海带岩藻聚糖硫酸酯抗血栓活性研究进展

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摘要 海带中提取的岩藻聚糖硫酸酯是一种含有岩藻糖和硫酸根离子的结构复杂的硫酸多糖,影响岩藻聚糖硫酸酯活性的因素有分子量、硫酸根含量、硫酸根的取代位置、单糖的组成等指标,不同物质不同提取方法和降解方法产生不同结构的多糖,其不同结构产生抗凝血、降血脂、抗病毒、抗肿瘤、提高免疫力、抗氧化、抗疲劳、促益生菌生长等特异药理学活性,硫酸多糖研究最早且最广泛的活性是其抗凝血活性。对海带岩藻聚糖硫酸酯的抗凝血活性进行了综述,并对其应用前景进行展望,为其深度开发利用提供参考。

关键词 海带;岩藻聚糖硫酸酯;抗血栓;活性
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Research Progress on Antithrombotic Activity of Fucoidan from *Laminaria japonica*

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Abstract Fucoidan extracted from *Laminaria japonica* is a sulfated polysaccharide with complex structure containing fucose and sulfate ion, the factors that affect the activity of fucoidan include the molecular weight, the content of sulfate radical, the substitution position of sulfate radical and the composition of monosaccharides, its different structures produce specific pharmacological activities such as anticoagulation, hypolipidemic, antivirus, anti-tumor, enhancing immunity, anti-oxidation, anti-fatigue, promoting probiotic growth, etc. In this paper, the anticoagulant activity of fucoidan from *Laminaria japonica* was reviewed, and the application prospect of fucoidan was forecasted, it provides a reference for its further development and utilization.

Key words *Laminaria japonica*; Fucoidan; Antithrombotic; Activity

海带是美味的食品,药用价值较高,能缓解血液酸碱度过低引起的碱性元素被过多消耗的现象,被称为“碱性食物之冠”,热能较低,营养丰富,是一种高蛋白低卡路里食品,在我国的食用历史悠久,是食用量最大的褐藻。

多糖是能在生物体内对细胞的分裂和分化进行调控的一种生物大分子,在生命活动中承担着维持人体基础代谢,调节细胞生长进程等较多功能。研究表明,海带的较多生物活性与多糖关系密切。海带多糖具有保健作用,岩藻聚糖硫酸酯不同结构产生抗凝血、降血脂、抗病毒、抗肿瘤、提高免疫力、抗氧化、抗疲劳、促益生菌生长等特异药理学活性[1-4]。岩藻聚糖硫酸酯的结构和活性与藻类的来源、气候和制备方法等都具有相关性。岩藻聚糖硫酸酯的分子量较大,几万甚至几十万道尔顿,Alban 等[5]研究发现高分子量岩藻聚糖硫酸酯很难被吸收,低分子量多糖溶解性好、黏度小、吸收利用率高,能显著提高多糖的生物活性。低分子量岩藻聚糖硫酸酯的生物活性与分子量、硫酸根的含量和取代基位置等因素有很大关系[6]。

脑动脉或者皮质动脉粥样硬化后,引起管腔内狭窄闭塞、血管增厚、血栓脱落,引起局部血流减少、供血不足,最终导致脑组织细胞坏死的现象,称为脑血栓。脑血栓的形成机制是能激活某些血细胞和蛋白质的活性,扰乱正常凝血机制,产生血小板-纤维蛋白血栓。血液的高凝状态是脑血栓形成和发展的重要因素,脑血栓导致的脑卒对人类健康造成很大威胁,且发病率逐年升高,该病死亡率较低,但致残率较高,不能彻底预防和治疗,通常会有失语、大小便失禁、瘫痪等后遗症,对患者的日常生活影响严重,所以研究有效的抗栓溶栓药物受到了国内外学者的重视。

目前国内外主要研究的是鼠尾藻、泡叶藻、墨角藻等褐藻的多糖结构和活性,而对于海带硫酸多糖的研究较少。随着海洋天然产物研究的深入,岩藻聚糖硫酸酯是海洋多糖药物研究的新热点。笔者对海带岩藻聚糖硫酸酯抗血栓活性进行综述,为其进一步开发利用提供理论依据。

1 岩藻聚糖硫酸酯简述

岩藻聚糖硫酸酯,又名褐藻糖胶,是含有岩藻糖和硫酸根的一类多糖,在褐藻和海参的海洋无脊椎动物中含量丰富。18 世纪,Kylin 从海带中提取而后命名了 fucoidin,后来国际上将其更名为 fucoidan。Duarte 等[7]定义为:富含岩藻糖的一类多糖的统称。国内研究者们之所以称之为岩藻聚糖硫酸酯,是因为硫酸多糖拥有较高的硫酸根。

