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· 综述 ·

玻璃离子水门汀天然抗菌成分研究进展

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【摘要】 玻璃离子水门汀(glass ionomer cement, GIC)作为口腔临床常见的充填修复材料应用广泛,但仍面临继发龋和充填体折裂的问题,GIC的抗菌防龋性能有待进一步提高。近年来,天然抗菌成分凭借良好的生物学性能、低耐药性等成为研究热点。本文依据抗菌成分的不同来源将GIC改性中的天然抗菌成分进行分类综述。动物源性方面,壳聚糖、酪蛋白磷酸肽-无定形磷酸钙发挥抗菌性能,且不影响材料机械性能;蜂胶、生物活性酶类具备良好生物相容性;植物源性方面,多酚类化合物有助于改善材料的抗菌和机械性能;精氨酸发挥良好的再矿化作用;植物精油有一定的离子释放作用;微生物源性方面,抗生素使材料的抗菌性能大幅提高;另外天然抗菌成分的联合应用也展现出优异性能。尽管天然抗菌成分优点较多,但实现临床应用之前,对于其的最适添加浓度、体内生物安全性等问题仍需进一步探讨。

【关键词】 玻璃离子水门汀; 继发龋; 天然抗菌成分; 壳聚糖; 酪蛋白磷酸肽-无定形磷酸钙; 蜂胶; 生物活性酶; 酚类化合物; 精氨酸; 植物精油; 抗生素; 机械性能

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【Abstract】 Glass ionomer cement (GIC) is widely used as a common filling material in dentistry but still exhibits problems with secondary caries and fractures. Thus, the antibacterial and anti-caries performance of GIC needs to be further improved. In recent years, natural antimicrobial components have become more desirable due to their good biological properties and low drug resistance. In this review, the natural antimicrobial ingredients in GIC modification are classified, reviewed and summarized according to the different sources of antimicrobial ingredients. In terms of animal origin, chitosan and casein phosphopeptide-amorphous calcium phosphate exhibit antimicrobial properties without affecting the mechanical properties of materials; propolis and bioactive enzymes have good biocompatibility; in terms of plant origin, polyphenols help improve the antimicrobial and mechanical properties of the material; arginine has a good remineralization effect; and plant essential oils have a certain ion release effect. In terms of microbial origin, antibiotics greatly improve the antibacterial properties of materials; in addition, the combined application of natural antimicrobial ingredients also exhibited excellent performance. Despite these advantages, the optimal addition concentration and biocompatibility *in vivo* are questions that need to be further explored before clinical applications can be achieved.

【Key words】 glass ionomer cement; secondary caries; natural antibacterial ingredients; chitosan; casein phosphopeptide amorphous calcium phosphate; propolis; bioactive enzyme; phenolic compounds; arginine; plant essential oil; antibiotic; mechanical properties

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龋病是导致牙体硬组织缺损的一种慢性进行性的细菌感染性疾病。传统玻璃离子水门汀(glass ionomer cement, GIC)于1972年由Wilson等^[1]首次报道,因氟离子释放性而具有一定防龋及再矿化作用,被广泛应用于粘接、充填、垫底等方面,但在临床应用中仍存在诸多问题。近年来,研究者一直关注GIC的抗菌改性,其中源于自然界动物、植物以及微生物的天然抗菌成分,凭借良好的生物学特性发挥着有效的抗菌防龋作用。本文从GIC的研究历史出发,依据抗菌成分的不同来源即:动物源性、植物源性以及微生物源性进行分类,就近年来加入GIC中的天然抗菌成分的研究进展作一综述。

1 动物源性天然抗菌成分

1.1 壳聚糖

甲壳素在虾蟹等海洋节肢动物、昆虫和软体动物的甲壳、菌类、藻类细胞膜中大量存在。壳聚糖(chitosan, CS)作为甲壳素的部分脱乙酰基产物,可以通过促进细菌表面阴离子静电堆积来影响细菌的正常代谢,分子结构上的反应性官能团可嵌入细菌脱氧核糖核酸链来阻断转录过程。抗菌性能方面,研究表明CS-GIC较传统GIC、氯己定-西曲肽-GIC的抗菌性能更优。CS-GIC对变异链球菌(*Streptococcus mutans*, *S. mutans*)、嗜酸乳杆菌(*Lactobacillus acidophilus*, *L. acidophilus*)的生长、黏附均有明显抑制作用^[2]。此外,Del Prado-Audelo等^[3]发现5%、10%(v/v)CS-GIC可有效提高材料对*S. mutans*的抗菌性能,且不影响材料与牙本质的粘接;另有研究表明10%(v/v)CS-GIC可提高材料的牙釉质粘接性^[4]。机械性能方面,一定浓度CS对材料抗压强度及抗弯强度的增强效果较为明确^[5],Sharafeddin等^[6]进一步发现15%(v/v)CS-GIC的表面粗糙度降低且对显微硬度无明显影响。此外,CS-GIC的氟、铝、钠离子释放量较传统GIC均有明显提高^[7-9]。随着纳米技术的进步,CS纳米颗粒在材料改性方面更具优势。研究者将10%(w/w)CS纳米颗粒(110~225 nm)加入到传统GIC,结果显示

