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在线全文

天然产物在维护口腔微生态平衡中的研究进展*

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【摘要】 口腔是复杂的微生态系统，为细菌、古细菌、真菌、病毒及原生动物等种类繁多的微生物提供适宜的生存环境。口腔中的微生物群落通过复杂的相互作用和环境适应等形成稳定的微生态系统。健康口腔微环境中各种微生物通过信号交流与物质交换、资源环境的竞争与协作、群体感应、环境适应等方式实现口腔微生态平衡，而失衡的口腔微生态将导致牙体牙髓病、牙周病等口腔疾病发生，甚至影响全身健康。天然产物因其潜在的抗菌、抗炎、抑制生物膜和调节微生态的特点，在维护口腔微生态平衡方面备受关注。本文系统地对天然产物的特性、其调节口腔微生态平衡的机制及在口腔疾病防治中的应用前景及局限性进行综述，为天然产物在维护口腔微生态平衡中的应用提供参考。

【关键词】 口腔微生态 天然产物 口腔疾病 抗菌 微生态平衡 综述

Research Advances on Natural Products in Maintaining Oral Microecological Balance

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[Abstract] The oral cavity is a complex microecosystem that provides a suitable habitat for diverse microorganisms, including bacteria, archaea, fungi, viruses, and protozoa. The microbial communities in the oral cavity form a stable microecology through complex interactions and environmental adaptation. In a healthy oral microenvironment, various microorganisms maintain microecological balance through signal communication, material exchange, competition and cooperation for resources and environmental conditions, quorum sensing, and environmental adaptation. In contrast, an imbalanced oral microecology can lead to oral diseases such as endodontic and periodontal diseases, and may even affect systemic health. Natural products have attracted significant attention for maintaining oral microecological balance due to their potential antibacterial, anti-inflammatory, biofilm-inhibiting, and microecology-regulating properties. This article systematically reviews the characteristics of natural products, their mechanisms for regulating oral microecological balance, and their application prospects and limitations in oral disease prevention and treatment, providing a reference for the use of natural products in maintaining oral microecological balance.

[Key words] Oral microecology Natural products Oral diseases Antibacterial Microecological balance Review

口腔是一个包含了细菌、真菌、病毒等多种微生物的复杂微生态系统[1]。在健康状态下，这些微生物通过信号交流、资源环境竞争与协作等机制维持生态平衡[2]。然而，食物、温度、氧气含量等均可影响该平衡。口腔微生态失衡可引发口腔疾病，还与糖尿病、心脏系统疾病等全身健康问题相关[3]。

目前，口腔感染主要依靠清除病原体及抗生素治疗。但抗生素不当使用会导致口腔微生物耐药性增强[4-5]。因此，寻找安全且经济实惠的替代药物势在必行。天然产物来源于动植物或微生物，具有抗菌、抗炎、抑制生物膜及调节微生态的作用[4-6]，长期以来因其多样功能、成本较低和较高安全性受到关注。本文旨在综述天然产物的特性、其调节口腔微生态平衡的作用机制，以及在口腔疾病防治中的应用前景及局限性，以期为相关研究和临床实践提供参考。

1 口腔微生态失衡与口腔疾病

正常情况下，口腔内的细菌、古细菌、真菌、病毒及原生动物等微生物群处于动态多变的平衡中，形成口腔微生态稳态，共同抵御病原体入侵并维持宿主健康[7]。当外界环境发生剧烈变化或微生物之间的相互作用平衡被打破时，口腔微生态无法保持平衡，可能导致多种口腔疾

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病的发生,包括牙体牙髓病、牙周病、口腔黏膜疾病及口腔肿瘤等。

1.1 牙体牙髓病

龋病的发生与微生物失衡密切相关,这种失衡主要是口腔微生态中产酸耐酸性微生物增多,而共生菌减少引起牙齿硬组织脱矿,进而导致龋病发生[8]。微生物组学结果显示,龋病状态下口腔微生物组的α多样性降低,产酸相关细菌如变异链球菌、乳杆菌、双歧杆菌等构成微生物群落的主体[9]。这些细菌利用糖类化合物合成有机酸,随着有机酸的堆积,耐酸性细菌增加,导致牙齿脱矿形成龋病[10]。当龋病进展到一定程度,细菌及其毒素侵入牙髓组织,引起牙髓感染即牙髓炎或根尖周炎[11]。感染牙髓中,厌氧菌群,如卟啉单胞菌属(*Porphyromonas*)、普雷沃氏菌属(*Prevotella*)等,发挥着重要作用。这些细菌在缺氧环境中大量繁殖,产生内毒素、酶和其他代谢产物,引起牙髓组织的炎症反应、坏死,并可能通过根尖孔扩散到根尖周组织,引发根尖周炎,甚至形成囊肿[12]。粪肠球菌通常在难治性根尖周炎中分离出来,是难治性根尖周炎的主要致病菌[13]。

