



具有抗牙龈卟啉单胞菌功效的天然植物提取物在牙周炎防治中的研究进展

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摘要 牙周炎是影响人类健康的一种慢性感染性疾病, 牙龈卟啉单胞菌被认为是其重要致病菌之一, 以抗牙龈卟啉单胞菌为目标的牙周炎防治策略受到关注. 传统抗菌药物已广泛应用于牙周炎的临床防治, 但其局限性仍不可忽视. 多种天然植物提取物已被报道具有优越的抗菌性能且不易产生耐药性等独特优势, 有望为牙龈卟啉单胞菌抗菌防治提供新的策略. 本文回顾总结了具有抗牙龈卟啉单胞菌功效的天然植物提取物对牙周炎的防治效果及其机制, 在此基础上纳入了天然植物提取物与抗菌剂联用和(或)结合纳米技术的最新研究进展, 以期天然植物提取物抗菌相关研究和牙周炎的防治策略提供通用思路和理论基础.

关键词 牙周炎, 牙龈卟啉单胞菌, 天然植物提取物, 抗菌

牙周炎是一种侵犯牙周组织的慢性炎症性疾病, 全球超过半数成年人患有不同程度的牙周炎, 其中10%左右患有重度牙周炎^[1], 第四次全国口腔流行病学调查数据显示, 我国老年人牙周炎患病率高达74.2%^[2]. 牙周相关致病菌不仅是牙周炎发生发展的关键起始因素, 而且与糖尿病^[3]、类风湿关节炎^[4]和阿尔茨海默症^[5]等系统性疾病密切相关. 它们一方面可入侵循环系统、消化系统及呼吸系统并释放毒力因子; 另一方面可通过骨髓造血干细胞的反应性等因素诱导全身炎症, 最终引起或加重全身系统性疾病的发生^[6]. 针对牙周炎发病机制及其防治策略的探索是近几十年

来受到广泛关注但尚未解决的重要问题.

牙龈卟啉单胞菌(*Porphyromonas gingivalis*, *P. gingivalis*)是牙周炎的重要致病菌之一^[7]. 口腔微环境中*P. gingivalis*菌群数量的少量增加即可干扰宿主免疫系统, 并为其他共生菌群提供丰富的炎性渗出物作为营养物质, 引起口腔共生菌群数量和组成变化, 显著促进牙周炎的发生发展, 进而导致牙槽骨吸收及牙齿脱落^[8]. *P. gingivalis*对牙周组织的破坏机制主要包括: (i) *P. gingivalis*借助其毒力因子黏附定植于宿主口腔组织, 促进生物膜的成熟, 为细菌提供保护使其更难被清除, 降低抗菌剂的原有抗菌效力^[9]. (ii) *P. gin-*

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Yin D R, Wang Y W, Yang Y H, et al. Role of natural plant extracts with anti-*Porphyromonas gingivalis* function in the prevention and treatment of periodontitis (in Chinese). Sci Sin Vitae, 2023, 53: 825–840, doi: [10.1360/SSV-2022-0269](https://doi.org/10.1360/SSV-2022-0269)

*givalis*攻击宿主细胞并激活宿主免疫防御系统, 该过程产生的炎性因子可引起宿主组织破坏性炎症进程并在牙周组织中蔓延, 导致牙周支持组织破坏及牙齿脱落^[10]. (iii) *P. gingivalis*亦可促进免疫细胞和黏膜细胞分泌基质金属蛋白酶(matrix metalloproteinases, MMPs)进而破坏牙周组织^[11].

目前, 牙周炎的治疗策略主要包括非手术和手术治疗, 同时辅以抗生素治疗. 但近年来, 抗生素的局限性逐步受到广泛关注. 首要问题是耐药性问题, 近年来四环素类、大环内酯类、林可酰胺类和氟喹诺酮类药物对*P. gingivalis*的最小抑菌浓度(minimum inhibitory concentration, MIC)均有所增加^[12], 表明其抗菌性能下降, 且生物膜可显著降低细菌对此类抗生素的敏感性^[13]. 此外, 特定抗生素的副作用, 如氯己定引起的牙齿变色、味觉改变、口腔黏膜损伤及腮腺肿胀等问题也被相继报道^[14].

天然植物提取物是指植物内源性的化学成分. 在植物的长期进化过程中, 一些植物形成了对病原菌的天然抗性, 这部分植物提取物被认为具有卓越的抗菌性能. 同时, 天然植物提取物作用靶点与传统抗生素不同, 微生物针对传统抗生素建立的耐药机制无法对其发挥有效作用, 因此天然植物提取物不易产生耐药性^[15]. 此外, 天然植物提取物亦可辅助机械治疗, 如葡萄籽提取物(grape seed extract, GSE)可辅助常规刮治和根面平整术(scaling and root planning, SRP)治疗深牙周袋, 治疗效果较仅SRP治疗组更佳^[16]. 姜黄素(curcumin)作为天然光敏剂可介导光动力治疗, 其被蓝光激活后可产生活性氧(reactive oxygen species, ROS), 辅助SRP治疗时能显著减少龈下菌斑中牙周致病菌数量, 改善牙周状况^[17,18]. 此外, 天然植物提取物因其成本低廉、不易产生耐药性以及对人体副作用小等诸多优势受到广泛关注^[9]. 其中, 丁香酚(eugenol)、天然辣椒素(capsaicin)以及肉桂醛(cinnamaldehyde, CA)等多种天然植物提取物已被证实对*P. gingivalis*具有明确的抗菌作用.

本文从天然植物提取物破坏*P. gingivalis*细胞结构、干扰*P. gingivalis*代谢及影响*P. gingivalis*生物膜三个方面回顾总结了天然植物提取物对*P. gingivalis*的抗菌效果及作用机制(表1), 同时归纳整理了天然植物提取物对*P. gingivalis*引起的氧化应激、宿主炎症以及牙槽骨吸收的抑制作用(表2). 本文重点介绍天然植

物提取物与抗菌剂和(或)结合纳米技术联用的研究的最新进展, 以期天然植物提取物抗菌相关研究和牙周炎的防治策略提供通用思路和理论基础.