GIC抗弯强度从12.67 MPa提高到21.26 MPa,且氟离子释放量各时间段均高于对照^[10]。

虽然CS-GIC展现出良好的抗菌、机械性能及氟离子释放性,但在实际应用中的,其凝固时间、边缘封闭性、颜色稳定性等问题仍需进一步探讨。

1.2 蜂胶

蜂胶(propolis)是蜜蜂工蜂从植物顶芽和渗出液中采集的树脂类物质,其所含的酚类、黄酮类和萜类化合物可抑制细菌葡糖基转移酶和二氢叶酸还原酶活性,作用于细菌细胞膜使细菌裂解。研究发现,50%(v/v)蜂胶乙醇提取物(ethanolic extract of propolis, EEP)-GIC对材料抗压性能无显著影响,且对*S. mutans*、*L. acidophilus*生长产生明显抑制作用^[11]。有研究发现,25%红蜂胶乙醇提取物(ethanolic extract of red propolis, EERP)-GIC对白色念珠菌(*Candida albicans*, *C. albicans*)也产生明显抑制,且对材料机械强度和氟离子释放无显著影响^[12]。而Andrade等^[13]研究发现EEP中黄酮类物质的释放与EEP-GIC的抗菌性能密切相关,同时37%(w/w)EEP-GIC的抗压强度显著高于对照组,可达(216.66 ± 5.01)MPa。此外,Altunsoy等^[14]证实EEP-GIC具有更好的显微硬度及边缘密合性。

蜂胶改性GIC优异抗菌性能和生物相容性是其较传统GIC的主要优势,但在机械强度方面,有研究发现EEP-GIC会增加材料的吸水量^[15],此外,EEP-GIC存在较大的分子量、不易溶于水、乙醇介质的稳定性差等缺点,如何寻找性质更好的水溶介质有待进一步研究。

1.3 酪蛋白磷酸肽-无定形磷酸钙

酪蛋白磷酸肽(casein phosphopeptides, CPP)来源于牛奶中的酪蛋白,是钙、磷与酪蛋白磷酸化后产生的磷酸多肽之间非共价结合的产物。作为CPP与钙盐和磷酸盐的结合产物,酪蛋白磷酸肽-无定形磷酸钙(casein phosphopeptide-amorphous calcium phosphate, CPP-ACP)一方面可以在牙体表面产生梯度CaHPO₄,为牙齿表面再矿化提供充足的钙、磷支持,另一方面可以与氟离子结合产生Ca₈(PO₄)₅F₃H₂O₁₇,延缓氟离子释放。

研究表明,3%(w/w)CPP-ACP-GIC对*S.mutans*具有抑制作用^[16]。Zhao等^[17]研究发现3%(w/w)CPP-ACP-GIC可有效抑制前磨牙根面龋进展,且与38%(w/w)氟化银联用对*S.mutans*有更好抑制作用;同时3%(w/w)CPP-ACP-GIC展现出良好的抗弯强度。另有报道发现5%(w/w)CPP-ACP-GIC对格式链球菌(*Streptococcus gordonii*,*S.gordonii*)生长产生抑制作用^[18]。还有学者发现1.56%(w/w)CPP-ACP-GIC较1%、2%组具有更优的抗压强度和耐磨性^[19]。此外Shen等^[20]证实经CPP-ACP糊剂(1g粉剂和4 mL蒸馏水)连续处理3 d后的GIC与对照组相比,有更高的钙、磷、氟离子释放量及表面硬度。目前CPP-ACP-GIC的抗菌作用主要体现在于单菌种链球菌属,对其他口腔微生物的作用有待研究;另外,关于最适添加浓度、生物安全性等方面的研究仍缺乏。