岩藻聚糖硫酸酯分子结构复杂,由特定的岩藻糖残基构成,与哺乳动物体内发挥生物活性的糖链结构相似。海参和海胆的岩藻聚糖硫酸酯主要是直链的岩藻多糖,无支链,岩藻糖含量占总糖含量的 90%以上,而褐藻中的岩藻聚糖硫酸酯存在较多支链,组成较为复杂,相对分子质量分布范围较广,几万至几十万道尔顿。多糖的生物活性与多糖的分子量、高级结构(如侧链的位置、单糖糖苷键的结合形式、分支的密度以及硫酸根的位置和含量等)都具有很强的相关性[8]。

2 岩藻聚糖硫酸酯抗血栓活性研究

2.1 岩藻聚糖硫酸酯结构与抗血栓活性研究 岩藻聚糖硫酸酯研究最早、最广泛的活性是其抗凝血活性[9-10]。国内外大量报道证实,从多种褐藻中提取的硫酸多糖均具有较好的体外抗凝血功效[11-12]和体内抗血栓功效[13]。

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海带岩藻聚糖硫酸酯能抑制内源性和外源性凝血过程中凝血酶的产生,对内源性凝血因子的抑制作用较强,对纤溶系统也有影响,能加强 t-PA、u-PA 对纤溶酶原的活化,从而促进纤溶酶产生[14]。硫酸多糖能够增强 t-PA 的活性,进而激活纤维酶原的作用[15]。岩藻聚糖硫酸酯抗凝血活性随着硫酸根含量增加而增强,样品脱硫后活性降低,当 SO_4^{2-} 含量下降 20%后,抗凝活性消失[16-19]。硫酸根与岩藻糖比值大于 1.5 的岩藻聚糖硫酸酯抗凝血活性较强,双硫取代的硫酸多糖活性较高,尤其 C-2 和 C-2,3 位硫酸根取代的硫酸多糖抗凝活性最高[20]。核磁共振分析发现,硫酸根含量不变,将硫酸基团从 C4 位上改变到 C6 位上,硫酸软骨素的抗凝血活性完全消失,说明硫酸多糖的抗凝血作用主要是 C4 位上的硫酸基发挥作用。L-岩藻糖一般链接一个硫酸根,也有无硫酸根或者 2 个硫酸根,硫酸根的位置和数量影响多糖的活性[21-22]。Jin 等[23]比较了 11 种褐藻岩藻聚糖硫酸酯体外抗凝血活性,结果发现相对分子质量对药物影响作用比硫酸根含量大,岩藻糖与半乳糖的比例也会对药物效果产生影响。大量研究证实,影响硫酸多糖抗凝血活性的有分子量、硫酸根含量、硫酸根的取代位置、单糖的组成、多分散体系、多糖的纯度等指标[24-26]。

岩藻聚糖硫酸酯既能预防血栓形成又能溶解血栓,具有双重功效,在临床应用中具有无法替代的作用。但岩藻糖结构复杂,结构如何影响抗血栓活性仍亟待解决。

2.2 国内外岩藻聚糖硫酸酯抗血栓活性研究进展 目前国内提取和分离的植物多糖超过 100 种。常用的提取方法有水提、碱提、酸提、酶解、超声波、微波等,或混合提取。不同提取方法得到的多糖结构差异较大,李苗苗等[27]用热水和热 Na_2CO_3 提取的硫酸多糖,结构和分子量均不同。海带硫酸多糖有多种降解方法,如酸降解、碱降解、酶降解、盐降解、超声波降解和 γ-射线以及自由基降解方法等。岩藻聚糖硫酸酯抗血栓作用机制包括抗凝血活性、抗血小板活性、调节花生四烯酸级联反应、激活纤溶系统、提高 TFPI 含量和内皮细胞硫酸乙酰肝素合成等[28-33]。

