–	Gal-Rha-Man-Glu-Xyl(63.50:25.14:8.04:1.75:1.57)	–	4
PSP1	4.42×10^3	Man-Glu-Gal(14.96:2.13:82.91)	β-Gal	9
PSP2	2.24×10^3	Rha-Glu-Gal-Xyl(20.51:2.06:74.37:3.03)	β-Gal	9
PSP3	7.74×10^3	Man-Rha-Glu-Gal-Xyl(1.38:57.69:2.02:37.17:1.74)	β-Gal	9
PSP4	6.47×10^3	Man-Rha-Gal-Xyl(2.00:72.63:20.74:4.63)	β-Gal	9
PSP	9.51×10^4	Gal-Rha-Ara-Man-Glu(11.72:1.78:4.15:1.00:2.48)	α-*D*-Gal	10
PSP50-2-1	7.70×10^3	Gal-Glu-Fru(53.22:15.59:31.18)	β-*D*-Fru*f*-(2→, →2)-β-*D*-Gal*p*-(1→,→2,6)-β-*D*-Gal*p*-(1→,α-*D*-Glc*p*-(1→	11

续表 1(Continued Tab. 1)

组分 Component	相对分子质量 Relative molecular mass	单糖组成 Monosaccharide composition	构型及糖苷键 Conformation and glycosidic bond	参考文献 Ref.
PSP50-2-2	7.00×10^3	Gal-Glu-Fru(64.85:27.22:7.92)	β-D-Galp-(1→,→2)-β-D-Galp-(1→,→6)-α-D-Galp-(1→,→2,6)-β-D-Galp-(1→,β-D-Glcp-(1→,β-D-Fruf-(2→	11
PS-WNP	7.60×10^4	Gal-Man(12.1:5.4)	Manp-(1→,6→)-Galp-(1→,2,6→)-Galp-(1→	12
PSW-1a	–	Man-Gal(88.8:11.2)	β-D-Galp-(1→,→4)-β-D-Manp-(1→,→4,6)-β-D-Manp-(1→	13
PSW-1b-2	4.20×10^4	Gal	β-D-Galp-(1→,→4)-β-D-Galp-(1→,→4,6)-β-D-Galp-(1→	13
PSPJWA	1.41×10^5	Gal-Ara-Rha(14:4:1)	→2,4)-α-L-Rhap-(1→,α-L-Araf-(1→,→3,5)-α-L-Araf-(1→,→5)-α-L-Araf-(1→,→4)-β-D-Galp-(1→,→4,6)-β-D-Galp-(1→,β-D-Galp-(1→	14
PSP	–	Ara-Glu-GlcA-Gal-Gala-Man-Rha-Rib(13.7:82.9:3.7:36.2:4.3:52.5:3.3:1.0)	–	15
PsPs	–	Man-Rha-Gala-Glu-Xyl-Ara(6.6:15.4:4.5:8.8:40.7:24)	–	16
PSP	6.06×10^3	Man-Glc-Gal-Ara(51.23:21.39:26.92:0.46)	–	17
PSPC	4.01×10^3	Gal-Man-Glc-Gala(29.63:36.1:15.09:10.20)	–	18
PSPW	1.42×10^4	Gal-Man-Gala-Rha(78.77:5.50:13.84:1.85)	–	18
F1	1.03×10^5	Man-Glc-Ara-Gal(76.3:15.2:4.00:4.5)	–	19
F2	6.28×10^5	Man-Glc-Ara-Gal(67.7:20.3:7.65:4.35)	–	19
PSP1	3.22×10^5	Gal-Man-Glc-Fru	→1)-β-D-Fruf-(2→,→6)-α-D-Glcp-(1→,→4)-β-D-Manp-(1→,→1,6)-β-D-Fruf-(2→,β-D-Fruf-(2→,→6)-β-D-Fruf-(2→,→4)-β-D-Glcp-(1→,	20
PSP-1	3.87×10^4	Glc	β-D-Glcp-(1→,→4)-α-D-Glcp-(1→,→4,6)-α-D-Glcp-(1→	21
滇黄精 *Polygonatum kingianum* Coll. et Hemsl				
P1	1.80×10^3	Fru-Glc(10:1)	α-D-Glcp-(1→,→1,6)-β-D-Fruf-(2→,→1)-β-D-Fruf-(2→,β-D-Fruf-(2→	22
PKPS-1	1.40×10^4	Glc-Man-Gala-Gal-Glca-Ara(7.22:1.0:0.16:0.11:0.05:0.02)	–	23
PSF	1.79×10^5	Man-Gala-Gal-Fuc	–	24
PS	1.35×10^5	Man-Gala-Gal-Fuc	–	24
PKP	–	Gal-Gala-Ara-Glc(57.67:26.82:4.59:4.54)	–	25
多花黄精 *Polygonatum cyrtonema* Hua				
HPGPC	3.60×10^4	Man-Gal-Glc-Ara-Xyl-GalN-Fuc-GlcN-Rha-Glca-Gala(43.32:20.04:19.87:8.67:2.21:2.12:1.11:0.95:0.91:0.52:0.29)	–	26
PCP-1	4.80×10^3	Fru-Glc(28:1)	→1)-β-D-Fruf-(2→,→6)-β-D-Fruf-(2→,→1,6)-β-D-Fruf-(2→,β-D-Fruf-(2→,→6)-3-acetyl-α-D-Glcp-(1→	27

