·综述·

白藜芦醇治疗牙周炎和糖尿病的新进展

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【摘要】 牙周炎和糖尿病是临床上常见的疾病,对患者的健康及生活产生巨大影响。近年来学者研究证实这两种疾病具有很强相关性,因此治疗牙周炎和糖尿病的药物也成为研究热点。白藜芦醇是一种来自于天然植物的多酚类化合物,具有抗炎、抗氧化、降低血脂和调节代谢等作用,同时白藜芦醇不良反应少,获取途径广泛,价格低廉,是一种在牙周炎和糖尿病治疗中应用潜力巨大的辅助药物,也是解决关于慢性炎症性疾病中细菌耐药性问题的一个新思路。本文综述了近年来白藜芦醇应用于牙周炎及糖尿病治疗中的新进展,为进一步研究与应用提供新的思路。

【关键词】 白藜芦醇; 牙周炎; 糖尿病; 多酚类
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New study progress of resveratrol in the treatment of periodontitis and diabetes

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【**Abstract**】 Periodontitis and diabetes are common diseases in clinic, which have a huge impact on the health and life of patients. In recent years, it was proven that these two diseases have a strong correlation, so drugs for treating periodontitis and diabetes have also become a research hotspot. Resveratrol is a kind of polyphenol compound from natural plants, which has anti-inflammatory, antioxidant, lipid lowering and metabolic regulating effects. At the same time, it also has the advantages of small toxic side effects, wide access, low price, etc. It is a kind of auxiliary antibacterial drug with great potential in the treatment of periodontitis and diabetes, and also a new way to solve the problem of bacterial resistance in chronic inflammatory diseases. This article reviewed the new progress of resveratrol in the treatment of periodontitis and diabetes in recent years, in order to provide new ideas for its further research and application.

【**Key words**】 Resveratrol; Periodontitis; Diabetes mellitus; Polyphenols
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牙周炎是一种慢性炎症性疾病,在临床上常表现为附着丧失及牙槽骨吸收,最终导致牙齿松动、脱落,对患者口腔功能与美观产生巨大影响。研究发现,牙周组织长期的慢性炎症还会与一系列全身系统性疾病产生关联[1],例如心血管疾病、糖尿病等。近年来,随着更深入的实验室与临床研究发现,糖尿病与牙周炎之间存在互相影响的双向关系[2],控制牙周炎症更利于糖尿病的治疗[3]。因此,在临床上能同时治疗牙周炎和糖尿病的药物成为了研究热点,而白藜芦醇是一种来自于天然植物的多酚类化合物,具有抗炎、抗氧化、降低血脂和调节代谢等作用,近年来受到学者们的广泛关注。本文对白藜芦醇应用于牙周炎及糖尿病治疗中的新进展进行综述,为进一步开发应用提供新的思路。

一、白藜芦醇的简介

白藜芦醇是一种植物来源的非黄酮类多酚化合物,可从不同植物品种中获得[4],具有抗炎、抗氧化、降低血脂和调节代谢等多种药理作用。学者们发现,白藜芦醇不仅可以降低糖尿病患者胰岛素抵抗水平、保护胰岛功能,还可以降低牙周炎患者的局部炎症水平,维持口腔菌群的稳定,减少牙槽骨吸收、改善深牙周袋[5-7],有利于伴糖尿病牙周炎患者的治疗[8]。与其他药物相比,白藜芦醇具有不良反应小、获取途径广泛和价格低廉等优点,患者接受度高,有大规模推广应用的潜力,也是解决目前细菌耐药性问题的新思路之一[9]。白藜芦醇的化学名称为3,4′,5-三羟基-1,2-二苯基乙烯(3,4′,5-芪三酚),分子式为$C_{14}H_{12}O_3$,相对分子质量228.25,纯品外观为白至淡黄色粉末,无味,难溶于水,易溶于乙醚、甲醇等有机溶剂。天然的白藜芦醇有顺、反两种结构,在自然界中反式构象存在较多,它们分别与葡萄糖结合会形成顺式和反式白藜芦醇糖苷,在肠道中糖苷酶的作用下可以释放出白

