

DOI: 10.12287/j.issn.2096-8965.20260301

·口腔微生态与组织修复专题·

纳米氧化铜在口腔医学中的应用

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【摘要】铜基纳米粒子因独特的理化性质和生物学活性, 已成为生物医学领域的研究热点之一。在既往的研究中, 铜基纳米粒子已被证实具有广泛的抗菌、抗真菌和抗病毒的活性。其抗菌机制在于改变细胞膜结构、增加细胞膜通透性等使细菌死亡。基于上述特性, 纳米氧化铜被应用于口腔医学的多个亚专科领域, 如引导组织再生膜、活动义齿丙烯酸树脂、种植治疗的钛涂层、正畸粘接材料中均可见氧化铜纳米粒子在其中发挥重要作用。然而, 纳米氧化铜的生物安全性始终存在显著争议, 需进一步开展系统性研究, 其对环境的影响亦有待评估。本文综述了纳米氧化铜在口腔医学领域的抗菌应用, 重点介绍了其抗菌机制、潜在应用和临床治疗中的安全性。

【关键词】纳米氧化铜; 抗菌机制; 口腔医学; 临床应用; 生物安全性

中图分类号: R318.08, R780.2

文献标识码: A

文章编号: 2096-8965 (2026) 03-0001-09

Applications of copper oxide nanoparticles in stomatology

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【Abstract】 Copper-based nanoparticles are a research hotspot in the biomedical field owing to their unique physicochemical properties and biological activities. Previous studies have demonstrated that copper-based nanoparticles possess a wide range of antibacterial, antifungal and antiviral properties. Their antibacterial mechanism involves altering the cell membrane structure and increasing its permeability, ultimately leading to bacterial cell death. Based on these properties, copper oxide nanoparticles are used in various subspecialties of stomatology, including guided tissue regeneration membranes, removable denture acrylic resin, titanium coatings for implant treatment, and orthodontic adhesive materials, among which copper oxide nanoparticles play an important role. However, the biosafety of copper oxide nanoparticles remains highly controversial and warrants further systematic investigation, and their environmental impact requires further assessment. This article summarizes the antibacterial application of copper oxide

收稿日期: 2026-06-23; 修回日期: 2026-08-25

基金项目: 宁夏回族自治区中央引导地方科技发展专项项目 (2024FRD05108); 宁夏临床病原微生物重点实验室开放课题项目 (2025-04)

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nanoparticles in the dental field, focusing on their antibacterial mechanism, potential applications and safety in clinical treatment.

【Keywords】 Copper oxide nanoparticles; Antibacterial mechanism; Stomatology; Clinical application; Biosafety

0 引言

近年来, 纳米技术在科学和技术领域被广泛研究, 其中金属及金属氧化物纳米粒子因独特的理化性质在材料和生物学方面备受重视, 铜纳米粒子作为代表性材料位列其中^[1-2]。因纳米氧化铜 (Copper Oxide Nanoparticles, CuO NPs) 表面积与体积比较大, 所以 CuO NPs 在低浓度下具有着显著的抗菌活性^[3]; 同时, 相较于银、金等贵金属纳米粒子, CuO NPs 具有成本低、细胞毒性低等优势^[4]。基于以上特点, 铜纳米粒子具有潜在的生物学应用, 如药物输送、医学成像和分子诊断^[5]; 在治疗领域也被广泛应用: 如外科网片、人工关节置换物、伤口敷料以及促进伤口愈合的药物的制造^[6]。

口腔作为一个复杂的微生态系统, 栖息着种类繁多的细菌、真菌等微生物。在口腔临床实践中, 义齿修复、树脂充填、正畸矫治及种植手术等操作, 往往因材料表面细菌黏附和生物膜形成引发继发感染或治疗失败。因此, 基于 CuO NPs 优异的抗菌性能, 研究者尝试将其掺入各类口腔材料中, 以提升材料的抗感染能力。目前, CuO NPs 已被应用于聚甲基丙烯酸甲酯 [Poly (Methyl Methacrylate), PMMA] 义齿基托、复合树脂充填体、根管冲洗液、正畸粘接剂、牙周引导组织再生膜以及种植体钛涂层等多

