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植物提取物治疗牙龈组织创伤愈合的研究进展

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摘 要

牙龈创伤愈合对牙周病和外科手术具有重要意义。牙龈创伤愈合是一个复杂的过程，涉及细胞与细胞外基质的各种成分以及细胞的迁移和增殖。与皮肤创伤相似，牙龈创伤愈合主要经历了止血、炎症、增殖和重塑四个阶段。口腔内的创伤是常见的，然而使用传统的外用药难以保护创口，容易使创伤部位受到微生物感染而进一步加剧。近些年来，科学家们一直在开发使用天然植物提取物作为外用药物治疗牙龈创伤，是目前治疗牙龈组织创伤愈合的研究热点。本文就目前用于治疗牙龈创伤常用的植物提取物类药物作一综述。

关键词

牙龈，创伤愈合，植物提取物，外用药物

Advances in the Treatment of Gingival Tissue Wound Healing with Plant Extracts

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Abstract

Gingival wound healing is of great importance in periodontal disease and surgery. Gingival wound healing is a complex process involving cells with various components of the extracellular matrix as well as cell migration and proliferation. Similar to skin wounds, gingival wound healing under-

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goes four main stages: hemostasis, inflammation, proliferation, and remodeling. Because wounds in the oral cavity are common, however, it is difficult to protect the wounds using traditional topical medications, which can easily further aggravate the wound site by microbial infection. In recent years, scientists have been developing the use of natural plant extracts as topical agents for the treatment of gingival wounds, which is currently a hot research topic in the treatment of gingival tissue wound healing. In this paper, we present a review of the plant extracts commonly used for the treatment of gingival wounds.

Keywords

Gingiva, Wound Healing, Plant Extracts, Topical Medicine

1. 引言

创伤愈合药物的研究是现代生物医学科学的一个发展领域[1]。许多药物，如干扰血栓形成或血小板功能、炎症反应和细胞增殖的药物，都有能力影响伤口愈合[2]。但仍然缺少可以直接改善创伤愈合的口服药物，在现有的多数口服药物的作用是在辅助伤口，如疼痛管理、感染缓解和营养改善。这一点导致全身用药对于创伤愈合的疗效仍然存在不确定性[3]。因此药物的局部使用在创伤治疗方面的应用越来越受到人们的重视，不仅能够减少其潜在毒性，更能最大限度地发挥药物有效成分的作用。

随着科技发展，人们对天然植物的价值及其利用性的关注度越来越高[4] [5]，针对药用植物中的活性物质的开发与应用进行了更多的研究。许多植物提取物中发现并提取了能促进皮肤创伤愈合的活性物质[6]。当前，国内外药用植物对创伤的治疗主要以皮肤创伤的治疗为主，少有研究者将药用植物应用于牙龈组织创伤愈合的治疗中。然而，口腔与饮食及言语等功能密切相关，口腔颌面创伤更是常见的口颌疾病[7]，其中牙周组织的创伤尤其在牙周手术后牙龈的创伤极为常见，这些创伤不仅给患者带来痛苦，同时也对患者的正常的生活带来诸多不便，因此通过治疗引导创伤的早期、高质量愈合就显得更加重要，为研究者将药用植物局部应用于牙龈组织创伤愈合提供了研究前景。本文简述牙龈组织创伤愈合的基本生物学过程，并就近十年热点研究的用于牙龈组织创伤愈合的药用植物作一综述。

2. 牙龈组织伤愈合生物学过程

创伤愈合(wound healing)是一个复杂的过程，有多种因素参与。创伤形成后，组织损伤愈合大致经历止血期、炎性反应期、增殖期、组织重塑期 4 个阶段[8]。2014 年第十届欧洲牙周病研讨会第一组共识报告指出口腔黏膜软组织的创伤愈合与皮肤创伤愈合相同，同样遵循四个阶段的愈合模式[9]。

随着创伤的形成，修复过程立即开始[8]。首先，创伤处的血小板与暴露的胶原纤维接触，释放凝血因子止血的同时，在血清中释放各种生长因子、细胞因子和低分子量化合物。在此过程中，血管破裂时由交联纤维蛋白和细胞外基质蛋白组成的血凝块，为入侵的微生物提供载体，同时成为愈合过程后期所需的生长因子的储备。受伤后数小时内，血小板所释放的信号因子刺激炎性细胞侵入创伤组织。进入创伤组织后，中性粒细胞首先死亡，接着是单核细胞和淋巴细胞[10]。它们产生各种各样的蛋白酶和活性氧，作为对污染微生物的防御，并吞噬细胞碎片、坏死组织及异物等。除了这些防御功能外，炎性细胞同样也是生长因子和细胞因子的重要来源，它们启动创伤修复的增殖阶段。增殖阶段开始于边缘角质形成细

胞的迁移和增殖，然后是伤口附近皮肤成纤维细胞的增殖。这些细胞随后迁移到临时基质中，并沉积大量的细胞外基质。新血管的张入，神经在伤口边缘扩张，此时形成的伤口结缔组织被称为肉芽组织。最后阶段创伤组织发生从肉芽组织到成熟组织的转变，与此同时创伤修复进入重塑期其特征是持续的胶原合成和胶原分解代谢。这一阶段需要经历相当长的时间，伤口外观可能出现疤痕组织[11] [12] [13] [14]。