1.2 牙周病

牙周病是牙周组织长期的慢性感染造成的组织破坏性疾病,包括牙龈炎、牙周炎等疾病。微生物组测序结果显示牙周疾病发生时口腔微生物群落由共生状态转变为致病性失调状态,具体表现为牙龈卟啉单胞菌(*Porphyromonas gingivalis*)、齿垢密螺旋体(*Treponema denticola*)、福塞斯坦纳菌(*Tannerella forsythia*)等炎症相关细菌的增加[14]。这些细菌通过产生毒力因子及彼此之间的协同相互作用引起宿主的免疫炎症反应,增加促炎因子如白介素-6(interleukin-6, IL-6)的产生,从而加剧炎症反应及组织破坏[15]。

1.3 口腔黏膜病

口腔念珠菌病是口腔黏膜最常见的感染性疾病,其中白色念珠菌(*Candida albicans*)是最常见的致病菌[16]。念珠菌常作为共生微生物存在于健康个体中。当机体出现免疫状态受损(如癌症化疗患者、老年人或免疫缺陷者),广泛使用抗生素、唾液腺功能减退、全身性疾病(如糖尿病),不良口腔卫生习惯、饮食习惯及不良嗜好(如吸烟饮酒)时,口腔微生态平衡可能被打破,口腔内的微生物组成发生变化,例如有益细菌减少,而白色念珠菌等机会性病原体增多,从而导致口腔念珠菌病的发生[16-19]。这种失衡不仅涉及细菌群落的变化,也包括真菌群落的变化(即真菌组失调)。放射性口腔黏膜炎患者的口腔黏膜层病变部位的微生物常出现细菌群落的变化,表现为溶血孪生球菌(*Gemella haemolysans*)和缓症链球菌(*Streptococcus mitis*)占主导地位[20]。口腔微生态失衡与口腔溃疡的发生也具有相关性。STEHLIKOVA等[21]研究发现龋齿罗斯菌(*Rothia dentocariosa*)和约氏不动杆菌(*Acinetobacter johnsonii*)与复发性阿弗他溃疡显著相关,在溃疡性样本中毛厌氧杆菌属(*Lachnoanaerobaculum*)、心杆菌属(*Cardiobacterium*)以及纤毛菌属(*Leptotrichia*)和梭杆菌属(*Fusobacterium*)等机会性病原体增加,但唾液链球菌(*Streptococcus salivarius*)、奈瑟球菌属(*Neisseria*)和韦荣球菌(*Veillonella*)减少。

1.4 口腔肿瘤

口腔肿瘤的发生发展与口腔微生态失衡之间存在密切关联,这已成为当前肿瘤研究领域的一个重要焦点[22-23]。研究显示具核梭杆菌(*Fusobacterium nucleatum*)、牙龈卟啉单胞菌(*Porphyromonas gingivalis*)和伴放线菌团聚杆菌(*Aggregatibacter actinomycetemcomitans*)在口腔肿瘤的发生发展中发挥了重要作用[24-26]。口腔微生态失衡可通过改变肿瘤微环境,慢性炎症及免疫抑制,远端效应与菌群迁移,影响肿瘤干细胞特性,产生致癌物质或促进致癌物质的活性等促进包括口腔鳞状细胞癌在内的多种肿瘤的发生、发展及其恶性潜能[22-23, 27-31]。

2 天然产物的特点及功能

天然产物具有生物来源多样性、化学结构多样性与复杂性、生物活性广泛与特异性和环境友好性[32-35]。天然产物独特而复杂的化学结构通常包含多个手性中心、独特的骨架结构和功能基团,使其在化学空间中占据生物学相关性极高的位置,并能与生物大分子相互作用[33]。天然产物具有广泛的生物活性,包括抗菌、抗肿瘤、免疫抑制、抗炎、神经保护、抗氧化和抗糖尿病等作用[34-37]。广泛的生物活性使天然产物成为新型药物开发的重要来源。此外,天然产物的生物活性通常表现出高度的特异性,能够精确地作用于特定的生物靶点[38]。例如,一些二酮哌嗪类生物碱,由于其环二肽亚结构具有结构刚性和抗蛋白水解稳定性,使其成为潜在的医疗应用候选物[39]。基于上述特点,天然产物在药物发现与开发有巨大的潜力,可用于癌症临床治疗(例如紫杉醇)[32, 40],在农业中可作为杀菌剂、除草剂使用[41],在食品工业中作为食品添加剂、防腐剂、香料和着色剂等使用[36, 42-43],在化妆品工业中用于作为香料、护肤成分和护发产品[42],也可以用于开发新型生物材料,并在多种工业过程中发挥作用[36]。因此,天然产物是现代药物发现、农业、食品和化妆品工业以及生物材料开发等领域不可或缺的宝贵资源。