1 天然植物提取物对*P. gingivalis*的抗菌效果及机制

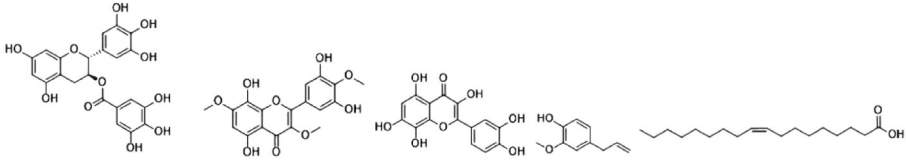
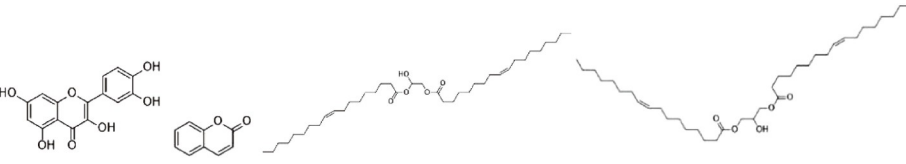
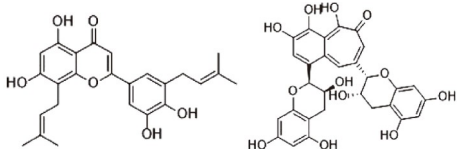
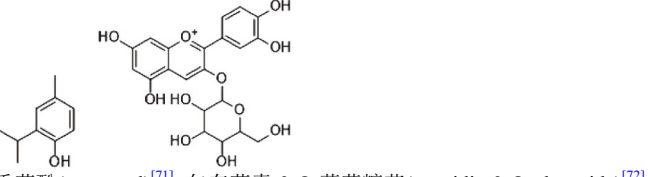
1.1 破坏*P. gingivalis*细胞结构

(1) 直接破坏作用. 儿茶素(catechin)是一类在绿茶中含量丰富的酚类活性物质, 具有优越的抗氧化和杀菌活性. 作为儿茶素的主要有效成分, 表没食子儿茶素没食子酸酯(epigallocatechin-3-gallate, EGCG)对*P. gingivalis*表现出显著的抗菌作用^[19]. EGCG与*P. gingivalis*细胞膜的脂质双分子层以及膜蛋白进行物理结合后, 其羟基将位于脂质双分子层中间的溶解氧还原成 H_2O_2 , 导致细菌细胞膜破裂, 细菌内容物流出, 进而发挥杀菌作用^[20-22]. 此外, 玫瑰茄粗提取物(roselle calyx extract, RCE)中富含的玫瑰茄红素(hibiscetin)和棉花素(gossypetin)等黄酮类物质亦能与*P. gingivalis*结合并发挥抗菌作用, 其还原能力和抗菌能力随黄酮类物质中羟基数量的增加而增强^[23]. 由此可推测, 含羟基的天然植物提取物, 可通过羟基的还原作用产生 H_2O_2 , 直接破坏*P. gingivalis*的细胞膜, 发挥抗菌作用^[24].

丁香酚是丁香油(clove oil)的主要成分, 常作为水门汀充填材料添加物, 现已被证明对*P. gingivalis*具有抗菌作用^[25]. 从构效关系出发, 疏水性的丁香酚通过插入磷脂双分子层而改变细胞膜结构和通透性, 扰乱细胞膜功能的同时增加ATP和 K^+ 外流, 导致细菌死亡^[26]. 黑樱桃(*Monechma ciliatum*)种子提取物中含有油酸(oleic acid)、香豆素(coumarin)、1,2-二油酰基甘油(1,2-dioleoylglycerol)和1,3-二油酰基甘油(1,3-dioleoylglycerol)等化合物, 对*P. gingivalis*均有杀菌作用. 油酸利用亲水头部和疏水尾部穿透*P. gingivalis*细胞膜, 其他成分通过与蛋白质结合影响蛋白质运动和聚集, 最终影响细胞膜结构和功能^[27]. AmyI-1-18是一种来自大米 α -淀粉酶(rice alpha-amylase)的肽, 首先可通过疏水作用插入细胞膜, 再利用静电相互作用影响*P. gingivalis*细胞膜功能, 进而发挥杀菌作用并抑制生物膜的形成^[28]. 此外, AmyI-1-18被观察到在无细胞快速翻译系统(rapid translation system, RTS)中能够抑制蛋白质的翻译和合成, 证明其杀菌作用可独立于膜失稳

表 1 天然植物提取物对 *P. gingivalis* 的抗菌效果及作用机制

Table 1 Antibacterial effects and mechanism of natural plant extracts on *P. gingivalis*

作用机制	天然植物提取物及其化学结构式
破坏 <i>P. gingivalis</i> 细胞结构	 从左到右依次为: 表没食子儿茶素没食子酸酯(epigallocatechin-3-gallate, EGCG)^[19], 玫瑰茄红素(hibiscetin)^[23], 棉花素(gossypetin)^[23], 丁香酚(eugenol)^[25]; 油酸(oleic acid)^[27] AmyI-1-18^[29]; 茴香(fennel)提取物^[30]
间接破坏细菌细胞结构	EGCG^[35,36](见上图); 红厚壳籽油(<i>Calophyllum inophyllum</i> oil, CIO)^[37]
抑制血凝素作用	 从左到右依次为: 槲皮素(querletin)^[39]; 香豆素(coumarin)^[27], 1,2-二油酰基甘油^[27](1,2-dioleoylglycerol); 1,3-二油酰基甘油(1,3-dioleoylglycerol)^[27] 油酸^[27](见上图)
干扰 <i>P. gingivalis</i> 代谢	 肉桂醛(cinnamaldehyde, CA)^[46] 儿茶素(catechin)^[45]
抑制 <i>P. gingivalis</i> 对宿主的黏附	 从左到右依次为: 朝藿素B(epimedinokoreanin B)^[53], 茶黄素(theaflavins, TFs)^[65] 丁香酚^[25](见上图); EGCG^[19](见上图); 香豆素^[27](见上图)
影响 <i>P. gingivalis</i> 生物膜	大米蛋白提取物(rice protein extract)^[54]; 玫瑰茄提取物(roselle calyx extract, RCE)^[23]; 黄酮和单宁酸类物质; 原花青素(proanthocyanidins, PACs)^[61],
破坏成熟生物膜	 香芹酚(carvacrol)^[71]; 矢车菊素-3-O-葡萄糖苷(cyanidin-3-O-glucoside)^[72]

效应而存在^[29]。茴香(fennel)是一种传统中药材,低浓度茴香提取物能够触发*P. gingivalis*膜应激,形成由外膜囊泡(outer membrane vesicles, OMVs)构成的纳米级的突出结构,造成*P. gingivalis*细胞膜结构的破坏。高浓度茴香提取物则可直接诱导细菌裂解,同时产生更多