近年来伴随学界对口腔组织创伤愈合的研究进一步发展，有研究指出口腔黏膜创伤愈合比皮肤愈合质量更高、速度更快[11]。并提供其可能的原因包括：与皮肤成纤维细胞相比，培养的牙龈成纤维细胞增殖性更强[15]，牙龈和粘膜创伤的炎症较皮肤创伤的炎症更为短暂[16] [17]，同时与皮肤角质形成细胞相比，口腔角质形成细胞表达的血管内皮生长因子水平降低，使得口腔伤口的血管生成反应更低，这种差异可能是有利的[18] [19]。

3. 促进牙龈组织创伤愈合的药用植物

3.1. 花青素(Anthocyanin)

花青素是存在于水果和蔬菜中的天然水溶性多酚。花青素的健康促进作用主要与氧化应激抑制和肠道微生物群调节有关[20]。含有花青素的局部凝胶被证明在口腔损伤中具有潜在的抗炎和癌症化学预防作用[21] [22]。一项细胞实验通过使用膳食来源的花青素开发为花青素复合物(Anthocyanin Complex, AC)，并配制成 AC 非离子表面活性剂的囊泡凝胶，可以促进非人类牙龈成纤维细胞的胶原生成，证明其在活体研究中的局部愈合作用[23]。此团队同样在动物实验中研究 AC 非离子表面活性剂的囊泡凝胶对 Wistar 大鼠口腔创伤的愈合特性，发现在创伤第 3 天后伤口大小，并在第 5 天时实现了 100%的伤口愈合。再次揭示了 AC 非离子表面活性剂的囊泡凝胶的伤口愈合潜力。局部应用 AC 非离子表面活性剂的囊泡凝胶显示出抗炎作用，并促进了大鼠口腔伤口的闭合，激活受伤区域内的成纤维细胞并加速伤口愈合[24]。

3.2. 姜黄素(Curcumin)

姜黄素主要从姜黄根茎中分离提取，因其具有多种治疗功效而备受关注，可在多种医学领域中发挥有益的作用[25]，包括抗氧化、抗菌、抗炎、抗癌、神经保护和辐射防护特性等[5] [26] [27] [28] [29]，尤其是用于愈合伤口[30]。在动物模型和临床研究中，姜黄素已显示出对皮肤创伤愈合的促进作用。姜黄素促进了大鼠皮肤伤口中成纤维细胞的增殖，并提高了抗氧化酶的水平，此外，姜黄素增强了大鼠皮肤创伤中胶原的产生，并减少了基质金属蛋白酶-9 的产生[31] [32] [33]。Lim [34]等发现姜黄素加速了兔子上唇龈粘膜溃疡的愈合，证实了姜黄素的局部应用促进了口腔溃疡的伤口愈合过程，然而在口腔伤口愈合过程中姜黄素对细胞的反应仍不清楚。Rujirachotiwat [35]等使用体外人牙龈成纤维细胞伤口愈合模型，发现姜黄素通过上调 TGF-β1、TGF-βRI、TGF-αRII 和 VEGF 的表达，其中 ERK 通路在此过程中起到不可或缺的作用。这些研究结果为姜黄素在创伤愈合中的应用提供的有力依据。因为近期的研究集中在创建姜黄素的新型药物输送系统[30]，通过使用纳米[36] [37]、水凝胶[38] [39]等材料及巨噬细胞外泌体[40]负载的方式增强姜黄素分子在治疗靶向中的作用。

3.3. 石榴皮提取物(Pomegranate Peel Extract, PPE)

石榴是原产于中东的石榴科的一种，是一种公认的民间药材，主要种植于伊朗、印度、美国以及大部分的近东和远东国家。在许多文化中，它被用于传统医学中的痢疾、腹泻和口腔炎的治疗[41]。最近的研究表明，石榴由于其抗癌、抗菌、抗炎和抗氧化特性，在治疗多种疾病方面显示出优势[42]。石榴的果实外果皮(果皮)特别富含可水解鞣质，尤其是安石榴甙，它是一种大分子由没食子酸和鞣花酸通过葡萄糖部分连接而成[43] [44]。这些化合物被认为是石榴理想药用特性的主要生物活性来源，包括其皮肤伤口愈

合功效[45] [46] [47] [48]。Celiksoy [41]等评估了 PPE 促进牙周疾病或创伤所致口腔伤口愈合的潜力。实验结果表明安石榴甙不仅表现出抗氧化能力，同时也提高了迁移过程中成纤维细胞的速度和行进距离。Zhang [49]等通过研究 PEE 对烧伤创面愈合的影响，对其促进愈合机制进行了进一步探究，结果表明 PPE 可能是通过上调 TGF-β1 和 VEGF-A 的表达，最终加速皮肤创面愈合。

3.4. 橙皮油素(Aurapene, AUR)