藜芦醇,然而因其不能被肠道完全吸收及代谢清除,所以其口服的生物利用度较低,这会影响部分药理作用。

二、白藜芦醇在牙周炎治疗中的作用

1. 降低牙周致病菌的致病性:在亚抑制浓度下,白藜芦醇具有抑制牙周致病菌增殖的能力[10],它能改变细菌毒力性状,减少细菌产生的毒素,抑制细菌生物膜的形成,损害细菌的运动能力,影响细菌的聚集性[11]。同时,将白藜芦醇与抗菌药物联合使用,可以增强药物的抗菌效果[12]。Ben Lagha等[13]研究发现,天然白藜芦醇可以降低牙龈卟啉单胞菌(*Porphyromonas gingivalis*,*P.g*)的致病性,通过破坏*P.g*的生物膜,减少细菌对基质蛋白的黏附作用,抑制*P.g*对角质形成细胞连接的破坏,减少*P.g*介导的核因子κB(nuclear factor kappa-B,NF-κB)信号通路的激活,并减弱单核细胞中髓样细胞表达的激发受体1(triggering receptor expressed on myeloid cell,TREM-1)的表达和减少可溶性TREM-1的分泌来实现。Kugaji等[14]发现,在最低抑制浓度(minimum inhibitory concentration,MIC)范围内,白藜芦醇剂量依赖性地通过减少*P.g*毒力因子基因如菌毛(Ⅱ型和Ⅳ型)和牙龈蛋白酶牙龈素包括精氨酸-牙龈素(arginine-gingipains,Rgps)和赖氨酸-牙龈素(lysine-gingipain,Kgp)的表达来减弱*P.g*的毒力,减少*P.g*对牙周组织的破坏。此外,白藜芦醇还可以减少*P.g*脂多糖对细胞造成的破坏[15-16]。

2. 改善牙周组织炎症反应:牙周炎是一种慢性炎症性疾病,牙周炎患者体内促炎因子过量表达导致的免疫调节功能紊乱会通过各种途径影响全身健康,而白藜芦醇可以抑制促炎细胞因子的产生,改善其牙周组织的炎症反应。Li等[17]通过体外实验发现,白藜芦醇可以通过失活人磷脂酰肌醇三羟基激酶(human phosphoinositide-3 kinase,PI3K)/苏氨酸蛋白激酶(threonine protein kinases,AKT)和Wnt/β-catenin信号通路,剂量依赖性地下调炎症因子白细胞介素1β(interleukin-1β,IL-1β)、IL-6、IL-8和肿瘤坏死因子α(tumor necrosis factor-α,TNF-α)的表达。在牙周炎动物模型中,以口服的方式应用白藜芦醇降低牙周炎小鼠牙周组织中的IL-1β、IL-17、IL-4和γ干扰素(interferon-γ,IFN-γ)等促炎因子,改善小鼠牙周组织炎症反应[18-19]。另外,白藜芦醇也可以通过减少细胞活性氧(reactiveoxygenspecies,ROS)和一氧化氮(nitrogen monoxide,NO)的产生,减少氧化应激反应,改善牙周组织的炎症反应。Tamaki等[20]发现服用白藜芦醇可以激活炎症牙龈组织中的沉默信息调节因子2相关酶(silent information regulator 2-related enzyme,SIRT)/腺苷酸活化蛋白激酶[(adenosine 5′-monophosphate(AMP)-activated protein kinase,AMPK)]和核因子E2相关因子2(nuclear factor-erythroid 2-related factor 2,Nrf2)抗氧化防御途径,改善氧化应激并防止炎症的进展。Corrêa等[21]研究表明,白藜芦醇能通过提高乙酰化酶(Sirtuin,SIRT)和超氧化物歧化酶(superoxide dismutase,SOD)水平,以及降低NADPH氧化酶(NADPH oxidases,NOX)等方式减轻牙周炎大鼠的氧化应激,这种抗炎作用还可以减少吸烟对牙周组织的损害。白藜芦醇抗氧化应激的能力不仅仅可以保护牙周组织,还可以保护胰岛功能,赵燕霞等[22]和Nikniaz等[23]研究发现,白藜芦醇联合牙周非手术治疗可以更好地降低伴糖尿病牙周炎患者炎症因子水平、降低血脂,提高非手术治疗效果。