个方向^[7]。

尽管相关应用研究日益增多, 但现有文献多聚焦于具体材料的性能测试^[1-2], 尚缺乏对 CuO NPs 在口腔医学中抗菌机制与应用进展的系统性梳理。基于上述现状, 本文梳理 CuO NPs 的抗菌作用机制, 分别从口腔修复、牙体牙髓、正畸、牙周几个方向整理现有研究, 同时讨论该材料的生物安全问题, 供后续相关研究作参考。

1 CuO NPs 的抗菌机制

铜是一种成熟的抗微生物和抗炎剂, 具有悠久的药用历史^[8-9]。纳米级粒子的高表面积特性使铜纳米粒子具有广谱抗菌和抗病毒性。CuO NPs 可能具有与其他金属纳米颗粒相似的作用模式。目前, CuO NPs 的抗菌机制尚无统一定论。但已有研究提出了3种主要假设 (如图1所示)。第一种假设认为: CuO NPs 通过在细菌膜表面聚集, 并改变细胞膜的渗透性, 同时去除膜蛋白、脂多糖及细胞内生物分子, 导致质膜周围的能量代谢紊乱^[10-12]。第二种假设认为: CuO NPs 以纳米颗粒或释放离子的形式诱导氧化应激, 使细胞内活性氧 (Reactive Oxygen Species, ROS) 生成增多, 进而损伤细胞结构^[13-16]。第三种假设机制则强调, CuO NPs 被细胞摄取后, 可干扰细胞内三磷酸腺苷的产生并抑制 DNA 复制,

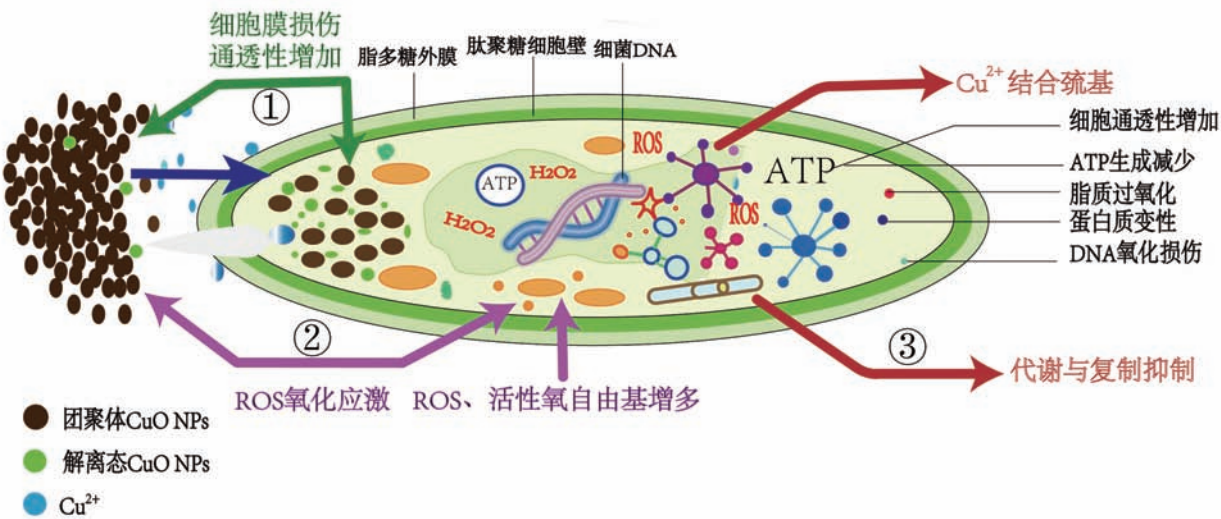


图1 CuO NPs 的多重抗菌机制示意图
Figure 1 Schematic diagram of the multiple antibacterial mechanisms of CuO NPs