具有特殊表面特性的OMVs,而OMVs在被细菌进一步排出的过程中又可以带走*ragA*和*ragB*基因编码的相关蛋白,导致细菌从外部环境获取、转运大分子物质受阻,从而抑制细菌生长和繁殖^[30]。因此,部分天然植物提取物可依靠特殊结构插入*P. gingivalis*细胞膜而直接

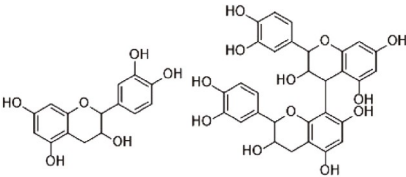
表 2 天然植物提取物的 *P. gingivalis* 相关宿主生物学功能

Table 2 Host biological functions of natural plant extracts associated with *P. gingivalis*

天然植物提取物的 *P. gingivalis*
相关宿主生物学功能

天然植物提取物及其化学结构式

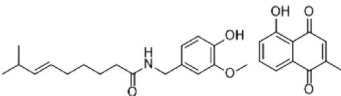
减轻宿主氧化应激



表儿茶(epicatechin)^[77]; 原花青素B2(Procyanidin B2)^[77]

传统槟榔(traditional betel quid, TBQ)^[76]; 甜槠水提取液(*Castanopsis lamontii* water extract, CLE)^[77]

抑制宿主炎症反应

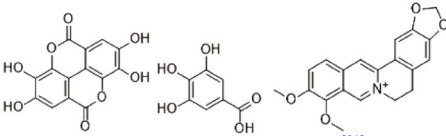


天然辣椒素(capsaicin)^[70]; 白花丹醌(plumbagin)^[84]

茶黄素^[65](见上图)

紫萁提取物(*Osmunda japonica* extract, OJE)^[79]; 山苍子叶提取物(*Litsea japonica* leaf extract, LJLE)^[83]

调控破骨细胞与成骨细胞活性

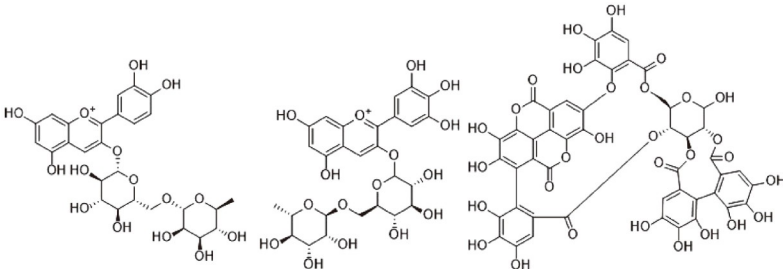


从左到右依次为: 鞣花酸(ellagic acid)^[91]; 没食子酸(gallic acid)^[91]; 黄连素(berberine)^[92]

天然辣椒素^[70](见上图)

化香树叶提取物(*Platycarya strobilacea* leaf extract, PLE)^[91]

抑制基质金属蛋白酶(Matrix metalloproteinase, MMPs)作用



从左到右依次为: 矢车菊素-3-O-芸香糖苷(cyanidin-3-O-rutinoside)^[102]; 飞燕草素-3-O-芸香糖苷

(delphinidin-3-O-rutinoside)^[102]; 诃子鞣质(Terchebulin)^[100]

茶黄素^[65](见上图); EGCG^[101](见上图); 矢车菊素-3-O-葡萄糖苷^[102](见上图)

车前草(*Plantago*)提取物^[99]; 黑醋栗提取物(*Sublackcurrant* extract)^[102]

破坏细胞膜结构, 导致细菌死亡.

(2) 间接破坏作用. β -防御素(human β -defensins, HBD)是由上皮细胞分泌的阳离子抗菌肽, 可延缓牙周炎的发生发展^[31,32]. HBD对牙周炎的防治作用源于其对 *P. gingivalis* 的杀菌作用, 研究表明, HBD与 *P. gingivalis* 细胞膜相互作用, 促进细胞膜孔隙形成, 破坏细胞膜完整性, 从而使细菌内容物流出, 并最终导致 *P. gingivalis* 死亡^[33,34]. 将EGCG作用于牙龈上皮细胞(gingival epithelial cells, GECs)后, HBD-1和HBD-2的分泌

呈剂量依赖性上调, 此外, EGCG还可通过氢键及疏水基团与 *P. gingivalis* 分泌的蛋白酶相互作用, 通过改变酶的二级结构而影响其功能, 减少蛋白酶对 *P. gingivalis* 培养基上清液中HBD-1和HBD-2的降解^[35,36]. 此外, 实验证明, 巨噬细胞在红厚壳籽油(*Calophyllum inophyllum* oil, CIO)中孵育后上清液中HBD-2含量提高, 表明CIO可通过刺激先天免疫防御促进巨噬细胞释放HBD-2, 对革兰氏阴性菌发挥抗菌作用^[37]. 因此, 天然植物提取物可能通过促进防御素的分泌并保护其不被

降解来破坏细菌细胞膜,起到间接杀菌作用。

1.2 干扰*P. gingivalis*的代谢

(1) 干扰*P. gingivalis*对营养物质的摄取。血凝素(hemagglutinins, Hag)是*P. gingivalis*的毒力因子之一,对其营养成分的摄取至关重要。*P. gingivalis*是一种营养缺陷型细菌,不具备合成血红素以及铁吸收能力,需通过Hag与红细胞结合,并利用牙龈素促进红细胞的凝聚(凝血)及裂解(溶血),后与血红蛋白结合并将其降解,吸收血红素及铁元素^[38]。黑樱桃种子提取物富含的油酸、香豆素、1,2-二油酰基甘油和1,3-二油酰基甘油已分别被证明能抑制*P. gingivalis*对Hag的分泌,其中油酸展现出最强的抗凝血能力^[27]。槲皮素(querce-tin)可通过与Hag表面结合而影响其结构和功能,进而抑制*P. gingivalis*凝血和溶血活性。此外,槲皮素可下调*P. gingivalis*参与铁获取和代谢的*ftn*基因表达^[39],抑制*P. gingivalis*在缺铁条件下的生存^[40],同时也可抑制血红素/血红蛋白利用受体基因 *hmuR*的表达^[39],导致*P. gingivalis*利用血红素途径受阻^[41,42]。由此可见,部分天然植物提取物可通过抑制Hag的作用而抑制*P. gingivalis*对营养物质的摄取进而起到抗菌作用。值得一提的是, Hag对*P. gingivalis*的定植也十分重要,因此,对Hag有抑制作用的天然植物提取物理论上也可抑制*P. gingivalis*对宿主的黏附,进而影响生物膜形成^[43]。