1.4 生物活性酶类

唾液中存在的溶菌酶(lysozyme)、唾液过氧化物酶(lactoperoxidase)等生物活性酶类能在细菌黏附、生物膜形成、产酸等龋病发展的多个阶段发挥作用。凭借生物活性酶类优异的抗菌效果以及生物学安全性,Pinheiro等^[21]将溶菌酶、乳铁蛋白和唾液过氧化物酶应用于GIC改性,发现酶的加入虽能增强材料的短期抗菌性能,但唾液过氧化物酶只有在pH 5~6时才有抗菌作用,且6个月后,实验组与对照组均出现*S.mutans*数量增加,原因推测与修复体老化导致边缘微渗漏有关。关于生物活性酶类改性GIC方面的研究仍欠缺,分析原因可能是酶的活性在材料中难以保持,且分子量和粒径过大对材料的机械性能产生不良影响,这些都可能限制生物活性酶类的进一步应用。

2 植物源性天然抗菌成分

2.1 多酚类化合物

多酚类化合物是许多中药发挥药理作用的主要成分之一,分子内含有多个酚羟基,易与其他结构结合,形成如儿茶素、单宁酸等多酚或酚酸类化合物,具有抗氧化、抗炎和抗菌等药理特性。现有对多酚类改性GIC的研究初步肯定了其良好的抗菌和机械性能,但相应离子释放性和细胞毒性等的进一步研究仍较欠缺。此外随着对多酚类物质研究的深入,其优异的抗菌、再矿化性能以及对牙釉质、本质的表面改性作用虽得到肯定,但其水溶性低、稳定性差的缺点也逐渐暴露。

2.1.1 表没食子儿茶素没食子酸酯 表没食子儿茶素没食子酸酯(epigallocatechin gallate, EGCG)是绿茶中主要的多酚类物质,具有抗氧化、抗炎、抗菌等性能,可以通过抑制细菌葡糖基转移酶、淀粉酶的活性和gtfB、gtfC、gtfD等基因表达来抑制生物膜形成。已有研究表明0.1%(w/w)EGCG-GIC能提高材料对*S.mutans*的抑制效果、材料抗折强度和显微硬度;此外氟离子的释放量在前24 h达到高峰,之后随着时间的延长而逐渐降低^[22]。另外一项针对5~9岁儿童龋坏的研究证实了0.1%(w/w)EGCG-GIC对*S.mutans*生长的抑制作用^[23]。

2.1.2 姜黄素 姜黄素(curcumin)是从姜黄根茎中提取的酚类物质,具有良好的抑菌、抗炎效果,但具体抗菌机制尚未明确。研究发现姜黄素最小抑菌浓度为7.81~62.50 μg/mL,可抑制*S.mutans*单菌种及多菌种生物膜生长代谢^[24-25]。有研究者将1%(w/w)姜黄素加入GIC,选取5~9岁儿童,选取治疗前、修复后及修复7 d后3个时间点对牙体样本进行微生物学评价,结果显示与传统GIC相比,姜黄素改性材料可显著减少*S.mutans*数量^[26]。但目前对于姜黄素GIC的最适添加浓度、改性后材料机械性能、生物学性能的评价较为欠缺,有待进一步研究。

2.1.3 可可碱 可可碱(theobromine)是可可豆或其树皮中提取的天然多酚类物质,可以促进牙釉质表面再矿化、减轻牙本质敏感、抑制细菌产酸,目前已应用到牙膏、漱口水当中,但在口腔材料改性方面的研究较为欠缺。目前研究肯定了1%(w/w)可可碱改性GIC对*S.mutans*生物膜的抑制作用和对材料显微硬度的提高,且与传统GIC相比,改性后材料的唾液吸附性、溶解度、氟释放量无差异^[27]。但考虑到多酚类物质水溶性低、稳定性差的缺点,可可碱改性GIC的作用长效性有待探究。

2.2 精氨酸

精氨酸(arginine, Arg)最早从植物羽扁豆幼苗中分离提取而命名。Arg可作为代谢底物参与细菌产碱代谢、封闭牙本质小管、促进再矿化。目前已被证明对*S.mutans*等产酸菌具有抑制作用^[28]。Sharma等^[29]将5%、7%、10%(w/w)L-Arg加入粘接剂,结果显示在不改变粘接剂机械性能的情况下7%L-Arg-GIC对*S.mutans*生物膜的抑制作用最强。但Bijle等^[30]对比1%、2%、4%(w/w)L-Arg-GIC机械性能和抗菌作用,发现在对材料机械性能无明显影响的基础上,4%Arg-GIC对*S.mutans*和血