3　天然产物对口腔微生态的调节机制

天然产物通过多种机制对口腔微生态进行调节，从而维持口腔健康或改善口腔疾病状态。口腔是一个包含细菌、真菌、古细菌和病毒等多种微生物的复杂微生态系统，口腔中复杂多样的微生物及其稳态在维持口腔和全身健康中发挥重要作用[1,7]。当口腔微生态平衡被打破出现菌群失调时，可能导致牙体牙髓病、牙周病、口腔黏膜病和口腔肿瘤等，甚至与全身性疾病如心血管疾病、糖尿病、类风湿性关节炎等疾病密切相关[3]。天然产物主要通过抑制致病性微生物、影响微生物黏附及其生物膜形成、维持口腔微生态平衡和调节宿主免疫反应及抗炎作用等机制调控口腔微生态。

3.1　抑制致病性微生物

抑制致病菌的生长是天然产物调节口腔微生态的重要方式。许多天然产物具有广谱或特异性的抗菌活性，能够抑制口腔致病菌的繁殖或破坏其生物膜结构。多酚类化合物如茶多酚含有丰富的表没食子儿茶素没食子酸酯(epigallocatechin gallate, EGCG)，可破坏变异链球菌细胞膜完整性，并与金属离子螯合，抑制细菌代谢关键酶(如葡糖基转移酶)，从而减少菌斑基质合成[44]。MARHAMAH等[45]研究发现黑米麸乙醇提取物作为天然漱口水可抑制变异链球菌和牙龈卟啉单胞菌的生长。BHATTACHARYA等[46]证明丁香和印楝提取物对念珠菌属具有抗真菌活性，能显著抑制念珠菌属的生长。SILVA等[47]的研究结果显示牛至精油和香芹酚可协同抑制变异链球菌的生长，可能是控制生物膜形成的潜在药物。

3.2　影响微生物黏附及其生物膜形成

口腔微生物常以生物膜形式存在于牙齿和口腔软组织表面，生物膜是多种口腔疾病发生发展的重要因素[6]。蜂胶、姜黄素、茶黄素、黄芩苷、红景天等可通过抑制变异链球菌黏附相关基因(*spap*、*gtfs*、*gbps*和*ftfs*等)等抑制变异链球菌生物膜形成和胞外多糖的产生[48-51]。姜黄素抑制白色念珠菌关键黏附素(Als1和Als3)基因表达、新鱼腥草素钠抑制Ras1-cAMP-Efg1通路相关基因、大蒜素抑制 *Hwp1* 基因表达减少白色念珠菌生物膜形成[52-54]。绿茶提取物如表没食子儿茶素没食子酸酯还可通过抑制牙龈卟啉单胞菌与宿主定植相关基因(*FimA*、*HagA*、*HagB*)、组织破坏相关基因(*RgpA*、*Kgp*)和血红素相关基因(*Hem*)等减少*P. gingivalis*的生物膜初始黏附，也可通过抑制硫化氢(H_2S)的产生抑制具核梭杆菌的生物膜形成[55-56]。天然产物对生物膜形成过程不同阶段包括黏附、增殖、成熟和分散等阶段均有抗生物膜作用，具有成为口腔感染性疾病的抗生物膜药物以恢复口腔微生态平衡的前景[6]。

3.3　维持口腔微生态平衡

口腔微环境的pH值、氧气和营养物质等因素都会影响微生物的组成[57-58]。天然产物可能通过改变这些物理化学条件来间接调节口腔微生态。宿主口腔上皮组织产生天然产物如抗菌肽能调节唾液分泌或改变唾液成分，从而影响口腔微生物的生长和代谢[59]。有研究表明茶黄素可显著增加唾液样本中的微生物群落多样性，改变唾液和龈上菌斑的口腔微生物群落组成，降低致病性口腔微生物(例如普雷沃菌属、月形单胞菌属和阿托波菌属)的丰度，同时增加口腔健康相关微生物(例如链球菌属和罗斯菌属)的丰度[60]。六堡茶提取物也被证实具有重构口腔黏膜屏障，促进组织再生，减轻微炎症的功能，改善口腔微环境[61]。LEE等[62]观察到以适当比例混合的天然提取物会影响致病性口腔细菌，而不影响非致病菌，以更温和的方式调节了口腔微生态平衡。