续表 1(Continued Tab. 1)

组分 Component	相对分子质量 Relative molecular mass	单糖组成 Monosaccharide composition	构型及糖苷键 Conformation and glycosidic bond	参考文献 Ref.
DPC1	3.80×10^3	Glc-Fru(1:26)	→6)-β-*D*-Fru*f*-(2→,→1,6)-β-*D*-Fru*f*-(2→,β-*D*-Fru*f*-(2→,→1)-β-*D*-Fru*f*-(2→,→6)-α-*D*-Glc*p*-(1→	28
PPC1	7.02×10^3	Gal	β-*D*-Gal*p*-(1→,→4)-β-*D*-Gal*p*-(1→,→4,6)-β-*D*-Gal*p*-(1→	28
PCP	8.50×10^3	Fru-Glc(28:1)	β-*D*-Fru*f*-(2→,→6)-β-*D*-Fru*f*-(2→,→1,6)-β-*D*-Fru*f*-(2→,→1)-β-*D*-Fru*f*-(2→,→6)-α-*D*-Glc*p*-(1→	29
PCP	8.84×10^3	Fru-Glc-Gal(92.73:6.37:0.90)	–	30
HPCP	5.52×10^3	Fru-Glc-Gal-Xyl-Ara(60.16:22.35:13.03:1.35:3.12)	–	30
PCP	8.91×10^3	Fru-Glc(8.7:1)	β-Gal	31
PCP1	2.09×10^3	Ara-Gal-Glu-Man-GluA-GalA(2.1:24:20.7:33.5:0.5:19.3)	–	32
PCP3	4.26×10^4	Ara-Gal-Glu-Man-Xyl-GluA-GalA(22.2:58.7:3.9:4.9:0.5:8.5:1.5)	–	32

注:Gal-半乳糖;Man-甘露糖;Glc-葡萄糖;Ara-阿拉伯糖;Rha-鼠李糖;Xyl-木糖;Rib-核糖;Glca-葡糖糖醛酸;Gala-半乳糖醛酸;GlcN-葡萄糖胺。
Note: Gal-Galactose; Man-Mannose; Glc-Glucose; Ara-Arabinose; Rha-Rhamnose; Xyl-Xylose; Fuc-Fucose; GlcA-Glucuronic acid; Gala-Galacturonic acid; GlcN-Glucosamine.

2.1 黄精多糖的相对分子质量

目前,从黄精中分离得到的均一多糖相对分子质量的主要分布范围为 1.80×10^3 ~ 6.28×10^5;从滇黄精中分离得到的均一多糖相对分子质量的主要分布范围为 1.40×10^4 ~ 1.79×10^5;从多花黄精中分离得到的均一多糖相对分子质量的主要分布范围为 2.09×10^3 ~ 4.26×10^4(见表 1)。Liu 等[11]从黄精根茎中分离得到两个均一杂多糖(PSP50-2-1、PSP50-2-2),采用高效凝胶渗透色谱法(high performance gel permeation chromatography, HPGPC)测得其平均相对分子质量分别为 7.7×10^3 和 7.0×10^3。从黄精根茎中分离得到的一个甘露半乳聚糖(PS-WNP),采用 HPGPC 检测其平均相对分子质量,根据标准葡聚糖的校正曲线,计算得出 PS-WNP 的平均相对分子质量为 7.60×10^4[12]。Li 等[14]采用碱提法从黄精根茎中分离得到一个新颖均一多糖(PSPJWA),通过 HPGPC 测得 PSPJWA 平均相对分子质量为 1.41×10^5。Li 等[23]从滇黄精中分离得到一种新型多糖(PKPS-1),采用 HPGPC 测得 PKPS-1 相对分子质量为 1.41×10^4。一个从多花黄精的根茎中分离得到新颖黄精果聚糖(PCP-1),采用 HPGPC 测定其平均相对分子质量为 4.80×10^3[27]。Zhang 等[28]从多花黄精根茎中分离得到一个黄精果聚糖(DPC1)和一个黄精半乳聚糖(PPC1),通过基质辅助激光解析电离飞行时间质谱法(matrix-assisted laser analytical ionization time-of-flight mass spectrometry, MALDITOF-MS)和 HPGPC 法测定它们的相对分子质量分别为 3.80×10^3 和 7.02×10^3。

2.2 黄精多糖的单糖组成

黄精多糖的单糖组成种类丰富,但主要以 Gal 和 Man 为主,此外还含有少量的 Glc、Ara、Rha、Xyl、Rib、Glca、Gala 等(见表 1)。Liu 等[11]从黄精根茎中分离得到 2 个杂多糖(PSP50-2-1、PSP50-2-2),采用高效阴离子交换色谱-积分脉冲安培检测法(high-performance anion-exchange chromatography with integral pulse amperometric detection, HPAEC-PAD)分析它们的单糖组成,结果表明 PSP50-2-1 和 PSP50-2-2 均由 Glc、Gal 和 Fru 三种单糖组成。1 个新颖均一杂多糖(PS-WNP)从黄精中分离得到,采用气相色谱法(gas chromatography, GC)分析表明 PS-WNP 由 Gal 和 Man 组成,摩尔比为 12.1:5.4[12]。Li 等[23]从滇黄精中分离纯化得到一个新型多糖(PKPS-1),采用 HPAEC-PAD 分析表明 PKPS-1 主要由 Glc、Man、Gala、Gal 组成,并含有少量的 Glca 和 Ara,摩尔比为 7.22:1.0:0.16:0.11:0.05:0.02。从多花黄精中分离纯化得到均一果聚糖(PCP-1),用高效液相色谱-示差折光检测(HPLC-RID)法分析表明 PCP-1 主要由 Fru 组成,还含有少量 Glc,摩尔比为