橙皮油素是自然界中最丰富的异戊烯氧基香豆素。它已从芸香科(Rutaceae family)集中下属植物中分离出来，包括几种可食用的水果和蔬菜，柑橘类水果、胡萝卜和芹菜。虽然橙皮油素早已为人所知，但仅在过去十年中，才发现橙皮油素是一种高度多效性的分子可以调节控制炎症、细胞生长和凋亡的细胞内信号通路[50]，同时作为口服活性癌症化学预防剂、抗菌剂、抗原虫剂、抗真菌剂、抗炎剂和抗氧化剂等有价值的药理作用[51]。Marquis [52]等通过实验发现橙皮油素可以抑制牙龈卟啉单胞菌的生长，同时剂量依赖性地减少脂多糖(LPS)诱导的巨噬细胞分泌细胞因子 IL-8 和 TNF-α，由此证明了其具有抗菌性和抗炎性。Vu Dang La [53]等，研究确定橙皮油素具有治疗牙周病的潜力，同时橙皮油素在体外通过增加使用牙龈成纤维细胞迁移的能力显示出显著的伤口愈合效果，证明橙皮油素具有促进伤口愈合和控制牙周疾病的前景。

3.5. 鳄嘴花(Clinacanthus Nutans)

鳄嘴花在传统医学中被用于治疗癌症、疱疹、糖尿病、痢疾、皮疹和蛇咬伤[54]。一项体外实验研究发现鳄嘴花显示出抗炎活性[55]。此外，据报道鳄嘴花具有抗氧化作用[56]及抗微生物作用[57]。在临床研究中，鳄嘴花减少复发性阿弗他溃疡愈合时间[58]，这一发现表明。鳄嘴花可能影响伤口愈合过程中的细胞迁移。Roeslan [59]等从鳄嘴花页的氯仿提取物中分离出一种纯化合物 P18PE，研究发现 P18PE 具有抗炎、体外创伤愈合和抗生物膜活性。在体外细胞实验中，低浓度 P18PE 可以显着诱导人牙龈成纤维细胞的创伤闭合，同时显着抑制 LPS 诱导的巨噬细胞中的 NO 产生。高浓度 P18PE 对变形链球菌生物膜形成具有显著的抑制作用。Aslam [60]等，提出鳄嘴花中的黄酮类化合物可以增加其抗氧化活性，加快伤口收缩速度，并与其他生物活性化合物协同作用，是使鳄嘴花起到促进创伤愈合作用的关键成分。与此同时，2022 年 Ban [61]等在体外实验中发现，鳄嘴花对人成纤维细胞的愈合具有显著促进作用。

3.6. 大麻二酚(Cannabidiol, CBD)

大麻属植物，包括大麻和大麻亚种[62]。CBD 是大麻植物的一种非欣快成分，已在体内和体外模型中被证明具有抗炎作用[63] [64]。据报道，CBD 已经完全抑制了诱导型一氧化氮合酶(iNOS) [65]和一氧化氮(NO) [66]、TNF-α [67]的产生。2022 年 Kongkadee [68]等，通过体外细胞实验评估两种大麻提取物的抗炎和牙龈创伤愈合活性，研究表明 CBD 可以抑制细胞中 TNF-α 和 IL-1β 的产生，并促进牙龈成纤维细胞的伤口愈合，对治疗口腔炎症和溃疡及创伤愈合方面具有潜在益处。然而，由于 CBD 高亲脂性及化学不稳定性影响了其在促进创伤愈合中的临床应用，因此近年来研究者们从材料学的角度试图寻找应对的方式。Zhang [69]等制作出一种含有 CBD 的水凝胶敷料，在体内研究中该水凝胶通过控制炎症浸润、促进胶原蛋白沉积并有利于血管形成，从而显着促进伤口愈合过程。与此同时对于 CBD 与纳米材料的联合应用也有了进展，一项体外实验中与 CBD 相结合的药物载体纳米颗粒在创伤形成各前 6 小时显著促进了伤口的愈合[70]。同时实验发现纳米乳液可以增强 CBD 的稳定性和生物活性[71]。

4. 展望

创伤发生时急性炎症对于启动细胞向伤口部位的募集和诱导导致修复的因子的表达是必要的。虽然

正常愈合需要短暂的炎症，但长期的炎症限制了修复过程。因此感染控制对于未受干扰的口腔伤口愈合十分重要，是将炎症阶段转移到增殖阶段的先决条件。天然植物提取物作为药物，通常作用于愈合的炎症及增殖这两个阶段。具有良好的抗炎、抗氧化、抗菌能力，同时对牙龈成纤维细胞细胞的迁移、增殖产生影响，从而促进牙龈组织创伤愈合。尽管目前针对牙龈创伤愈合的天然植物提取物药物研发较少，对其作用机制的研究尚不深入，开发和利用天然植物提取物作为外用药物治疗牙龈组织创伤有相当大的空间。近年来对于新型生物材料与药物联合使用，试图解决此类药物化学稳定性不佳、生物利用度较弱等问题，为天然植物提取物类药物的使用提供了更大的临床应用空间。

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