3.4　调节宿主免疫反应及抗炎作用

许多天然产物具有抗炎特性，能够降低由致病菌感染引起的炎症反应，也可以通过调节宿主的局部免疫反应，从而削弱病原菌的感染能力[4]。姜黄素已被证实能通过上调IL-6和肿瘤坏死因子-α(tumor necrosis factor α, TNF-α)等促炎细胞因子的表达增强黏膜免疫反应[63]。天然产物如小檗碱和表没食子儿茶素没食子酸酯可以通过调节巨噬细胞的极化，促进M1巨噬细胞转化为抗炎的M2巨噬细胞来发挥抗炎作用，为治疗口腔炎症性疾病提供了潜在思路[64]。天然产物可通过干预关键的炎症信号通路，如核因子-κB(nuclear factor kappa-B, NF-κB)和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)通路，减少炎症反应对口腔微生态的不良影响。口腔中的微生物群落及其代谢产物对宿主免疫系统也有深远影响，天然产物可通过影响这些微生物代谢产物，间接或直接地调节免疫反应[65]。

4　天然产物在口腔疾病防治中的应用

目前，天然产物已被广泛用于口腔护理产品开发，并在龋病、牙周病、口腔黏膜感染及创面修复等领域开展了大量基础与转化研究。其应用路径总体可归纳为两类：一是作为活性成分直接干预口腔疾病关键环节，例如影响致病菌生长、抑制黏附与生物膜形成、调控局部炎症免疫反应、改善口腔微环境从而促进菌群稳态恢复[66-68]；二是作为载体/递送体系的功能组分或与递送系统联合，实现活性成分在口腔局部的黏附、保护与缓释，提高在复杂口腔环境中的有效暴露时间与治疗效率[69]。基于其化

学结构与来源差异,当前研究较多的天然产物主要包括多酚类、萜烯类与生物碱等。

4.1 多酚类化合物

多酚是植物中广泛存在、至少含有一个酚羟基的化合物,具有突出的抗氧化、抗菌与抗炎特性[68]。在口腔领域,多酚类不仅可直接抑制致病菌及其关键毒力过程(如黏附与生物膜形成),还可能通过降低氧化应激与炎症反应,改善局部微环境并促进微生态稳态恢复。蜂蜜、蜂胶、蜂王浆等蜂产品以及绿茶提取物中的表没食子儿茶素没食子酸酯(EGCG,图1A)、蔓越莓提取物等富含多酚成分,已被添加至牙膏、漱口水、口香糖及膳食补充剂等产品中,用于日常口腔健康维护与龈炎/龋病风险管理[68-71]。

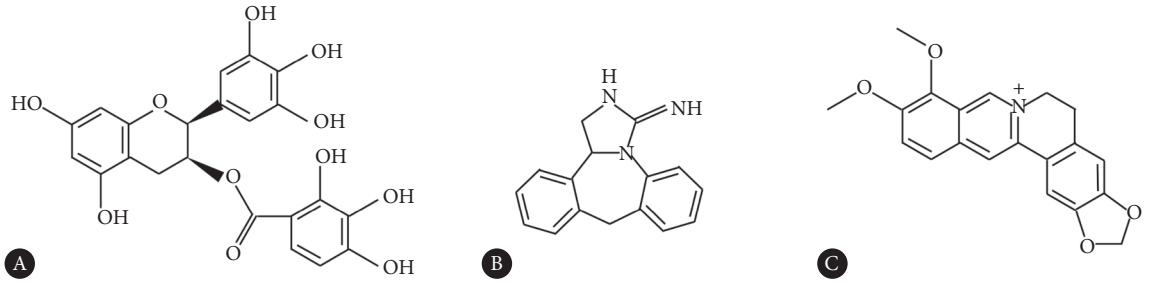

图 1 常见天然产物的化学分子结构

Fig 1 Chemical molecular structures of common natural products

A, Chemical molecular structure of the polyphenol compound epigallocatechin gallate; B, chemical molecular structure of the terpene compound oregano oil; C, chemical molecular structure of the alkaloid berberine.