(2) 影响集落感应系统。集落感应(quorum sensing, QS)是发现于微生物群落中的一种自诱导现象,可调节群落中细菌的生理功能并协调与细菌毒性相关基因的表达,其调控基因包括*luxI*基因和*luxR*基因。*luxI*基因指导合成自诱导物合成酶——LuxI蛋白, LuxI蛋白能进一步合成包括酰基高丝氨酸内酯(N-acyl homoserine lactones, AHLs)、寡肽类(auto inducer peptides, AIPs)以及自诱导因子 II (autoinducer-2, AI-2)等信号分子。这些信号分子可扩散转移到细菌外并不断累积,随着浓度达到启动阈值后,这些信号分子会再次进入细菌内并与*luxR*基因合成的LuxR蛋白结合,形成的复合物可激活相关基因的表达,进而调控碳水化合物代谢、促进生物膜形成或参与细菌耐药抵抗及侵袭因子合成等过程^[44]。

印楝(*Azadirachta indica*)中富含儿茶素,且经儿茶素处理后的*P. gingivalis*培养上清液中QS系统特殊信号分子含量显著降低^[45],证明儿茶素可通过促进信号

分子的降解影响QS系统的功能,进而影响*P. gingivalis*生物膜的形成及其对血红素及铁元素的摄取,促进细菌死亡,同时减少*P. gingivalis*对宿主免疫系统的干扰。作为肉桂提取物中的主要杀菌成分,肉桂醛及其类似物被证明可以降低LuxR蛋白与DNA的结合能力,导致信号分子与LuxR蛋白结合后无法进一步有效激活相关基因的表达,进而影响QS系统介导的侵袭因子合成以及细菌的生理活动^[46]。因此,部分天然植物提取物可通过干扰QS系统而从多方面影响*P. gingivalis*的代谢活动并降低*P. gingivalis*的侵袭性。

1.3 影响*P. gingivalis*生物膜

生物膜是由附着于生物或非生物表面的微生物及其分泌的基质共同形成的聚集体^[47],可增强细菌间的信息交流,帮助细菌抵抗宿主的防御机制并降低细菌对抗生素的敏感性^[48]。其形成过程具有复杂、动态以及多阶段的特点:第一步,细菌黏附于生物或非生物表面;第二步,细菌之间的相互作用驱动微菌落进一步发展并形成成熟的生物膜;第三步,细菌从生物膜中扩散,形成新的生物膜^[49]。*P. gingivalis*是典型的龈下生物膜晚期定植菌^[50],黏附是其形成生物膜的关键一步,天然植物提取物可以通过影响*P. gingivalis*对宿主的黏附而抑制其生物膜形成。此外,部分天然植物提取物还可破坏已成熟的生物膜(图1)。

(1) 抑制*P. gingivalis*对宿主的黏附。牙龈素是*P. gingivalis*的主要毒力因子,分为精氨酸半胱氨酸牙龈素(Arg-gingipain, Rgp, 包括RgpA和RgpB)和赖氨酸半胱氨酸牙龈素(Lys-gingipain, Kgp)。RgpA和Kgp均参与*P. gingivalis*在口腔上皮的黏附以及与其他细菌的共聚^[51]。Kgp可通过增强*P. gingivalis*与伴放线聚集杆菌(*Aggregatibacter actinomycetemcomitans*, *A. actinomycetemcomitans*)的竞争优势而对牙齿表面菌斑的成熟起到一定的促进作用^[52]。实验证明,亚MIC剂量的淫羊藿提取物(*Epimedium extract*)能够抑制*P. gingivalis*单菌种生物膜形成。研究者从其混合物中进一步提取出17种异戊二烯类黄酮化合物,其中朝藿素B(epimedo-koreanin B)可作为牙龈素的非竞争性抑制剂抑制*P. gingivalis*的黏附,从而影响其生物膜的形成^[53]。大米蛋白提取物(rice protein extract)中的酶类亦可通过抑制Rgp的作用进而抑制*P. gingivalis*的黏附,还能有效阻止牙龈素引起的牙周组织降解^[54]。亚MIC剂量的玫

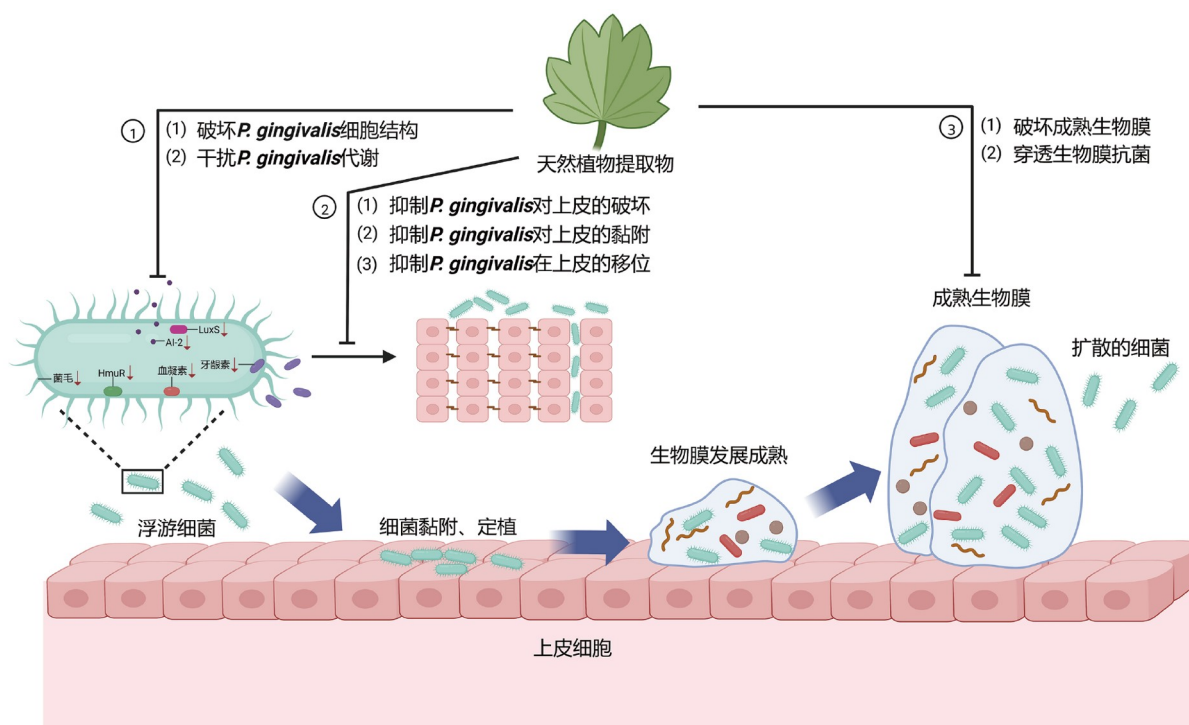


图1 天然植物提取物通过多种途径对*P. gingivalis*发挥抗菌作用并影响其生物膜. ①: 天然植物提取物破坏*P. gingivalis*细胞结构并干扰*P. gingivalis*代谢; ②: 天然植物提取物抑制*P. gingivalis*对上皮的破坏和黏附并阻止其在上皮的移位; ③: 天然植物提取物破坏*P. gingivalis*成熟生物膜并穿透生物膜抗菌

