综述

多酚类化合物的抗皮肤光老化作用

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摘要：皮肤光老化是由于长期暴露于紫外线下而导致的皮肤损害，是现代皮肤健康领域面临的一大挑战。伴随着公众对绿色植物源性产品的兴趣日益浓厚，天然多酚成为研究的新焦点。多酚作为一种常见的天然产物，因其显著的抗氧化、抗炎、抗过敏等特性而备受瞩目。越来越多的研究表明，多酚能有效缓解皮肤光老化。本文综述了多酚在抗皮肤光老化方面的作用，为光老化的治疗和预防新策略开发提供参考。

关键词：光老化；多酚；皮肤

Roles of polyphenols against skin photoaging

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Abstract: Skin photoaging, which is a kind of skin damage caused by long-term exposure to ultraviolet rays, has becoming a major challenge in the field of modern beauty and skin health. With the growing public interest in green plant-derived products, natural polyphenols have become a new focus of researches. As a common natural product, polyphenols have attracted a lot of attention for their significant antioxidant, anti-inflammatory, and anti-allergic properties. More and more studies have shown that polyphenols are effective in alleviating skin photoaging. This paper reviews the role of polyphenols in anti-skin photoaging, and summarizes how polyphenolic compounds can protect the skin from photoaging through their unique biological activities, providing a theoretical basis for the development of new strategies for the treatment and prevention of photoaging.

Key Words: photoaging; polyphenols; skin

随着环境挑战的加剧，紫外线(ultraviolet，UV)的潜在危害日益突出。紫外线不仅会导致皮肤晒伤和晒黑，引起皮肤水分丢失，还会深入破坏皮肤底层的细胞外基质，削弱皮肤的韧性和紧实度[1]。研究显示，高达80%的皮肤老化是由光老化(photoaging)引起的[2]。光老化过程及发病机制非常复杂，涉及氧化应激[3]、DNA损伤[4]、炎症反应与免疫抑制[5]、色素增加与分布失调[6]、皮肤屏障功能受损[7]、细胞外基质损伤[8]及细胞自噬的激活[9,10]等。抗氧化、改善炎症及免疫损伤、修复皮肤屏

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障以及恢复细胞外基质等是对抗光老化的关键措施。

目前，在皮肤健康领域，众多植物来源的化学物质资源正受到深入研究。多酚类化合物(polyphenol)是一种广泛分布于植物中的次生代谢产物，多元酚结构中的多个酚羟基官能团赋予了其强大的自由基清除能力，有助于减轻皮肤损伤，延缓老化过程[11,12]。本文综述了多酚在抗皮肤光老化方面的作用，为光老化的治疗和预防新策略开发提供参考。

1 多酚类化合物简介

目前已有大量研究探讨了多酚改善光老化的作用机制，多酚可通过以下机制发挥作用[13-19]。(1)强大的抗氧化性：多酚类化合物能有效中和自由基，减少活性氧(reactive oxygen species，ROS)，减轻氧化压力，减缓皮肤的光老化进程[13]。(2)DNA修复：多酚能促进DNA的自我修复过程，增强基因序列的稳定性[14]。(3)抗炎作用：多酚能够减少炎症介质的产生，减轻UV引起的皮肤炎症[15]。(4)色素调控：多酚可通过调节酪氨酸酶的活性，减少黑色素的形成和积累，有助于防止皮肤色斑和晒黑[16]。(5)维护皮肤屏障：多酚有助于恢复受损的表皮结构，保持皮肤的屏障功能完整[17]。(6)细胞外基质保护：多酚能抑制基质金属蛋白酶(matrixmetalloproteinase，MMP)的活性，抑制胶原蛋白和透明质酸(hyaluronic acid，HA)的分解，维持皮肤的弹性和紧实度[18]。(7)促进细胞自噬：多酚可能参与清除细胞内的受损成分，维持细胞内环境稳定，减缓皮肤细胞的衰老[19]。