4.2 萜烯类化合物

萜烯类是精油中常见的主要活性成分,通常具有广谱抗菌、抗炎与抗氧化活性。牛至精油(图1B)、茶树油、薄荷油等含萜烯成分的天然产物已在多种口腔护理产品中应用,并被用于探索对龋病相关菌群及牙周致病菌的抑制潜力[47,66,72]。

4.3 生物碱

生物碱为含氮天然有机化合物,药理活性多样,常见作用包括抗菌、抗炎与镇痛等[66]。ZHANG等[73]研究发现小檗碱(图1C)通过Wnt/β-catenin信号通路参与诱导的骨生成分化,其抗菌作用结合促进骨生成分化作用,使其成为牙周组织再生的潜在药物。此外,云南白药等中药复方制剂中亦含多类天然活性成分(包括部分生物碱成分),在口腔创伤、出血与炎症相关问题的辅助处理方面具有较长应用历史[74]。

4.4 天然产物递送与缓释系统

口腔环境具有高流动性(唾液持续冲刷)、微生物易于定植并形成生物膜屏障、局部免疫炎症反应活跃等特点[75],导致许多天然产物在口腔局部应用时面临停留时间短、稳定性不足、生物利用度低、易被快速清除等问题。为提升天然产物在口腔中的有效暴露与疗效,近年来研究逐渐从“筛选有效成分”拓展到“优化局部递送”,即将天然产物与不同递送体系结合,实现对活性成分的保护、黏附与持续释放,从而增强其在龋病、牙周病及黏膜病等复杂场景下的应用可行性[69,76]。

目前用于口腔天然产物递送的策略主要包括:纳米颗粒与纳米载体、水凝胶体系、天然聚合物薄膜/黏附材料等。其中,水凝胶因生物相容性好、可塑性强且可黏附于口腔黏膜或牙面,能够实现局部持续释放,被认为是口腔给药与创面修复的重要载体方向[77]。例如,LIN等[78]研究将单宁酸增强明胶水凝胶与非精神活性植物大麻素大麻二酚结合,通过控制释放整合单宁酸的抗氧化活性与大麻二酚的镇痛作用,从而促进修复并缓解口腔病变相关疼痛。

除人工合成或改性的材料载体外,植物来源的外泌体样纳米颗粒(plant-derived exosome-like nanoparticles, PELNs)作为富含脂质、蛋白质与RNA等活性分子的天然纳米载体,具有进入哺乳动物细胞并调节细胞活动的能力,在免疫调节、炎症控制、微生物组成调控与组织再生方面显示出潜力;同时也可用于提高药物稳定性与细胞摄取效率,并在牙周炎等研究中呈现抗微生物、抗炎、抗氧化与骨保护等综合效应[79]。总体而言,递送与缓释体系为天然产物在口腔复杂环境中的稳定发挥提供了关键支撑,也为其从基础研究走向产品化与临床应用奠定了技术基础。

5 局限性与挑战

尽管天然产物在维护口腔微生态平衡方面前景广阔,但也面临诸多挑战。首先是天然产物成分复杂,活性成分的分离和鉴定存在技术难度[4]。天然产物的成分组成受产地、生长条件、提取方法等多种因素影响,导致批次间差异大,难以实现标准化生产。虽然天然产物通常

被认为安全性较高,但仍需进行严格的毒理学评估,以确保其长期使用的安全性。许多天然产物在体外和动物模型中表现出良好的药效,但缺乏充分的临床试验数据来支持其在人体中的疗效和安全性,特别是对于复杂口腔疾病的长期管理。针对口腔微生态的临床研究需要大规模、多中心、随机对照试验,以提供强有力的证据支持其有效性。而口腔微生物群落的个体差异性也增加了临床研究的复杂性。

6　展望

未来,天然产物在维护口腔微生态平衡方面的研究将趋向多学科交叉和精准化发展。整合基因组学、宏基因组学、代谢组学、蛋白质组学和生物信息学等“组学”技术,将有助于更全面地解析天然产物与口腔微生物群落及宿主之间的相互作用机制。利用合成生物学和纳米技术,开发智能载药系统,实现活性成分的靶向、缓释和按需释放,提高治疗效果。同时应促进基础研究、临床应用和产业转化之间的协同互作,推动天然产物口腔护理产品的创新和发展。

综上,天然产物通过抗菌、抗炎、调节菌群和抑制生物膜等多种机制,为预防和治疗口腔疾病提供了新的策略,在维护口腔微生态平衡中具有巨大潜力。随着研究技术的不断进步和跨学科合作的加强,天然产物有望成为未来口腔健康管理的重要组成部分,为实现口腔健康和全身健康提供更安全、有效的解决方案。

*　　*　　*

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