Figure 1 Natural plant extracts exert antibacterial effects on *P. gingivalis* and affect its biofilm in various ways: ① destroying the cell structure of *P. gingivalis* and interfering with its metabolism, ② inhibiting the damage and adhesion of *P. gingivalis* to the epithelium and preventing its translocation in the epithelium, and ③ destroying mature biofilms of *P. gingivalis* and penetrating biofilms to exert antimicrobial effects

瑰茄提取物呈剂量依赖性抑制*P. gingivalis*生物膜的形成, 其有效成分黄酮和单宁酸类物质可与牙龈素结合并显著抑制其活性, 影响细菌的黏附^[23]. 上述天然植物提取物可通过抑制牙龈素的作用抑制*P. gingivalis*的黏附, 进一步影响生物膜的形成. 值得一提的是, 牙龈素作为*P. gingivalis*的关键毒力因子, 在*P. gingivalis*的营养物质摄取、外膜蛋白加工、宿主免疫反应调节以及组织破坏中起重要作用^[51], 故抑制牙龈素的作用不仅可以抑制生物膜的形成, 还可直接对*P. gingivalis*起到杀菌作用, 减轻炎症并保护口腔组织, 从多方面抑制牙周炎的发生发展.

FimA是*P. gingivalis*在生物膜形成过程中起重要作用的一种菌毛, 缺乏FimA的突变体无法有效形成生物膜^[55]. 血凝素作为*P. gingivalis*的关键毒力因子, 其编码基因中的*hagB*也在*P. gingivalis*的黏附过程中发挥重要作用, 缺乏*hagB*的突变体对口腔鳞状上皮细胞(oral squamous cell carcinomas, OSCCs)的黏附率低于

正常型的十分之一. 此外, *hagC*基因也与生物膜形成有关, 缺乏*hagC*的突变体所形成的生物膜更少^[43]. 亚MIC剂量的丁香酚和EGCG均可显著下调*fimA*, *hagA*, *hagB*和*kgp*基因的表达, 抑制*P. gingivalis*的黏附, 进而抑制生物膜的形成^[19,25]. 香豆素是一种具有铁整合特性的酚类化合物, 可竞争结合铁离子导致*P. gingivalis*在合成血凝素时无法获取足够铁元素, 最终导致*P. gingivalis*的黏附能力下降^[27]. 上述天然植物提取物可通过抑制菌毛和血凝素的作用而有效抑制*P. gingivalis*的黏附能力. 此外, 血凝素也参与*P. gingivalis*对营养的摄取, 抑制血凝素可直接对*P. gingivalis*起抗菌作用.

*P. gingivalis*定植于口腔黏膜时首先破坏宿主细胞之间的连接, 进一步黏附于失去紧密连接的宿主细胞并侵入更深的结缔组织^[56]. 宿主细胞可以通过密封蛋白(claudin)、闭合小环蛋白(zonula occluden, ZO)和闭合蛋白(occludin)等细胞间紧密连接蛋白形成屏障作

用^[57], 防止细菌和毒素通过^[58]. 其中, GECs紧密连接蛋白的减少会导致跨上皮电阻降低^[59], *P. gingivalis*能通过侵袭GECs, 在上层GECs完全断裂前转移到下层GECs最后进入上皮下结缔组织^[60], 这种复杂的移位机制帮助*P. gingivalis*逃脱宿主的防御机制并更好地黏附定植. 据报道, 高丛蓝莓原花青素(proanthocyanidins, PACs)能防止跨上皮电阻的降低和细胞旁通量的增加, 保护细胞屏障的完整性, 进而抑制*P. gingivalis*诱导的细胞间闭合蛋白的减少, 阻止*P. gingivalis*在牙龈角质细胞(gingival keratinocyte)屏障模型的移位^[61]. EGCG^[62]和酸樱桃提取物(tart cherry extract)^[63]可阻止*P. gingivalis*对紧密连接蛋白的破坏, 此外, EGCG还可引起闭合小环蛋白-1和密封蛋白的再分配, 进一步保护口腔上皮屏障的完整性, 其机制可能与抑制DNA甲基化有关^[64]. 红茶中的茶黄素(theaflavins, TFs)亦可以保护牙龈角质细胞的完整性^[65], 并通过调节腺苷单磷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)活性增强闭合蛋白、密封蛋白-1和闭合小环蛋白-1的表达^[66]. 综上, 天然植物提取物在保护口腔黏膜免受*P. gingivalis*破坏的同时可抑制*P. gingivalis*对宿主的黏附及对细胞屏障完整性的破坏等不利因素^[67-69], 提示天然植物提取物可能通过抑制以上毒力因子的作用来保护上皮屏障, 然而相关分子机制有待进一步深入的研究.

(2) 破坏成熟生物膜. 部分天然植物提取物可直接破坏成熟生物膜. 经天然辣椒素处理后, *P. gingivalis*生物膜完整性被破坏, 生物膜厚度变薄, 经天然辣椒素处理后的*P. gingivalis*生物膜的完整性被破坏, 厚度更薄, 且表现出更低的耐药性, 这种破坏作用与天然辣椒素可有效穿过生物膜并抑制*P. gingivalis*的生长有关^[70]. 香芹酚(carvacrol)亦可破坏生物膜并对成熟生物膜中的细菌产生杀菌作用, 实验表明于1%香芹酚中暴露一分钟的*P. gingivalis*单菌种生物膜以及多菌种生物膜中的细菌数量均明显下降, 且生物膜结构遭到破坏, 同时, 通过对不同时间细菌量的测定, 证明成熟生物膜对天然植物提取物的敏感性并不会随时间的延长而降低^[71]. 忍冬提取物(*Lonicera caerulea* var. *emphyllolalyx* extract, LCEE)及其成分之一的矢车菊素-3-O-葡萄糖苷(cyanidin-3-O-glucoside)对*P. gingivalis*生物膜形成的显著抑制作用呈浓度和时间依赖性^[72]. 上述天然植物提取物可直接破坏成熟生物膜, 一定程度上弥补

部分抗菌物质针对生物膜药效降低的缺陷. 但相关报道多局限于表型, 缺乏机制的深入研究.