28∶1[27]。2 个中性多糖 PSW-1b-2、PSW-1a 从黄精根茎中分离纯化得到,经气液色谱(gas-liquid chromatography,GLC)分析发现,PSW-1b-2 只含有 Gal,红外光谱和间羟基二苯法表明其不含糖醛酸,因此 PSW-1b-2 为中性高半乳聚糖;而 PSW-1a 由 Man 和 Gal 组成,摩尔比为 7.9∶1.0[13]。一种新颖均一多糖(PSPJWA)从黄精根茎中分离得到,使用离子色谱仪进行分析表明 PSPJWA 由 Gal、Ara 和 Rha 组成,其比例为 14∶4∶1[14]。一个黄精果聚糖(DPC1)和一个黄精半乳聚糖(PPC1)从多花黄精中分离得到,对 DPC1 和 PPC1 的单糖组成采用 PMP 柱前衍生-HPLC-RID 法进行分析,结果表明 DPC1 由 Glc 和 Fru 组成,摩尔比约为 1∶26,而 PPC1 则完全由 Gal 组成[28]。一种新颖的黄精多糖(PsPs)从黄精叶子中分离提取得到,采用 PMP 衍生化-HPLC 法测得 PsPs 由 Man、Rha、Gala、Glc、Xyl 和 Ara 组成,摩尔比为 6.6∶15.4∶4.5∶8.8∶40.7∶24[16]。

2.3　黄精多糖的糖链结构

目前大部分黄精多糖的结构解析只是对单糖组成和糖苷键构型的测定,只有少部分报道了完整的糖链重复单位结构。黄精和多花黄精多糖的一级结构已经有研究报道,而滇黄精多糖的一级结构研究较少。两个杂多糖(PSP-50-1、PSP-50-2)从黄精根茎中分离得到[11]。PSP-50-1 主链由→2)-*β*-*D*-Gal*p*-(1→和→2,6)-*β*-*D*-Gal*p*-(1→残基组成,两条支链则是分别由末端残基 *β*-*D*-Fru*f*-(2→和 *β*-*D*-Fru*f*-(2→组成,连接在→2,6)-*β*-*D*-Gal*p*-(1→残基 O-6 位上。PSP-50-2 主链由 *β*-*D*-Gal*p*-(1→、→2)-*β*-*D*-Gal*p*-(1→、→2,6)-*β*-*D*-Gal*p*-(1→和 *β*-*D*-Fru*f*-(2→组成,一条支链由→2)-*β*-*D*-Gal*p*-(1→、→6)-*α*-*D*-Gal*p*-(1→和末端残基 *β*-*D*-Glc*p*-(1→连接于→2,6)-*β*-*D*-Gal*p*-(1→残基上,另外两条支链则分别由末端残基 *β*-*D*-Fru*f*-(2→、*β*-*D*-Glc*p*-(1→连接于→2)-*β*-*D*-Gal*p*-(1→残基的 O-6 位上。两种中性多糖(PSW-1b-2、PSW-1a)从黄精根茎中分离纯化得到[13]。PSW-1b-2 是以→4)-*β*-*D*-Gal*p*-(1→连接为主链,每 7 个→4)-*β*-*D*-Gal*p*-(1→残基通过 *β*-(1,6)-糖苷键连有 1 个 *β*-*D*-Gal*p*-(1→残基构成支链的半乳聚糖。而 PSW-1a 则是以→4)-*β*-*D*-Man*p*-(1→连接为主链,每 9 个→4)-*β*-*D*-Man*p*-(1→残基通过 *β*-(1,6)-糖苷键连有 1 个 *β*-*D*-Gal*p*-(1→残基为支链的半乳甘露聚糖。Xu 等[22]从蒸制黄精中分离纯化得到一小分子多糖(P1)。P1 主链由 *α*-*D*-Glc*p*-(1→、*β*-*D*-Fru*f*-(2→、→1,6)-*β*-*D*-Fru*f*-(2→和→1)-*β*-*D*-Fru*f*-(2→残基组成,支链由末端残基 *β*-*D*-Fru*f*-(2→和→1)-*β*-*D*-Fru*f*-(2→残基依次连接构成,连接于→1)-*β*-*D*-Fru*f*-(2→残基的 O-6 位。一种新颖均一多糖(PSPJWA)从黄精根茎中分离得到[14]。PSPJWA 主链由→4,6)-*β*-*D*-Gal*p*-(1→、→4)-*β*-*D*-Gal*p*-(1→和→2,4)-*α*-*L*-Rha*p*-(1→残基组成,1 条支链由 *α*-*L*-Ara*f*-(1→、→5)-*α*-*L*-Ara*f*-(1→和→3,5)-*α*-*L*-Ara*f*-(1→残基依次连接构成,连接于→2)-*α*-*D*-Rha*p*-(1→残基的 O-4 位上;另一条支链则是末端残基 *β*-*D*-Gal*p*-(1→连接于→4)-*β*-*D*-Gal*p*-(1→残基的 O-6 位。黄精中分离得到均一多糖可能的重复单元结构见图 2。