2 多酚在皮肤光老化中的具体应用

不同来源的多酚因各自独特的结构特性而具有不同的生物活性[20]。近年来，研究人员深入分析了多酚在预防或治疗皮肤光老化方面的具体应用及其潜在的作用机制。

2.1 茶多酚

茶多酚(tea polyphenols，TPs)是一类主要存在于绿茶等茶叶中的活性化合物，其中儿茶素类化合物的含量最为丰富。在儿茶素中，表没食子儿茶素-3-没食子酸酯(epigallocatechin gallate，EGCG)的含量最高[21]。Jia等[22]的研究表明，EGCG能有效抑制UVA辐射对人皮肤成纤维细胞(human skin fibroblasts，HSF)的损伤，包括抑制端粒缩短和细胞周期停滞，提高超氧化物歧化酶(superoxidedismutase，SOD)的表达，抑制MMP活性等。Zhang等[23]发现，EGCG在UV诱导的斑马鱼和HSF细胞中表现出显著的抗氧化和抗炎特性，可减少p38丝裂原活化蛋白激酶(mitogen activated protein kinase，MAPK)的磷酸化，抑制核转录因子-κB(nuclear factor kappa B，NF-κB)的活性，降低转录因子激活蛋白-1(activator protein-1，AP-1)和MMP-1的表达，降低炎症因子如肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)、白细胞介素-1α(interleukin-1α，IL-1α)和IL-6的水平，从而改善氧化应激、炎症和胶原降解。Kim等[24]研究发现，EGCG能增加人永生化表皮细胞(HaCaT)的中间丝相关蛋白(filaggrin，FLG)、转谷氨酰胺酶1(tissue transglutaminase 1，TGM1)以及两种HA合酶HAS-1和HAS-2的基因表达，下调半胱氨酸蛋白酶caspase-8和caspase-3的表达，预防自由基诱导的细胞凋亡。此外，EGCG还可减少黑色素瘤细胞中黑色素的分泌和生成。这些结果进一步揭示了EGCG在抗皮肤光老化中的应用潜力。Yi等[25]探讨了苦丁茶多酚(kuding tea polyphenols，KTPs)对UVB诱导的SKH1无毛小鼠皮肤衰老的保护作用。结果显示，KTPs显著提高了血清中SOD和过氧化氢酶(catalase，CAT)的水平，降低了MDA、IL-6、IL-1β和TNF-α的水平，增加了小鼠受损皮肤组织中Ⅰ型胶原蛋白(collagen type Ⅰ，ColⅠ)、羟脯氨酸(hydroxyproline，HYP)和HA的水平，上调基质金属蛋白酶组织抑制剂-1(tissue inhibitor of metalloproteinase-1，TIMP-1)、TIMP-2、SOD、CAT和谷胱甘肽过氧化物酶(glutathioneperoxidase，GSH-Px)的mRNA和蛋白质表达，下调MMP-2和MMP-9的表达。组织病理学分析表明，KTPs能保护皮肤细胞、胶原和弹性蛋白，减少肥大细胞数量，效果优于同浓度维生素C。这些研究共同揭示了茶多酚在保护皮肤免受UV损伤、抑制炎症反应、增强抗氧化能力以及改善皮肤结构和功能方面的潜在价值。

2.2 白藜芦醇

白藜芦醇(resveratrol，Res)是最初从白藜芦中提取得到的一种多酚类化合物，而后发现在葡萄中含量较高[26]。Kim等[27]发现，口服葡萄皮提取物和Res，可抑制UVB诱导的小鼠皮肤皱纹形成，可能与激活核因子E2相关因子2/血红素加氧酶-1(nuclear factor E2 related factor 2/heme oxygenase-1，Nrf2/HO-1)信号通路有关。Subedi等[28]使用基因工程技术制备了富含Res的大米，与单独使用正常大米或Res相比，富含Res大米提取物作用于UVB诱导的正常人真皮成纤维(normal human dermal fibroblasts，NDHF)细胞后，可显著降低MMP-1水平，上调转化生长因子-β(transforming growth factor-β，TGF-β)的表达，促进Col Ⅰ的产生，减少促炎细胞因子TNF-α、IL-1β和IL-6的产生，抑制炎症介质如诱导型一氧化氮合酶(inducible nitric oxide synthase，iNOS)和环氧化酶-2(cyclooxygenase-2，COX-2)的表达，降低促凋亡蛋白p53的表达，减少Bcl-2相关X蛋白(Bcl-2 associated X protein，Bax)的转录，并裂解caspase-3，从而保护HSF细胞免受UVB诱导的皮肤衰老影响。Zhou等[29]发现，Res可上调UVB照射后HaCaT细胞中热休克蛋白(heat shock protein，HSP)、抗凋亡蛋白Bcl-2的表达，减少促凋亡蛋白如p65、Bax等的产生，提高细胞存活率。Cui等[30]用UVB照射建立HaCaT细胞和小鼠光老化模型，发现Res通过抑制ROS介导的MAPK和COX-2信号通路，减少MMP的表达和胶原蛋白的分泌，减轻细胞外基质的降解，促进Nrf2信号通路，提高SOD活性，减少氧化应激，抑制caspase活化，减轻细胞凋亡，激活血管内皮生长因子(vascular endothelial growth factor，VEGF)，发挥抗氧化和抗凋亡作用，从而缓解UVB照射引起的光老化。以上研究表明，Res可通过激活抗氧化应激通路、抑制炎症、抑制细胞凋亡等多种机制，抑制UV诱导的皮肤损伤。