最终导致细菌死亡^[17-19]。

在上述假设的基础上,更细致的机制解析如下:带正电荷的铜离子首先被带负电荷的细菌(革兰阳性菌为细胞壁磷壁酸中的磷酸基团,革兰阴性菌为外膜脂多糖中的磷酸基团与羧基)吸引并结合,使细胞膜通透性发生改变,铜离子得以进入胞内。进入细胞后,铜离子可与含磷或含硫的大分子(如DNA)结合,改变核酸结构与相关蛋白功能,从而抑制生化过程并引发细胞死亡^[20-21]。此外,铜离子还可以干扰DNA或蛋白质的合成,使关键酶失活,并促进过氧化氢产生,纳米颗粒则通过与巯基相互作用^[22],诱导蛋白质分子变性,导致DNA、核糖核酸、蛋白质及胞质内容物外泄,加剧细胞损伤。除上述途径外,部分研究^[23]还提示可能存在其他相互作用模式,如膜脂的过氧化、蛋白质组装抑制及核酸变形等,但具体机制尚待进一步研究证实。

除抗菌作用外,CuO NPs的抗病毒潜力亦受到关注,尽管相关研究相对有限。已有证据表明,CuO NPs在病毒包膜或衣壳中可诱导类似ROS氧化损伤^[24]。由于病毒缺乏修复机制,其遭受损伤后无法恢复,往往立即失活,这一特性被称为“接触杀灭”。基于此,研究者尝试将CuO NPs功能化于材料表面,以构建兼具抗菌与抗病毒性能的复合涂层,拓展其在医疗器械及口腔材料中的应用。

2 CuO NPs在口腔科中的应用

2.1 在口腔修复学中的应用

口腔修复学是口腔医学的重要组成部分,与材料科学密不可分,修复体主要包括固定义齿和可摘局部义齿,常用材料涉及金属、树脂和陶瓷材料三大类^[25]。然而,金属修复材料在口腔环境易被腐蚀,释放金属离子影响口腔健康^[26]。树脂基材料存在聚合收缩、边缘微渗漏及老化等问题^[27]。陶瓷材料虽兼具美观性、耐磨性和生物相容性,被认为是目前口腔修复材料中最有前景的修复材料^[28],但上述材料均存在口腔微生物黏附引发的继发感染风险。

为此,研究^[29]尝试将CuO NPs掺杂进各类修复材料中以增强其抗菌性能。例如,将CuO NPs掺杂进纳铝硅酸盐陶瓷后,铜离子可持续释放,通过影响膜通透性、破坏呼吸链活性及干扰基因复制,从而杀灭变形链球菌;将CuO NPs掺杂进PMMA义齿基托材料,对金黄色葡萄球菌和白色念珠菌有一定抑制作用,但同时会对材料颜色产生不利影响^[30]。Giti等^[31]发现,在PMMA中分别加入CuO NPs和纳米

氧化钛(Titanium Dioxide Nanoparticles, TiO₂ NPs),均可显著提高对唾液链球菌、血链球菌和都柏林念珠菌的抗菌活性,且CuO NPs对变形链球菌的抑菌效果优于TiO₂ NPs。

软义齿衬垫作为一种弹性材料,置于义齿下方起减震作用,使咬合力均匀分布于支持组织^[32]。然而,真菌和细菌微生物易在衬垫表面附着并堆积^[33-35]。因此,Ansarifard等^[36]将浓度为500 µg/mL的CuO NPs添加至软衬材料中,结果显示其对白色念珠菌的抑制率可达75%,且呈现剂量依赖。此外,使用CuO NPs填充物还可以作为抛光剂减少磨损、修复邻近牙齿^[37-38]。综合上述研究,将CuO NPs掺杂至陶瓷、PMMA义齿基托及软衬材料中,可有效提升材料抗真菌、抗细菌能力;但材料变色、铜离子持续释放带来的体内风险尚缺少足够数据支撑。