黄精果聚糖(DPC1)和黄精半乳聚糖(PPC1)从多花黄精中分离得到[28]。DPC1 主链由 *β*-*D*-Fru*f*-(2→、→6)-*α*-*D*-Glc*p*-(1→、→1,6)-*β*-*D*-Fru*f*-(2→和→6)-*β*-*D*-Fru*f*-(2→残基组成,支链由末端残基 *β*-*D*-Fru*f*-(2→和→1)-*β*-*D*-Fru*f*-(2→残基构成,连接于→6)-*β*-*D*-Fru*f*-(2→残基的 O-1 位上。PPC1 是以→4)-*β*-*D*-Gal*p*-(1→连接为主链,每 9 个→4)-*β*-*D*-Gal*p*-(1→残基通过 *β*-(1,6)-糖苷键连有 1 个 *β*-*D*-Gal*p*-(1→残基为支链的半乳聚糖。一个新颖黄精果聚糖(PCP-1)从多花黄精的根茎中分离得到[27]。PCP-1 主链是由 *β*-*D*-Fru*f*-(2→、→6)-3-acetyl-*α*-*D*-Glc*p*-(1→、→1,6)-*β*-*D*-Fru*f*-(2→和→1)-*β*-*D*-Fru*f*-(2→残基组成。一条支链是由末端残基 *β*-*D*-Fru*f*-(2→、→6)-*β*-*D*-Fru*f*-(2→残基组成,连接于→1)-*β*-*D*-Fru*f*-(2→残基的 O-6 位上;另一条支链则是由末端残基 *β*-*D*-Fru*f*-(2→和→6)-*β*-*D*-Fru*f*-(2→残基组成,连接于→1)-*β*-*D*-Fru*f*-(2→残基的 O-6 位上。一个新颖黄精果聚糖(PCP)从多花黄精中分离得到[29]。PCP 主链由 *β*-*D*-Fru*f*-(2→、→1)-*β*-*D*-Fru*f*-(2→和→6)-*α*-*D*-Gal*p*-(1→残基组成,支链由末端残基 *β*-*D*-Fru*f*-(2→和→6)-*β*-*D*-Fru*f*-(2→残基依次连接构成,连接于→1)-*β*-*D*-Fru*f*-(2→残基的 O-6 位。多花黄精中分离得到均一多糖可能的重复单元结构见图 3。

3　黄精多糖的生物活性及其作用机制

3.1　抗氧化

“氧化应激”一词最早是由 Helmut Sies 提出,指的是机体内氧化剂的产生和抗氧化防御之间的失衡,这可能会导致生物系统的损害,进一步的损伤可能会导致各种疾病[33,34]。黄精多糖可显著降低丙