3. 减少牙槽骨吸收,促进组织再生:牙槽骨吸收、附着丧失是导致晚期牙周炎患者牙齿松动、脱落的根本原因,如何控制牙槽骨丧失和促进牙槽骨的再生一直是在研究中需要攻克的难题之一。有研究发现,白藜芦醇可以通过减少促炎因子水平和抑制破骨细胞形成来减缓牙槽骨吸收、促进组织再生[24-25]。Ikeda等[26]研究发现,应用富含白藜芦醇的蜂蜜籽提取物抑制了粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor,GM-CSF)/重组人可溶性RANK配体(recombinant human soluble RANK ligand,sRANKL)介导的破骨细胞形成和下调的破骨细胞活动,降低破骨细胞活性并加强成骨分化;Matsuda等[27]发现,白藜芦醇的应用抑制了小鼠单核巨噬细胞白血病细胞(RAW 264.7)和骨髓源性巨噬细胞分化为破骨细胞。而白藜芦醇促进牙槽骨再生的能力可能通过其增强间充质干细胞聚集体的功能并改善其再生能力的作用实现。牙周炎患者的间充质干细胞聚集功能下降,这导致了患者牙周组织再生能力降低,Wang等[28]研究发现,白藜芦醇可以改善患者间充质干细胞的聚集能力从而加强牙周组织成骨再生的能力。

4. 应用方式新进展:由于存在一系列难题,白藜芦醇并没有在牙周炎的临床治疗上大规模地应用。白藜芦醇来源于天然物质,目前主要以口服应用为主,而其溶解度仅约为0.03 g/L,且口服生物利用度低于5%[29],多需要助溶剂辅助以增加其溶解度,而其常用的助溶剂二甲基亚砜的毒性问题在临床上备受关注,这些问题大大影响了其药效及安全性。同时,口服类药物作用于口腔的药效有限,若想将白藜芦醇应用于口腔疾病的治疗,需突破其局限性。近年来,Lim等[30]使用具有更好安全性的2-羟丙基-β-环糊精(2-Hydroxypropyl-β-cyclodextrin,HPβCD)替代二甲基亚砜作为白藜芦醇及其类似物助溶剂,并在体外细胞实验中取得了良好的效果。Ikeda等[31]对比了给小鼠腹腔注射白藜芦醇单体与白藜芦醇二聚体对牙周组织的抗炎作用发现,白藜芦醇二聚体效果更佳。同时,Shi等[32]开发了一种具有良好生物相容性的治疗性白藜芦醇脂质体系统(liposome system of resveratrol,Lipo-RSV),发现其在体外实验中可以通过激活磷酸化信号传导子及转录激活子3(phosphorylated signal transducer and activator of transcription 3,p-STAT3)和下调p-STAT1,将炎症巨噬细胞从M1型重新培养为M2型,同时可以清除ROS,抑制NF-κB信号和炎症小体,降低促炎细胞因子IL-1β、IL-6和TNF-α,具有巨大的应用潜力。Tan等[33]设计了一种白藜芦醇接枝介孔二氧化硅纳米粒子(MSN-RSV)药物载体系统,有效提高了白藜芦醇的稳定性并延长其持续时间,有望成为一种新型药剂。解健等[34]尝试构建了一种载白藜芦醇及骨形态生成蛋白2(bone morphogenetic protein 2,BMP-2)同轴纳米纤维膜并应用于动物骨缺损模型中作为有效的药物缓释