2 天然植物提取物的*P. gingivalis*相关宿主生物学功能

2.1 减轻宿主氧化应激

宿主氧化应激时ROS含量显著高于生理水平, 可激活NF- κ B通路并刺激炎症因子产生, 促进牙周炎发生发展^[73]. *P. gingivalis*的外膜脂多糖(lipopolysaccharide, LPS)一方面可诱导人牙龈成纤维细胞(human gingival fibroblasts, HGFs)和牙周韧带细胞(periodontal ligament cells, PDLs)产生大量ROS, 另一方面可降低过氧化氢酶的活性进一步增加牙周组织中的氧化应激^[74]. 此外, *P. gingivalis*的LPS还通过抑制丙酮酸脱氢酶激酶的表达而上调宿主线粒体中ROS水平^[75]. 研究发现, 部分天然植物提取物可抑制*P. gingivalis*对宿主造成的氧化应激.

斯里兰卡传统槟榔(traditional betel quid, TBQ)是一种天然抗氧化剂, 其乙酸乙酯提取物对*P. gingivalis*有抗菌作用, 同时可以保护HGFs免受*P. gingivalis*诱导的氧化应激. TBQ可直接清除进入HGFs的H₂O₂, 亦可通过提高HGFs内过氧化氢酶和过氧化物酶等抗氧化酶的活性间接清除进入HGFs的H₂O₂^[76]. 甜槠水提取液(*Castanopsis lamontii* water extract, CLE)可降低培养基中H₂O₂的浓度, 且具有清除自由基的能力. CLE主要成分包括表儿茶素(epicatechin)和原花青素B2(procyanidin B2), 表儿茶素主要促进CLE的抗菌活性, 原花青素B2主要促进CLE的抗炎活性, 同时二者均有抗氧化作用. 表儿茶素能够直接清除宿主细胞的自由基, 如超氧阴离子自由基和羟基自由基. 原花青素B2能够提高抗氧化酶的活性间接清除自由基, 包括超氧化物歧化酶、过氧化氢酶和谷胱甘肽过氧化物酶^[77]. 此外, CLE中还存在其他抗氧化成分, 如皂苷等.

许多天然植物提取物具有抗氧化作用, 未来可继续深入研究其抗*P. gingivalis*氧化应激的效用, 为牙周炎的防治提供新思路.

2.2 减轻宿主炎症反应

宿主过度的炎症反应是牙周炎的重要致病机制. *P. gingivalis*的LPS诱导GECs和HGFs等宿主细胞产生

TNF- α , IL-6和IL-1等炎症因子, 同时招募免疫细胞聚集进一步产生炎症因子, 炎症因子的过度积累导致宿主过度的免疫反应以及进行性结缔组织损伤。此外, 局部感染可引起骨髓的防御性反应, 使单核细胞(monocytes)增多并进一步分化为破骨前体细胞(osteoclast precursors, OCPs)^[6], 同时炎症因子及LPS可通过激活RANK(NF- κ B)-RANKL系统促进OCPs分化为破骨细胞(osteoclast), 破骨细胞的过度激活最终导致牙槽骨吸收以及牙齿脱落^[78]。

紫萁提取物(*Osmunda japonica* extract, OJE)可通过活化NF- κ B通路而显著抑制LPS诱导的、牙周膜成纤维细胞(periodontal ligament fibroblasts, PDLFs)来源的IL-6和IL-8分泌^[79], 从而阻断由IL-6引起的OCPs分化^[6], B细胞分化和自身抗体产生^[80]等因素引发的严重牙周结缔组织损伤^[81,82]。山苍子叶提取物(*Litsea japonica* leaf extract, LJLE)亦可抑制PDLFs产生促炎因子的能力, 呈剂量依赖性降低LPS诱导的IL-6和IL-8的分泌以及mRNA和蛋白质的合成^[83]。白花丹醌(plumbagin)可以通过MAPK, NF- κ B和JAK/STAT等信号通路抑制人牙周韧带干细胞(periodontal ligament stem cells, PDLSCs)中TNF- α , IL-1 β 和IL-6的分泌而抑制炎症的进展^[84]。TNF- α 在牙周炎的炎症反应、牙槽骨吸收和结缔组织损伤中发挥关键作用, 还能刺激其他促炎因子的产生, 包括IL-1 β , IL-6和NO等, 这些因子均被证实参与免疫细胞迁移、破骨细胞分化和骨吸收^[85,86]。茶黄素可抑制*P. gingivalis*诱导的巨噬细胞NF- κ B磷酸化, 并阻止核因子转位到细胞核与DNA结合, 从而降低巨噬细胞CXCL8和TNF- α 的分泌^[65,87], 抑制因CXCL8引起的宿主过度免疫反应^[88]。天然辣椒素可显著降低大鼠牙周炎模型中TNF- α , IL-1 β , IL-6, NO和IL-12的水平, 还可通过作用于电容性Ca²⁺的内流通道(capacitative Ca²⁺ entry, CCE)而阻断Ca²⁺进入T淋巴细胞, 导致T淋巴细胞因缺乏持续的Ca²⁺信号而无法被激活, 从而抑制宿主免疫反应^[70]。

过度的炎症反应是导致牙周组织被破坏的重要原因, 上述天然植物提取物及其类似物可通过不同途径抑制*P. gingivalis*诱导的宿主炎症反应, 具体表现为降低炎症因子的水平, 抑制免疫细胞的活性及炎症因子对破骨细胞的激活, 进而达到防治牙周炎的效果。值得一提的是, 最近的研究发现牙周炎引起骨髓反应后造血干细胞向超反应性中性粒细胞(neutrophil)分化增

多, 进一步加剧全身或局部的炎症反应, 是牙周炎以及共病发生发展的重要因素^[6]。然而, 目前天然植物提取物针对中性粒细胞作用的研究尚缺乏, 未来可进行深入探究。