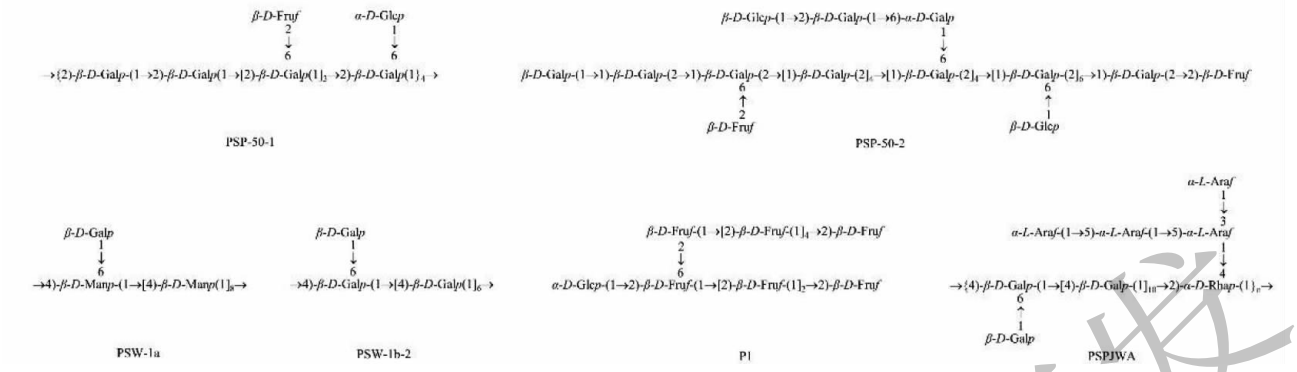

图 2 黄精多糖的重复单元结构

Fig. 2 Repeating unit structures of *P. sibiricum* polysaccharides

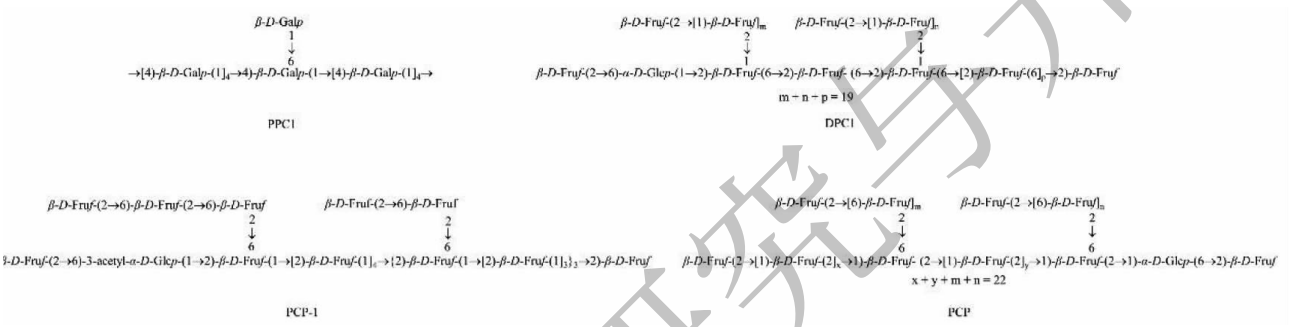

图 3 多花黄精多糖的重复单元结构

Fig. 3 Repeating unit structures of *P. cyrtonema* polysaccharides

二醛(malondialdehyde,MDA)含量,提高谷胱甘肽(glutathione,GSH)含量和超氧化物歧化酶(superoxide dismutase,SOD)活性,从而发挥抗氧化作用[35]。Trishna 等[36]研究发现黄精多糖能显著降低肝细胞中活性氧(reactive oxygen species,ROS)水平,并能清除羟基自由基(hydroxyl radical、·OH)。另有研究报道,从黄精根茎中分离纯化得到的四个多糖组分(PSPJWA、PSPJWB、PSPJWC 和 PSPJWD)对 ABTS+自由基、DPPH 自由基、·OH 均有较强的清除能力,其中,较低分子量的 PSPJWD 具有更好的 ABTS+清除效果,高分子量的 PSPJWA 对 DPPH 的清除能力强于其他组分[14]。从多花黄精中分离纯化得到的 4 种多糖(HBSS、CHSS、DASS、CASS)在体外均表现出较强的抗氧化活性,其中酸性 β-构型多糖 DASS 的抗氧化活性最强[37]。黄精多糖可改善线粒体功能,并激活沉默信息调节因子 1(silent mating type information regulation 2 homolog-1,SIRT1)/AMP 依赖的蛋白激酶(adenosine 5′-monophosphate(AMP)-activated protein kinase,AMPK)/过氧化物酶体增殖物激活受体 γ 的辅激活因子 α(peroxisome proliferator-activated receptor γ coactivator 1α,PGC-1α)通路发挥抗氧化活性,从而缓解 H_2O_2 诱导的 HT22 细胞抗氧化损伤[38]。也有研究表明黄精多糖可通过激活核因子 E2 相关因子 2(nuclear factor erythroid2-related factor 2,Nrf2)/血红素加氧酶 1(heme oxygenase 1,HO-1)信号传导来防止 *D*-半乳糖诱导的小鼠氧化损伤[39]。

此外,Ma 等[40]用 *D*-半乳糖诱导的小鼠心脏衰老模型,结果发现黄精多糖能降低小鼠心脏组织中的 ROS 和 MDA,升高 SOD 水平,可通过抑制氧化应激所致的 DNA 损伤和脂质过氧化来延缓小鼠心脏衰老。另有研究表明,黄精多糖还可以有效地改善小鼠大脑衰老过程中的认知功能障碍[41];Zheng 等[42]发现黄精多糖能降低 *D*-半乳糖诱导的衰老大鼠血液中 NO 和一氧化氮合酶(nitric oxide synthase,NOS)的含量,通过调节 Klotho-成纤维细胞生长因子 23(fibroblastgrowthfactor-23,FGF23)内分泌轴,上调肾 Klotho 的表达,下调股骨中 FGF23 蛋白的水平,从而缓解了大鼠体内氧化应激,在延缓衰老方面起重要作用。

由此可见,黄精多糖可通过增加抗氧化酶活性,清除自由基,改善线粒体功能等途径发挥抗氧化和抗衰老作用。

3.2　免疫调节

黄精多糖具有强大的免疫刺激活性,可通过加速免疫抑制动物模型胸腺、脾腺指数的恢复、增强 T 细胞和 B 细胞的增殖反应、调节巨噬细胞功能而发挥免疫调节作用。Liu 等[4]研究发现,黄精多糖能加速环磷酰胺(cyclophosphamide,Cy)处理的免疫抑制小鼠胸、脾腺指数的恢复,增强 T 细胞和 B 细胞的增殖活性,展现出显著的免疫调节活性,可用作潜在的免疫刺激剂。黄精多糖具良好的免疫调节功能,可能是通过调节巨噬细胞功能而发挥作用。多项研究表明,黄精多糖不仅可增加 Cy 诱导的免疫抑制小鼠血清中白细胞介素-2(interleukin-2,IL-2)、肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)、IL-8、IL-10 的水平[4,9,10];而且能显著增强巨噬细胞的吞噬活性,并刺激其分泌 NO、IL-1β、IL-6、IL-12 和 TNF-α,具有显著的免疫刺激活性[18,27,43,44]。此外,黄精多糖还能增加自然杀伤细胞(natural killer cells,NK)的活性[9,10,43]。Shu 等[45]研究表明黄精多糖可促进 Cy 处理的鸡免疫器官细胞进入 S 和 G2/M 期并抑制脾脏,胸腺和滑囊的细胞凋亡,可有效地保护免疫器官的结构和功能;还可显著刺激血清免疫球蛋白并提高体内抗氧化活性,改善外周血 T 淋巴细胞增殖,并上调 IL-2、IL-6 和 γ 干扰素(interferon-γ,IFN-γ)基因的表达,具有显著的免疫调节活性。Long 等[44]报道,黄精多糖可显著增加荷瘤小鼠外周血 CD4/CD8 T 淋巴细胞比值,并能刺激 RAW264.7 细胞分泌 NO 和细胞因子,进一步的研究证实黄精多糖可通过激活 Toll 样受体 4(toll-like receptor 4,TLR4)-活丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)/核因子-κB(nuclear factor kappa-B,NF-κB)信号通路发挥免疫调节作用。