2.2 在牙体牙髓病学中的应用

龋病是最常见的口腔感染性疾病之一,若未及时治疗,可引发牙髓及根尖周病变。口腔感染发病率高、医疗负担重,对患者口腔功能及全身健康均产生不利影响。目前,龋病治疗通常是在彻底清理污染后采用牙色修复材料进行充填,抗感染辅助手段包括激光、抗生素及漱口水等,并已取得一定疗效^[39]。然而,上述方法往往依赖经验丰富的医师及专业设备,且长期使用抗生素可能导致菌群失调及耐药性产生。

研究^[40-42]表明,CuO NPs在龋病预防、充填修复、根管治疗及牙本质粘接等多个环节均表现出潜力。在龋病预防方面,唾液铜浓度与龋病活性呈负相关,CuO NPs能选择性抑制变形链球菌等致龋菌的生长与生物膜形成,同时对口腔其他菌群影响较小,有利于维持口腔微生态平衡。在充填修复材料中,CuO NPs加入玻璃离子水门汀后,可显著增强充填材料对多种耐药菌的抗菌活性,且其压缩强度未见明显改变^[43-45]。在根管治疗领域,CuO NPs不仅提升了三氧化矿物聚合物的抗压强度与抗菌性能,还对氢氧化钙耐药的多菌种根管内生物膜表现出持续抗菌效应^[46-47]。此外,含CuO NPs的牙科粘接剂能通过抑制基质金属蛋白酶活性,在酸蚀牙本质上形成稳定的混合层,长期维持粘接强度^[48]。

综上所述,CuO NPs在龋病预防、修复体抗菌改性、根管消毒及牙本质粘接强化等方向都有研究潜力。但现有结论大多来自体外实验,还缺少临床试验来检验实际治疗效果与体内安全性。

2.3 在口腔正畸学中的应用

口腔正畸学已有百余年的发展历史,越来越多

的人选择正畸治疗以改善美观和功能。然而，固定矫治器易致菌斑滞留和牙齿脱矿，主要原因为牙菌斑的生成^[49]。托槽与弓丝之间的摩擦力也会消耗部分矫治力，降低矫治效率^[50-51]。不锈钢托槽和弓丝之间的摩擦系数较高^[52-53]，会降低治疗效率^[54]，且不锈钢易附着唾液蛋白质^[55-56]，促进牙菌斑和链球菌附着，并最终引发龋齿^[57-59]。因此，迫切需要找到具有适宜摩擦力和抗菌性能的材料。

研究^[60-61]发现，CuO NPs具有良好的抗菌性能，在正畸领域也有着广泛研究。如在粘接剂方面，CuO NPs作为纳米填料加入正畸粘接剂后，可在不降低剪切粘接强度的前提下提高材料抗菌性能^[62-63]。在用于固定保持器粘接的流动复合树脂中掺入2%~4% CuO NPs后，粘接强度仍远超临床可接受的阈值^[64-65]。此外，含CuO NPs的粘接剂还能通过抑制基质金属蛋白酶活性，在牙本质上形成稳定的混合层，2年后仍保持粘接强度与纳米渗漏值稳定^[65-67]。

在托槽涂层方面，氧化铜-氧化锌及银-氧化铜混合纳米涂层托槽的抗菌性能显著优于未涂层托槽^[68]。CuO NPs涂层托槽对变形链球菌的抑制率达87.6%，对嗜酸乳杆菌的抑菌率为68.9%，并能抑制变形链球菌、金黄色葡萄球菌和白色念珠菌的定植，但可能使托槽颜色变暗，需考虑美学问题。Mobeen等^[69]采用喷雾热解法在正畸托槽表面制备CuO NPs涂层，通过人工唾液浸泡实验评估铜离子释放行为，证实其释放浓度始终低于人体毒性阈值，初步验证了CuO NPs涂层托槽的体内应用安全性。在复合材料方面，将铜引入氮化钽薄膜形成的钽铜氮薄膜兼具优异的机械摩擦性能、生物相容性及抗菌能力^[70-72]。