Springer 等[34]首次证实岩藻中的硫酸多糖具有抗凝血活性。Nishino 等[35-36]试验表明海带中的岩藻聚糖硫酸酯分子量、硫酸根含量对凝血酶激活纤维蛋白原的抑制作用有一定的影响,分子量一定的情况下硫酸根含量越高抑制作用越强,硫酸根含量相同时分子量越大抑制作用越强,其抗凝血机制可能是与肝素因子Ⅱ(HE Ⅱ)结合。Alban 等[37]研究表明,硫酸多糖的抗凝活性与分子量的大小之间的曲线是哑铃型。闫相勇等[38]证实 5~50 ku 的岩藻聚糖硫酸酯生物活性较强。葛邕等[39]对海带岩藻聚糖硫酸酯的抗血栓活性与量效的关系进行了研究,证实在抑制血栓的形成方面硫酸多糖剂量存在较强的相关性。陈安进等[40]比较了不同分子量硫酸多糖对氯化铁诱导血栓模型的抗血栓活性的影响,证实不同分子量的硫酸多糖能抑制血小板聚集、提高纤溶系统的活性,表现出明显的抗血栓作用,相对分子量不同,作用机制不同。Zhao 等[41]从褐藻中提取岩藻聚糖,制作脑血栓动物模型,经静脉或皮下途径给药,比较不同分子量的海带岩藻聚糖硫酸酯在电诱导动脉血栓模型中的口服吸收、生物利用度和抗血栓活性及其分子机制,证实口服海带低分子量岩藻多糖比中分子量具有更好的抗血栓作用。因此,低分子量岩藻聚糖硫酸酯有可能成为一种口服抗血栓药物。Mourão 等[42]研究认为岩藻聚糖硫酸酯的结构分析对于调查其在哺乳动物体内的抗凝血活性和抗血栓活性是非常有用的。Zhang 等[43]研究表明岩藻聚糖硫酸酯促凝血活性与其分子量、分散程度、化学结构、杂质含量等具有相关性,可以用于止血药品的研发。刘海韵等[44]对马尾藻岩藻聚糖硫酸酯能降低角叉菜胶引起的小鼠尾部血栓的长度,延长凝血时间,纯化后的组分比粗多糖效果更佳。

3 岩藻聚糖硫酸酯临床应用

3.1 岩藻聚糖硫酸酯与肝素抗凝血作用比较 肝素应用于血栓性疾病的预防和治疗已有多年,但出血等副作用限制了其在临床上的应用,且污染事件报道多,人们开始寻找新的肝素类替代药物,岩藻聚糖硫酸酯的各种活性早有报道,从海带中提取,使用和食用均较为安全,国内外专家对海带岩藻聚糖硫酸酯的研究应运而生。

多糖的糖链较长时,糖链分子的结构比较复杂,溶解性也降低,在临床上的应用受到了限制。临床上使用的硫酸多糖抗凝血剂、低分子量肝素不能口服,因为肠道细菌产生的酶会使其在进入血液循环之前降解和脱硫,口服生物利用率低,注射会有各种副作用,通过 H_2O_2、超声波、酶法等方式进行降解,获得低分子量多糖,从而提高其生物利用率[45-47]。岩藻聚糖硫酸酯连续给药后,能够降低血浆纤维蛋白的含量,从而抑制静脉血栓的形成[48]。当浓度较低时,肝素的抗凝活性较好,但岩藻聚糖硫酸酯的作用较为平缓,不会产生类似肝素的出血等副作用,具有很好的研究前景。有研究证实,分子量为 3~40 ku 的低分子量多糖有类似肝素的显著抗凝血功效[49]。另有报道,岩藻聚糖硫酸酯与肝素一样,能够以 1∶1的比例与抗凝血酶结合,但牢固程度不如肝素[50]。

3.2 国内外临床研究进展 岩藻聚糖硫酸酯是目前海洋药物研究的热点之一。日本和美国已将岩藻聚糖硫酸酯作为临床药物应用于治疗血栓、癌症的研究,德国将其应用于艾滋病的治疗研究,挪威开展了白血病方面的研究[51]。俄罗斯 Fucolam 早已作为功能食品售卖[52]。我国岩藻聚糖硫酸酯作为主要成分的治疗肾功能障碍的胶囊已开发成功并上市[53-54]。赵义红等[55]用血栓通注射液与由黄芪、海藻、海带、莪术、乳香等组成的消积散结丸联合血栓通注射液做比较,发现消积丸联合血栓通注射液对脾切术后门静脉血栓有显著疗效。

4 总结与展望

岩藻聚糖硫酸酯结构受物种、产地、收获季节、藻龄、提取降解方式等影响,生物活性差异较大。岩藻聚糖硫酸酯相对分子量大、结构复杂,未系统地研究多样化的结构解析和构效关系,研究进展缓慢[56],未来的研究热点仍然是结构的研究和构效关系的研究。一级结构解析已系统化,但高级结

构解析仍进展缓慢。对岩藻聚糖硫酸酯进行结构测定和化学修饰,或者进行降解提纯,将大分子变成小片段进行分析,从而确定活性单元,不断开发岩藻聚糖硫酸酯抗血栓和其他药品保健品,发挥海带等褐藻的经济价值。

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