3.3　抗肿瘤

黄精多糖对多种肿瘤的生长均有明显的抑制作用,能通过诱导细胞自噬、细胞凋亡、调控肿瘤细胞周期以及调节免疫等多种途径发挥抗肿瘤活性。从黄精中获得水溶性多糖(PSP-1),在体外显著抑制 HepG2 细胞的增殖,可导致核损伤并降低 HepG2 细胞的线粒体膜电位;此外,PSP-1 还可增加 caspases-9 和 caspases-3 的活性,从而诱导 HepG2 细胞凋亡[46]。黄精多糖可以选择性地抑制前列腺癌相关成纤维细胞(cancer-associated broblasts,CAFs)的生长并刺激其自噬,介导癌细胞死亡[47]。Li 等[48]研究表明,从多花黄精中分离得到的多糖 CASS 对 Hela 细胞有毒性作用并抑制其生长,具体机制可能是 CASS 通过抑制细胞周期蛋白依赖性激酶 1(cyclin dependent kinase 1,CDK1)和细胞周期蛋白 B1(cyclinB1)基因的表达而阻断 Hela 细胞周期 G2/M 期;此外,CASS 还可调节 B 细胞淋巴瘤-2(B-cell lymphoma-2,Bcl-2)、FasL 和 caspases-8、-9、-10 的表达,增加含半胱氨酸的天冬氨酸蛋白水解酶-3(cysteinyl aspartate specific proteinase,caspases-3)的活性,进而导致 caspases-7 活性的增加,最终导致细胞凋亡。Long 等[44]报道肺癌荷瘤小鼠经黄精多糖处理可降低肿瘤重量,其机制可能是通过 TLR4-MAPK/NF-κB 通路增强机体免疫,从而抑制肿瘤的生长。Xie 等[49]报道,黄精多糖对三重阴性乳腺癌(triple negative breast cancer,TNBC)引起的骨髓造血干细胞和祖细胞(hematopoietic stem and progenitor cells,HSPCs)和常见淋巴样祖细胞的丢失具有保护作用,还减少了肿瘤浸润性细胞中免疫抑制髓系细胞的百分比,并减少了脾中的免疫细胞;这些结果表明,黄精多糖可以保护因肿瘤进展而受损的正常造血功能并参与免疫调节,有望用于辅助临床治疗并改善治疗结局。

3.4　抗骨质疏松

骨质疏松症是一种主要发生于绝经后妇女和老年人的慢性代谢性骨病,其特征是骨量减少和骨微结构恶化,导致骨脆弱和骨折风险增加,严重威胁公众健康[50,51]。黄精多糖具有较好的抗骨质疏松作用[52,53]。Peng 等[54]研究表明,25 mg/L 的黄精多糖可通过激活细胞外调节蛋白激酶(extracellular regulated protein kinases,ERK)/糖原合成酶激酶-3β(glycogen synthase kinase 3β,GSK-3β)/β-连环蛋白(β-Catenin)信号通路,促进成骨细胞(osteoblast,OB)的分化和矿化;黄精多糖还可在骨髓分化过程中可促进骨髓间充质干细胞(bone marrow mesenchymal stem cells,BMSC)的增殖并增强其生存能力[55]。Liu 等[11]人研究表明 2.59 μM 和 5.19 μM 的黄精多糖可显著促进小鼠胚胎成骨细胞前体细胞(MC3T3-E1)的分化并促进其矿化。Du 等[56,57]报道,黄精多糖可以通过 Wnt/β-catenin 通路可有效地促进小鼠骨髓基质细胞和骨质疏松小鼠脂肪干细胞

(adiposederived stem cells in osteoporosis mice, OP-ASCs)成骨分化,并抑制破骨细胞的形成;也有报道称黄精多糖可通过抑制 Hippo 途径表达的 miR-1224 的表达来抑制破骨细胞的生成[58]。体内研究表明,黄精多糖可减少卵巢切除大鼠的骨质流失并预防骨质疏松症[59]。Zhao 等[60]研究表明,25 mg/L 的黄精多糖显著促进 BMSC 的成骨分化,并可通过上调成骨细胞相关基因(COL1A1、OCN、Runx2 和 ALP)的表达和调节磷脂酰肌醇 3-激酶(phosphoinositide 3-kinase, PI3K)/蛋白激酶 B(protein kinase B, AKT)/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号通路促进多发性骨髓瘤(multiple myeloma, MM)患者的成骨分化。