综上所述，CuO NPs改性正畸粘接剂、托槽涂层的效果得到体外证实。但弓丝改性相关研究较少，涂层耐久度、合适添加浓度以及托槽变色的美学问题，仍需要更多实验探索。

2.4 在牙周病学中的应用

慢性牙周炎是常见的口腔疾病，初期临床表现

主要为牙龈红肿，若未及时治疗可进展为牙齿松动、移位、牙周溢脓等，对患者身心均产生不良影响，其主要致病因素为牙菌斑生物膜。此外，研究^[73]发现口腔微生物与全身感染密切相关。目前牙周病的治疗主要包括去除刺激物（龈上洁治、龈下刮治、根面平整等）及局部应用抗生素，但慢性牙周炎的治疗仍面临挑战。

近年来，CuO NPs在牙周病学领域展现出良好的应用前景，相关研究涉及抗菌治疗及组织再生等多个方面^[74-79]。在抗菌应用方面，CuO NPs对病原菌的生长具有显著的抑制作用，而对有益共生菌的影响甚微，不仅能预防生物膜的形成，还能破坏已形成的成熟生物膜^[41]。以针叶樱桃为媒介的绿色合成CuO NPs凝胶对糖尿病及非糖尿病患者的牙周炎均表现出抗菌活性^[79]，但植物提取物成分复杂，可能干扰对纳米粒子本身抗菌机制的判断，因此批次间稳定性和可重复性也是未来需要关注的问题。除抗菌作用外，CuO NPs还能增强牙周膜成纤维细胞的增殖能力^[76]，为牙周组织再生提供了新的思路。

在此基础上，含铜纳米颗粒的复合材料也受到广泛关注。氧化铜-镁纳米颗粒的协同抗菌和药理特性能够有效针对多种口腔病原体 and 癌细胞，抑制其存活并促进细胞死亡，同时能够减轻氧化应激，从而防止与口腔疾病相关的细胞损伤和炎症^[80]。氧化铜-银纳米颗粒对金黄色葡萄球菌、肺炎克雷伯菌和白色念珠菌具有抑制作用，且效果要优于单独银纳米颗粒和铜纳米粒子，并表现出一定的抗病毒活性^[81]。采用佩奇尼法合成的纯的及锆掺杂的CuO NPs研究^[82]表明，随着锆浓度的增加，纳米颗粒的抗菌活性增强，其机制涉及纳米颗粒与细菌膜的直接相互作用、铜离子释放以及ROS的生成。上述研究说明CuO NPs对牙周致病菌有抑制效果，对牙周组织再生也有一定作用，但复合材料的体内安全性、实际临床效果还有待更多研究去证实。

为直观比较CuO NPs在口腔各亚专科的应用差异，从应用材料、主要效果及局限性3个维度进行汇总（见表1）。

表 1 CuO NPs 在口腔不同学科应用场景的总结对比

Table 1 Summary and comparison of CuO NPs applications in different dental specialties			
学科	代表应用材料	抗菌效果	主要局限性
口腔修复学	钠铝硅酸盐陶瓷、PMMA 义齿基托、软义齿衬垫	释放 Cu ²⁺ 杀灭多种致病菌, 抗白色念珠菌(抑制率≥75%, 剂量依赖); CuO NPs 对变形链球菌抑菌效果优于 TiO ₂	高浓度易变色; Cu ²⁺ 长期释放动力学不明; 体内安全性数据缺乏