载体,促进牙槽骨再生,提高缺损修复的效果。就目前为止,这些新药的研究多停留在体外细胞实验以及动物模型实验阶段,在动物试验及临床中的疗效仍待进一步地探究。

三、白藜芦醇在糖尿病治疗中的作用

1. 炎症因子及炎症信号通路:慢性牙周炎会促进其他全身性疾病的发生、发展,糖尿病就是与牙周炎关联密切的疾病之一,其相互作用机制与炎症导致的胰岛素的抵抗有关,其中与两种主要的信号通路被激活有关:NF-κB通路和c-Jun氨基末端激酶(c-Jun N-terminal kinase,JNK)/转录激活蛋白-1(activator protein-1,AP-1)通路[35],这些信号通路同时介导促炎细胞因子和趋化因子的产生,如TNF-α、IL-6、IL-1β和单核细胞趋化蛋白1(monocyte chemotactic protein-1,MCP-1)等。白藜芦醇可以通过作用于这些信号通路,降低炎症反应及胰岛素的抵抗,保护胰岛β细胞。Darwish等[36]通过体外细胞实验和小鼠实验证明白藜芦醇可以通过抑制细菌LPS的受体Toll样受体4(Toll-like receptor 4,TLR4)下游因子NF-κB p65、p38MAPK和STAT3的磷酸化,降低小鼠牙龈组织中升高的IL-1β、IL-6、IL-8、TNF-α和TLR4,降低伴糖尿病牙周炎小鼠的血糖水平,减少其牙槽骨丧失。除此之外,炎症因子IL-6在牙周炎与糖尿病之间也起到非常重要的关联作用[37-38],在正常情况下,IL-6能够保护胰岛β细胞,参与维持血糖的平衡;但当机体处于高血糖的状态时,过高的IL-6水平反而使T淋巴细胞过度激活,造成胰岛β细胞出现损伤甚至死亡。白藜芦醇可以通过降低这一炎症因子保护胰岛β细胞,Javid等[39]在临床研究中发现,给伴糖尿病牙周炎患者服用白藜芦醇可以降低其血清IL-6水平,调整患者机体的免疫平衡、氧化水平,保护患者的胰岛功能。

2. 降低氧化应激:氧化应激(oxidative stress,OS)是指体内氧化与抗氧化作用失衡的一种状态,在糖尿病患者体内,OS通过损害葡萄糖摄取而对血糖控制产生有害影响[40],牙周炎症的存在也会进一步提高氧化应激水平,从而增加糖尿病的控制难度。白藜芦醇可以通过不同的机制发挥抗氧化作用,保护细胞免受氧化损伤,降低胰岛素抵抗[41-43]。其改善胰岛素抵抗的机制涉及减少氧化应激、增加AMPK、上皮型一氧化氮合酶(endothelial nitric oxide synthase,eNOS)和AKT磷酸化。实验室研究发现,用白藜芦醇干预糖尿病小鼠后其ROS水平降低,胰岛纤维化和退行性损伤减轻,胰岛结构改善,胰岛功能恢复[44]。

3. 降低血脂:患者的血脂水平与糖尿病之间存在密切的联系,胰岛β细胞在长期暴露于极低密度脂蛋白(very low density lipoprotein,VLDL)、低密度脂蛋白(low density lipoprotein,LDL)和一些饱和游离脂肪酸时会更容易出现损伤和凋亡,胰岛素抵抗及其葡萄糖摄取受损和胰岛素水平降低也与氧化型低密度脂蛋白(oxidized low density lipoprotein,ox-LDL)水平有关[45-46],而高密度脂蛋白(high density lipoprotein,HDL)和不饱和游离脂肪酸可以减少β细胞凋亡。一般来说,糖尿病患者相比于正常人更容易出现血脂代谢异常,这会导致一种趋向于破坏的恶性循环,提高了患者出现各类并发症(例如冠心病等)的发生率[47]。在糖尿病患者的治疗中,辅助控制体质量及血脂的药物也一直是研究的热点,白藜芦醇可以通过降低血脂防止β细胞死亡。Ma等[48]在临床研究中发现,对糖尿病患者使用白藜芦醇治疗能改善血脂状况(包括血清总胆固醇、LDL、HDL和甘油三酯),同时保护肾功能。白藜芦醇还可以通过抑制CXC趋化因子配体16/ox-LDL途径来缓解胰腺组织因子激活和自噬介导的β细胞死亡[35]。白藜芦醇这种能辅助降低血脂同时防止糖尿病并发症[49]的天然非抗生素药物在临床治疗上有非常大的潜力。

四、总结与展望

白藜芦醇的功效使它成为一种在治疗糖尿病和牙周炎中具有巨大潜力的辅助治疗药物,在临床上有大规模应用的潜力。然而,白藜芦醇存在的缺陷阻碍了其在临床大规模的研究应用,对牙周炎应用的研究多停留在动物实验阶段,临床应用成效仍然缺乏大量的临床数据支持。因此,关于白藜芦醇在牙周炎患者治疗应用中的剂量,以及剂型、用药方式等仍需要开展更多的临床研究以探明。

利益冲突 所有作者均声明不存在利益冲突

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