3.5 降血糖

Cai 等[62]研究表明 50,100 和 250 μg/ml 的黄精多糖可增加 Nrf2 和 HO-1 的表达,促进了细胞中的葡萄糖摄取,提示黄精多糖可能通过激活 Nrf2/HO-1 通路改善胰岛素抵抗[61];黄精多糖还可通过抑制 miR-340-3p/IL-1 受体相关激酶(IL-1 receptor associated kinase, IRAK3)通路来改善棕榈酸(palmitic acid, PA)诱导的骨骼肌细胞存活率、炎症和葡萄糖摄取从而改善了 IR,这说明黄精多糖可能是治疗 2 型糖尿病(diabetes mellitus type 2, T2DM)的潜在治疗剂。Li 等[23]研究指出,给予糖尿病小鼠滇黄精多糖(PKPs-1)15 天后,能上调胰岛素受体底物-1(insulin receptor substrate 1, IRS-1)、PI3K 和 AKT 的 mRNA 的表达,从而降低了血糖,改善了葡萄糖耐量,并影响了血清脂质的代谢。滇黄精多糖还可通过调节链脲佐菌素诱导的小鼠肾脏中炎症因子和纤维因子的含量而起到保护肾脏的作用[63]。近年来也有研究报道,黄精多糖可通过调节肠道菌群从而改善糖尿病。Gu 等[24]发现,经黄精多糖处理后,高脂饮食大鼠糖尿病症状和脂质代谢得到改善,进一步研究发现黄精多糖可通过调节肠道菌群,降低了肠道通透性,从而缓解了胃肠道炎症,改善了脂质代谢;也有研究表明黄精多糖通过调节肠道菌群和随后短链脂肪酸的变化来缓解糖尿病大鼠的高血糖状态,可用于预防 T2DM[64]。

黄精多糖在一定程度上对糖尿病诱导的眼损伤起保护作用。Wang 等[65]采用高糖(high glucose, HG)刺激的人视网膜色素上皮细胞(ARPE-19 细胞)建立体外糖尿病视网膜病变模型来研究黄精多糖对其的影响,结果发现给药剂量为 6.25、12.5 或 25 μmol/L 的黄精多糖可上调 Bcl-2、caspase-3、Nrf2 和 HO-1 的表达,下调 Bcl-2 相关 X 蛋白(Bcl-2 associated X protein, Bax),从而改善了 HG 诱导的 ARPE-19 细胞氧化应激,炎症和细胞凋亡。体内研究表明,糖尿病大鼠的给药剂量为 200、400 和 800 mg/kg 黄精多糖可明显降低血糖和糖化血红蛋白的水平,并升高血浆中胰岛素和 C 肽的水平;进一步的研究发现黄精多糖能减缓大鼠白内障的进展和抑制糖尿病视网膜病变,其眼保护作用可能与其降低血糖和改善氧化应激作用有关[66,67]。也有研究表明黄精多糖可通过下调 Bax、表皮细胞生长因子(epidermal growth factor, EGF)、p38MAPK 等蛋白的表达以及上调 Bcl-2 来降低血糖、限制病理性血管生成和抑制细胞凋亡,最终缓解了糖尿病诱导的大鼠视网膜损伤[68]。

3.6 降血脂和抗动脉粥样硬化

Li 等[69]研究表明,黄精多糖可调节血脂,并能改善高脂饮食诱导的大鼠肥胖与非酒精性脂肪肝,具有作为药物或饮食佐剂治疗高脂血症和动脉粥样硬化的潜力。Kong 等[70]通过研究发现,低、中、高剂量 PSP 组小鼠血清中 TC、TG、LDL-C 含量与高脂血症模型组相比显著下降;中剂量和高剂量黄精多糖处理可上调过氧化物酶体增殖物激活受体-α(peroxisome proliferators-activated receptor-α, PPAR-α)、PPAR-β 的蛋白和 mRNA 表达,下调 PPAR-γ、固醇调节元件结合蛋白 1c(sterol regulatory element-binding protein-1c, SREBP-1c)、IL-6 和 TNF-α 的表达;这表明黄精多糖可以抑制肝脂的氧化,调节与脂质代谢相关的相应基因和蛋白质,从而对降低血脂起到关键作用。Liu 等[71]报道,黄精多糖具有减少肝脏炎症,同时防止血脂异常,减轻肝脂肪变性和降低血糖的作用,其机制可能是激活了 AMPK 信号通路。还有研究表明黄精多糖可显著改善血脂、载脂蛋白和内皮功能障碍参数,从而对高脂血症诱导的仓鼠动脉粥样硬化具有保护作用[72]。Yang 等[73]报道,黄精多糖可以通过其降血脂活性,改善主动脉形态,减少泡沫细胞数量以及保护原代培养的内皮细胞免受细胞水平间接凋亡和坏死来发挥抗动脉粥样硬化作用。

3.7 其他生物活性

除上述生物活性之外,黄精多糖还具有其他生物活性。Shen 等[15]发现黄精多糖可通过减少 ROS/下丘脑-垂体-肾上腺轴功能亢进和炎症反应来

预防抑郁样行为并减轻突触和神经元损伤;另有证据表明,黄精多糖可通过调节氧化应激-calpain-1-NLRP3 信号轴,减轻氧化应激和炎症而发挥抗抑郁作用。Luo 等[16]报道黄精多糖可通过重塑肠道微生物群来改善阿尔茨海默病模型小鼠的认知功能。此外,黄精多糖可显著抑制 caspases-3 活化,降低 Bax/Bcl-2 比率,抑制了细胞凋亡,并通过 PI3K/Akt 通路缓解 β 淀粉样蛋白诱导的 PC12 细胞神经毒性[12]。Huang 等[74]报道,黄精多糖可通过 Akt/mTOR 和 Nrf2 通路发挥抗凋亡和抗氧化作用,在帕金森病(Parkinson disease,PD)小鼠模型中改善了帕金森病行为并保护多巴胺能神经元免受死亡。