2.3 调控破骨细胞与成骨细胞活性

破骨细胞与成骨细胞的相对活性决定着牙槽骨吸收的进程, 活化T细胞核因子(nuclear factor-activated T cell 1, NFATc1)被认为是破骨细胞中必不可少的转录因子, 其产物可驱动破骨基因表达, 包括与破骨细胞融合有关的*Dcstamp*和提高破骨细胞活性的*Ctsk*^[89,90]。化香树叶(*Platycarya strobilacea* leaf, PLE)提取物含有大量鞣花酸(ellagic acid)和没食子酸(gallic acid), 研究表明PLE可以抑制RANKL刺激后宿主细胞中*Nfatc1*, *Dcstamp*和*Ctsk*的表达^[91], 此外, 经PLE处理后的OGPs中碱性磷酸酶(alkaline phosphatase, ALP)活性显著提高^[91]。黄连素(berberine)能通过Wnt/ β -环连素信号通路抵抗*P. gingivalis*对骨间充质干细胞(bone mesenchymal stem cells, BMSCs)成骨相关基因表达的下调, 经黄连素处理后, 编码OSX, COL-1, ALP, OCN和OPN的成骨相关基因表达均明显增加, 宿主成骨更加活跃^[92]。天然辣椒素不仅可抑制炎症因子的分泌, 还可升高抗炎因子IL-10的水平^[70], 刺激成骨细胞分泌破骨生成抑制因子(osteoprotegerin, OPG), 进而干扰RANK和RANKL的结合而抑制破骨细胞的形成^[93,94]。

因此, 上述天然植物提取物除通过降低宿主炎症水平来抑制破骨细胞的活动外, 还可通过其他途径调节宿主破骨细胞及成骨细胞的活性来抑制牙槽骨的吸收。值得一提的是, *P. gingivalis*分泌的牙龈素能够降解OPG, 并增强TNF- α 和IL-1诱导的破骨细胞生成^[95], 故理论上能够抑制牙龈素作用的天然植物提取物也具有抑制牙槽骨吸收的功能^[53]。

2.4 抑制基质金属蛋白酶作用

*P. gingivalis*可促进免疫细胞和黏膜细胞分泌基质金属蛋白酶(matrix metalloproteinases, MMPs), 破坏牙周组织导致牙齿脱落^[96]。MMP-3, MMP-8及部分MMPs均密切参与牙周炎的进展^[97,98]。

车前草(*Plantago*)提取物被证明对*P. gingivalis*有抑菌作用, 同时降低炎症部位MMP-2以及MMP-9的水平^[99]。某种风车子属植物(*Combretum hartmannianum*)

树皮提取物中的黄酮酸二内酯(flavogalonic acid dilactone)和诃子鞣质(terchebulin)能够协同抑制MMPs活性^[100]. 茶黄素能够抑制巨噬细胞分泌MMP-3, MMP-8和MMP-9. 此外, 茶黄素还可以抑制MMP-9的催化活性^[65]. EGCG是MMP-9和MMP-12的有效抑制剂, 其作用机制与酶的构象变化有关^[101]. 黑醋栗提取物(Sublackcurrant extract)及其主要花青素包括矢车菊素-3-O-葡萄糖苷、矢车菊素-3-O-芸香糖苷(cyanidin-3-O-rutinoside)和飞燕草素-3-O-芸香糖苷(delphinidin-3-O-rutinoside), 对MMP-1和MMP-9均有明显的抑制作用, 并呈时间依赖性. 其中, 花青素可能和底物直接竞争或结合远处位点进而改变酶的空间构象^[102]. 虽然部分天然植物提取物可通过抑制宿主分泌MMPs或抑制其活性来保护牙周组织, 但相关研究多集中于表型发现, 缺乏机制的深入探究.

3 天然植物提取物抑制*P. gingivalis*的新策略

3.1 天然植物提取物与抗菌剂联合应用

机械清除菌斑是牙周炎防治的主要方法, 全身或局部使用抗菌药物可作为维持长期疗效的辅助手段. 但随着抗生素的广泛使用, 细菌耐药性增加, 常导致治疗失败甚至引起并发症^[103], 研究者在天然植物提取物与传统抗生素联用领域也做了诸多探索.

绿茶提取物和EGCG分别与甲硝唑(metronidazole)联用时均表现出明显的协同抗*P. gingivalis*作用^[19]. EGCG在细菌细胞膜的脂质双分子层中产生H₂O₂, 导致细胞膜破坏, 胞内物质泄漏^[22], 使抗生素更易进入细菌内部发挥作用而达到协同效果^[104]. 黄芩素(baicalein)具有抗菌抗炎等多种药理活性^[105,106], 实验表明黄芩素与庆大霉素(gentamicin)和氨苄西林(ampicillin)这两种常用抗生素联用时在MIC和最低杀菌浓度(minimal bactericidal concentration, MBC)都有明显的协同抗*P. gingivalis*作用^[107]. 石榴(*Punica granatum*)、哈地丁树(*Commiphora molmol*)和印楝这三种天然植物提取物与防治牙周炎常用抗生素(甲硝唑、阿莫西林、阿奇霉素和四环素)联合使用的协同作用亦被报道^[108].

除抗生素外, 天然植物提取物还可与其他抗菌剂联合使用. 富含多酚的海洋褐藻提取物(polyphenol-

rich extract of *A. nodosum*, ASCOP)具有明确抗炎作用^[109], 沸石捕获Ag⁺形成的复合物称为银沸石(Ag-zeolite), 可增强Ag⁺的抗菌作用. 实验结果显示, 银沸石和ASCOP联合作用时对*P. gingivalis*以及戈登链球菌(*Streptococcus gordonii*, *S. gordonii*)共聚生物膜具有协同抗生物膜作用, 但其机制有待探究^[110].

因此, 天然植物提取物与不同抗菌剂联用时可发挥对*P. gingivalis*的协同抗菌作用, 实际应用时可减少抗生素用量, 降低细菌耐药性, 为今后牙周炎的防治提供一种新思路.

3.2 天然植物提取物与纳米材料联合应用

天然植物提取物具有浓度变化快、作用效果不稳定等问题, 限制了其应用范围和应用场景. 随着纳米载药系统相关研究的不断发展, 其技术也已经应用于天然植物提取物药物缓释方面.