链球菌(*Streptococcus sanguinis*, *S. sanguinis*)生长的抑制效果最好。精氨酸改性GIC的优势主要体现在其良好的生物学安全性、再矿化性能以及一定的抗菌性能,机械性能方面目前研究并未展现出明显的改善效果;此外对于最适添加浓度、离子释放性及细胞毒性等性质仍需探究。

2.3 植物精油

植物精油是自然界芳香植物根、茎等提炼萃取出的具有一定香气的挥发性油状混合物,如肉桂、丁香等,对多种细菌具有抗菌效果,但具体抗菌机制不明。目前,植物精油改性GIC的优势主要体现在优异的抗菌性和离子释放性方面, Sherief等^[31]将5%(v/v)百里香和10%(v/v)肉桂香精油加入GIC,发现与传统GIC相比,改性后GIC对*S. mutans*和*C. albicans*的生长有明显抑制作用,5%肉桂-GIC对材料机械性能无明显影响。此外累积氟化物释放量为10%肉桂-GIC > 5%百里香-GIC > 5%肉桂-GIC > 10%百里香-GIC > 传统GIC。

3 微生物源性天然抗菌成分

微生物源性天然抗菌成分是指微生物分泌或从微生物中提取得到的,具有抗菌性能的物质。抗生素主要通过抑制细菌细胞壁、蛋白质的合成、DNA的转录等发挥抗菌作用。

抗生素凭借其优异的抗菌性能最先应用于GIC的抗菌改性研究当中,研究者最早通过体外实验证明抗生素改性GIC较传统GIC能有效减少感染牙本质、感染牙髓和根尖周病变病灶中*S. mutans*等龋源菌数量^[32-34]。但随着细菌耐药性的增加,抗生素联合应用逐渐成为常态,其中环丙沙星-甲硝唑与第三种抗生素联合的组合在GIC改性中较为常用。Sato等^[35]率先肯定环丙沙星-甲硝唑-头孢克洛(ciprofloxacin-metronidazole-cefaclor, Cipro-Metro-Cefa)组合对人乳牙龋坏及牙髓病中细菌生长的抑制作用;Yesilyurt等^[36]进一步发现环丙沙星-甲硝唑-米诺环素(ciprofloxacin-metronidazole-minocycline, Cipro-Metro-Mino)-GIC对*S. mutans*和*L. acidophilus*的抑制作用,并对抗生素添加浓度进行探究,发现1.5%组与3%、4.5%组相比,24 h及7 d后材料抗压强度未受到明显影响。近年来,有学者^[40]将4种常见抗生素组合添加后GIC的性能进行比较,发现Cipro-Metro-Cefa-GIC组对*S. mutans*生长抑制效果和显微硬度明显优于Cipro-Metro-Mino-GIC组、Cipro-Metro-GIC组和对照组。总之,虽然抗

生素或抗生素联用改性GIC有助于增强抗菌效果,但针对联合应用抗生素的种类、浓度的选择、释放的长期有效性以及如何避免过度使用等需要进一步探讨。

4 抗菌成分的联合应用

两种及多种抗菌材料联用不仅有助于减少耐药性产生,还可减少用药剂量、降低细胞毒性,获得更好的抗菌效果。随着纳米载体技术的进步,CS凭借其良好的载体性能常与其他抗菌物质联合应用。Ibrahim等^[38]将CS与TiO₂纳米颗粒(21 nm)联用对GIC进行改性实验,结果显示改性后材料对*S. mutans*抑制作用及材料抗折、抗压强度和表面硬度均有明显提高。此外研究发现CS与氯己定-西曲肽联用可增强材料的抗压强度、抗弯强度,提高对*S. mutans*和*L. acidophilus*的抑制作用^[39]。另有学者^[40]发现CS与纳米生物活性玻璃(bioactive glass nanoparticle, BGN)联用不仅能提高材料的抗弯强度、压缩强度及径向拉伸强度,对人牙髓干细胞也无毒性作用。

5 小结

天然抗菌成分凭借优良的生物学相容性、低耐药性等优势应用于GIC改性研究中,并取得较好的抗菌防龋效果,具有一定的应用前景,不过现有研究也存在一些不足:①目前大多研究仅停留在体外研究阶段,对于材料在复杂的口腔环境中使用时的效果无法进行有效评估;②对于天然抗菌成分的最优添加量仍需进一步明确,以寻求添加浓度、材料抗菌效果和机械强度之间的平衡;③天然抗菌成分的抗菌机制尚未明确,并且欠缺相应的生物安全性的实验评价。总之,天然抗菌成分改性应用于GIC仍需进一步深入研究。

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