Li 等[25]人报道,黄精多糖可通过调节线粒体介导的细胞凋亡并调节 GSK-3β/Fyn/Nrf2 通路来缓解铀诱导的人肾小管上皮细胞 HK-2 的毒性;体内实验发现,黄精多糖可通过降低大鼠肾脏组织中中性粒细胞明胶酶相关脂质运载蛋白(neutropil gelatinase-associated lipocalin,NGAL)或肾损伤分子-1(kidney injury molecule-1,KIM-1)mRNA 的表达,抑制 p38 MAPK/激活转录因子 2(activating Transcription Factor 2,ATF2)信号通路并减少炎症因子 TNF-α、IL-1β 和 IL-6 的产生,而对急性肾损伤大鼠起保护作用[75]。黄精多糖可通过 TLR4/髓样分化因子(myeloiddifferentiationfactor88,MyD88)/NF-κB 途径和 AMPK/Nrf2 途径发挥抗氧化和抗炎活性,从而减少了脂多糖(lipopolysaccharide,LPS)诱导的人正常肺上皮细胞(BEAS-2B)凋亡,并能有效改善大鼠急性肺损伤[30,76]。黄精多糖还具有良好的抗疲劳作用和益生元活性[28,77]。这些发现可能有助于扩大来自滋补草本植物黄精的多糖作为食品中功能性成分的应用。

黄精多糖的主要生物活性及其作用机制见图 4。

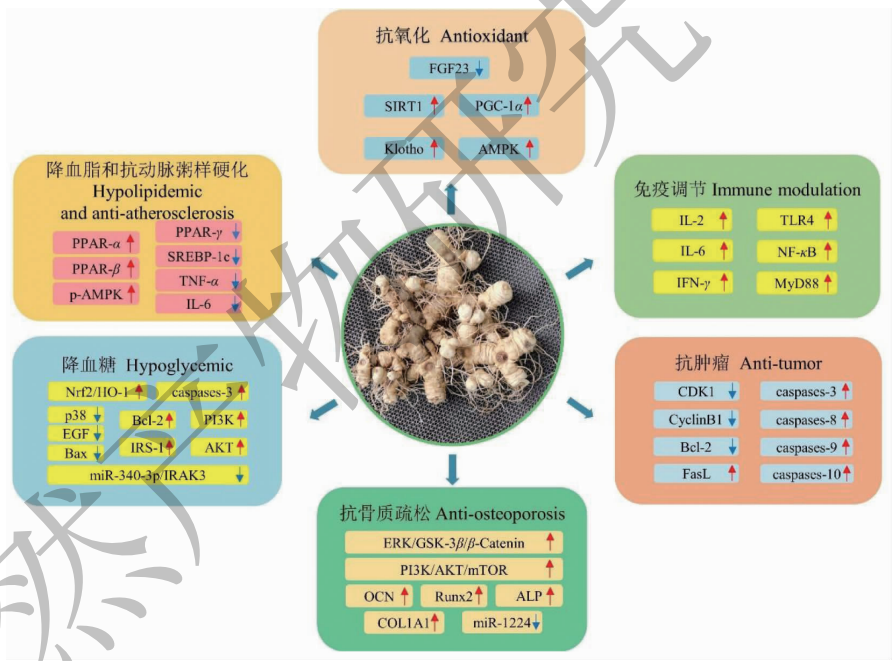

图 4　黄精多糖的主要生物活性及其作用机制

Fig. 4　Main bioactivities and mechanisms of the Polygonati Rhizoma polysaccharides

4　结语与展望

黄精具有悠久的药用历史,其化学成分复杂、生物活性多样。与此同时,黄精多糖作为黄精中最重要的活性成分,在抗氧化、免疫调节、抗肿瘤、抗骨质疏松、抗糖尿病及其并发症、降血脂与抗动脉粥样硬化等方面展现出巨大应用潜力,已经成为黄精开发应用研究的热点。近年来,黄精多糖的研究进展取得了极大的进步,但仍然存在一些不容忽视的问题。首先,不同原料和提取纯化方法所得多糖,可导致含量、理化性质、结构特征和生物活性的差异,因此制定黄精药材种植和黄精多糖的提取标准,开发简单、可靠的质量控制方法具有重要意义。其次,目前缺乏对构效关系的研究,单体化合物及其作用机制的研究仍存在瓶颈,许多目标靶点的分子机制尚不清晰。因此,深入研究其生物活性的确切机制和构效关系是至关重要的。同时,还应进一步研究黄精多

糖的毒性和潜在风险,为合成生物活性更高、毒副作用更少的黄精多糖衍生物提供坚实的科学基础和理论指导。最后,目前对黄精多糖的研究大多仍停留在细胞和动物水平,缺乏临床实验,尽管报道的黄精多糖生物活性丰富,但临床和商业应用非常有限;因此,应鼓励功能性食品和医药产品的开发,积极开展安全科学的临床实验,这样才有望使更多人可以从黄精多糖的多种生物活性中受益。

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