银纳米粒子(silver nanoparticles, SNs)可以提升没药(myrrh)对*P. gingivalis*的抗菌活性^[111]. 这是因为纳米载体表面积大, 可以使没药与*P. gingivalis*接触更广泛, 有助于其更有效地发挥抗菌作用^[112]. 黄芩(*Scutellaria baicalensis*, SB)具有抗炎、抗氧化和免疫调节作用^[113]. 洗必泰(chlorhexidine, CHX)是临床抑制口腔菌斑的常用药, 但使用时有一定的副作用, 如牙齿着色和过敏反应等^[114,115]. SB纳米粒子和CHX纳米颗粒联用时纳米包裹技术可以将抗菌药物输送到特定的生物龕^[116,117], 并通过增加药物与细菌的接触面积提高生物利用度^[118]. 二者联合应用时可减少CHX的用量, 有利于避免单独使用CHX时造成的副作用^[113]. 此外, 利用土荆芥进行绿色合成的氧化锌纳米粒子(zinc oxide nanoparticles, ZnO-NPs)对*P. gingivalis*有显著抗菌作用^[119], 一方面是因为ZnO-NPs体积远小于细菌而更易黏附, 带负电荷的细菌生物膜和带正电荷的纳米粒子之间产生的静电力可破坏细菌的完整性^[120]; 另一方面是因为ZnO-NPs能诱导ROS生成并导致细菌DNA和蛋白质变性^[121]. 此外, ZnO还可释放对细菌有毒性的锌离子, 引起细菌死亡.

综上, 纳米材料因其缓释作用可有效弥补天然植物提取物浓度变化快、作用不够稳定的缺陷. 纳米材料还可将天然植物提取物运送至特定部位发挥作用, 提高药物有效性. 此外, 绿色合成的纳米材料在满足健康理念的同时亦可发挥优越的抗菌性能. 因此天然植

物提取物与纳米材料的联用或许可成为防治牙周炎的一种新型应用策略。

4 现状、局限与展望

牙周炎是一种与全身健康相关的口腔慢性感染性疾病。*P. gingivalis*作为牙周炎的重要致病菌影响着牙周炎的发生发展,因此*P. gingivalis*抗菌治疗是牙周炎的重要防治策略之一。抗生素已普遍应用于临床防治牙周炎,但近年来其局限性逐渐显现,而天然植物提取物因其副作用少、不易产生耐药性且价格低廉等优势受到了研究者的广泛关注。本篇对具有抗*P. gingivalis*功效的天然植物提取物在牙周炎防治中的研究进展作一综述,以期天然植物提取物治疗牙周炎相关研究提供理论基础,丰富牙周炎的防治策略。

天然植物提取物对*P. gingivalis*的抗菌机制是多方面的。天然植物提取物可直接发挥抗菌作用,亦可抑制生物膜的形成或破坏已成熟的生物膜。此外,天然植物提取物能够抑制*P. gingivalis*引起的宿主氧化应激、炎症风暴,牙槽骨吸收以及牙周组织的破坏。同时,天然植物提取物还可与抗菌剂和纳米技术联用。

然而目前研究仍然存在局限性。首先是缺乏有效筛选相关天然植物提取物的方法,其次,目前不少研究仍局限于研究植物提取物这种复杂混合物的作用,还未提取有效成分。此外,药理学和毒理学的相关研究亦缺乏,不少天然植物提取物对*P. gingivalis*的抗菌作用仅有表型报道,但缺乏机制研究的文献,如大黄根提取物(*rheum palmatum* extract, RPE)^[122]、豆蔻(*cardamom*)^[123]和天竺葵(*pelargonium*)^[124]等。药理学为合理用药提供基本理论和科学思维方法,缺乏药理学研究的药物难以进行实际应用。在毒理学方面,天然植物提取物作为药物使用时需关注其安全性,如大剂量长

期摄入黄芩素可引起肾纤维化和肾损伤^[125]。另外,天然植物提取物相关研究的动物实验和临床试验极为不足。考虑到体内外环境的不同以及药物代谢和效应动力学,同种药物在实际应用时的效果可能与体外实验结果不同,因此应进行更多的体内实验,对天然植物提取物的剂型、给药途径、因子调控、药效学和毒副作用等方面进行深入的研究,建立系统、完整、可行的研究方法。

在未来的研究中,应建立有效的天然植物提取物筛选机制。此外,还可利用代谢组学探索天然植物提取物的有效活性成分,对其进行修饰并实现量产。亦可利用基因组学使相关植物基因过表达或反义抑制,以便获得更有效的产物。值得一提的是,最新的研究通过转录组分析发现了更多对*P. gingivalis*侵袭力及生理活动至关重要的蛋白质代谢基因,这些基因或许可成为天然植物提取抗菌的新靶点^[126]。在未来的临床应用中,天然植物提取物适合与传统抗菌剂联用。一方面,牙周炎的预防胜于治疗;另一方面,相比于传统抗菌剂,患者在心理上更易接受来源于植物的“天然提取物”,依从性更好;此外,植物天然提取物安全性高、可长期使用。考虑到以上因素,天然植物提取物尤为适合应用于牙周炎的预防和早期治疗,后期可作为传统抗菌药物之外的日常用药,降低传统抗菌剂的用量,减少耐药性和副作用的产生,最终建立中西医结合的牙周炎抗菌防治策略。

综上,具有抗*P. gingivalis*功效的天然植物提取物在牙周炎防治中的相关研究应进一步深化天然植物提取物的药理学和毒理学研究;展开更多的动物和临床研究;探索天然植物提取物与传统抗菌药物的综合防治以及和纳米技术的结合,中西医结合设计出新的牙周炎抗菌防治策略,为天然植物防治牙周病提供科学依据。

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Role of natural plant extracts with anti-*Porphyromonas gingivalis* function in the prevention and treatment of periodontitis

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Periodontitis is a chronic infectious disease affecting human health. *Porphyromonas gingivalis* is considered to be one of its important pathogenic bacteria. The prevention and treatment of periodontitis targeting *Porphyromonas gingivalis* have attracted much attention from researchers. Traditional antibiotics have long been used in the clinical prevention and treatment of periodontitis, but the limitations of their application must not be overlooked. A variety of natural plant extracts have been reported to have distinct advantages, such as superior antimicrobial activity and low drug resistance, providing new strategies for the antibacterial control of *Porphyromonas gingivalis*. In this study, the effect and mechanism of periodontitis of natural plant extracts with anti-*Porphyromonas gingivalis* effect were reviewed; on this basis, the most recent research progress of combining natural plant extracts with antibacterial agents and/or nanotechnology was included to provide a general idea and theoretical basis for the research on the antibacterial activity of natural plant extracts as well as the prevention and treatment of periodontitis.

periodontitis, *Porphyromonas gingivalis*, natural plant extract, antibiosis

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