续表

学科	代表应用材料	抗菌效果	主要局限性
牙体牙髓病学	玻璃离子水门汀、三氧化矿物聚合物、牙本质粘接剂、根管制剂	抑制致龋菌,改善充填材料抗菌性;强化根管消毒;稳定牙本质粘接	以体外实验为主;最佳剂型、浓度不明确;缺乏临床验证
口腔正畸学	正畸粘接剂、流动复合树脂、托槽涂层、钽铜氮薄膜	提升粘接剂抗菌能力;托槽涂层高效抑菌;钽铜氮薄膜优化摩擦性能,铜离子释放低于毒性阈值	弓丝涂层研究较少;涂层长期稳定性及机械性能未验证
牙周病学	CuO NPs凝胶、复合纳米颗粒(氧化铜-镁纳米颗粒、氧化铜-银纳米颗粒、钯掺杂的CuO NPs)	抑制牙周致病菌,对有益共生菌影响甚微;破坏成熟生物膜;复合材料可协同抗菌	复合纳米材料免疫原性及远期安全性未知;掺杂比例待优化

注:数据来源:口腔修复学^[25-38];牙体牙髓病学^[39-48];口腔正畸学^[49-72];牙周病学^[73-82]。

3 CuO NPs的安全性评价

尽管 CuO NPs 在牙科领域的应用前景广阔,但生物安全性始终制约其发展。铜是一种必需的微量元素,缺乏会导致人类患多种疾病。在生理条件下,铜离子起着辅助因子的作用,参与着重要的氧化还原反应。但是,如果铜的摄入量超过耐受限度,就会诱导氧化应激产生毒性作用,导致细胞损伤甚至死亡^[83]。目前对于 CuO NPs 的毒性研究大多局限于体外研究。多项细胞实验已经证明,含铜纳米粒子对多种细胞系表现出毒性作用,其毒性与浓度、粒子大小及表面特性相关^[84-85]。但是体内毒性只有少量报道^[86-87],长期暴露相关数据缺乏。

初步研究^[88-89]表明,CuO NPs 对人类和环境均存在一定毒性。虽然铜在人体内处于稳定状态,但过量的铜离子会对肾脏和肝脏产生毒性作用,诱发器质性损伤^[89-90]。现有研究^[86]虽提示 Cu NPs 危及人类健康的风险较低,但其亚急性毒性尚未阐明,以 23.5 nm 大小的含铜纳米颗粒为例,其半数致死量值为 413 mg/kg,属于中度(采用 Hodge-Sterner 分级)毒性材料。

毒性机制方面,CuO NPs 的毒性与其离子化有关^[86],其巨大的比表面积和高反应活性使其在胃液中与氢离子反应,产生大量碳酸氢盐,碳酸氢盐的排泄会加重肾脏负担,诱发病理改变。此外,性别也是影响毒性表现的重要因素,相同暴露条件下,雄性小鼠表现比雌性小鼠表现出更严重的毒性反应^[86]。同时,ROS 和活性氮物质的过度产生,在 CuO NPs 导致器官损伤中起着重要作用^[91]。值得注意的是,不同纳米颗粒与细胞和组织的相互作用方式、组织分布、粒径和渗透能力各异,合成方法亦显著影响毒性大小^[92]。

因此,鉴于目前有限的研究,很难得出一个关于 CuO NPs 安全性的全面结论,应不断研究纳米颗粒对人体的安全性,金属氧化物纳米颗粒对人体的影响。未来需要进行 CuO NPs 在肝、脑、肺、心、脾等主要器官中的毒性评估、生物利用度、体内动力学及生物分布研究。尽管部分研究表明铜及其他金属纳米粒子在牙科领域具有特定应用潜力,但其生物安全性尚未明确^[93-95]。此外,合成工艺、粒径调控及表面理化性质对其生物学行为的影响也需深入研究。

4 结论

综上所述,CuO NPs 主要依靠释放铜离子起到广谱抗菌效果,还可以改善部分牙科材料的力学性能,在口腔修复、牙体牙髓、正畸、牙周均有应用潜力。体外实验表明其毒性和使用浓度密切相关,理论上可以通过控制掺杂剂量降低毒副作用。但目前相关证据大多来自体外实验,缺少足够体内以及临床数据支持。后续还需要围绕合适掺杂浓度、体内长期安全性开展更多研究,推进铜改性牙科材料的相关探索。

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