2.3 槲皮素

槲皮素(quercetin)为类黄酮化合物，通常以苷的形式存在于多种植物中[31]。Shin等[32]发现，离体人皮肤组织用槲皮素处理并连续10 d暴露于紫外线下，槲皮素能直接靶向结合并抑制激酶PKCδ和JAK2，抑制MMP-1和COX-2的表达，减少UV诱导的胶原降解。Kwak等[33]发现，在HaCaT和HSF细胞中，多花蔷薇提取物可显著抑制UV引起的ROS、IL-6和MMP-1表达增加，小鼠口服该提取物，可减少UV诱导的皮肤中TNF-α、MMP-13的表达，缓解表皮增厚。对提取物成分进行鉴定，发现了包括槲皮苷(槲皮素-3-O-鼠李糖苷)在内的8种酚类化合物，当使用槲皮苷处理HSF细胞时，显著抑制了UV引起的MMP-1表达增加和Col Ⅰ表达减少。这些研究证实了槲皮素及其衍生物在UV防护中的重要作用。

2.4 花青素

花青素(anthocyanins)是一种广泛存在于蓝莓、黑加仑等深色水果中的色素，具有较好的抗氧化和抗炎特性[34]。Sim等[35]研究证实，给予SKH-1无毛小鼠口服含花青素的玫瑰花提取物12周后，可恢复UVB照射破坏的胶原蛋白和HA，抑制UVB引起的皱纹形成和经表皮水分流失。矢车菊素-3-葡萄糖苷(cyanidin-3-O-glucoside，C3G)是花青素的一种，在自然界中分布广泛。Wu等[36]研究发现，C3G处理能提高UVA照射后HSF细胞中自噬相关*Atg5*基因和LC3-Ⅱ蛋白的水平，而这一作用在自噬抑制剂3-甲基腺嘌呤处理后显著降低，表明C3G可能通过诱导自噬来抑制UVA对人皮肤成纤维(human dermal fibroblast，HDF)细胞的损伤。Wang等[37]发现，黑枸杞中的花青素能降低UVB诱导的细胞凋亡，抑制TNF-α、caspase-7表达，增加凋亡抑制基因*survivin*的表达。以上研究表明，花青素可通过促进胶原蛋白和HA的合成、诱导自噬、抑制凋亡等多种途径，为UV诱导的皮肤损伤提供保护。

2.5 姜黄素

姜黄素(curcumin)是从姜黄中提取的一种黄色酸性酚类物质，是姜黄发挥药理作用的主要活性成分[38]。Liu等[39]发现，姜黄素能减少ROS积累，恢复GSH-Px、SOD、CAT的活性，下调葡萄糖调节蛋白78(glucose regulated protein 78，GRP78)、C/EBP同源蛋白、NF-κB的表达，上调Bcl-2，减轻UVA诱导的内质网应激、炎症和细胞凋亡。Thapa Magar等[40]在UVB诱导的小鼠皮肤损伤模型中发现，局部涂抹姜黄素可显著减轻炎症细胞浸润、胶原堆积紊乱和脂质过氧化等损伤，在UVB诱导

的HaCaT细胞中发现姜黄素可激活Nrf2信号通路，显著减轻乳酸脱氢酶释放、ROS产生和DNA损伤，促进Nrf2信号通路中Ⅱ相解毒酶的表达，促进DNA修复。Muta等[41]从姜黄根茎的甲醇提取物中分离出姜黄素，通过在人面部皮肤局部应用含有该提取物的乳膏，发现能抑制UV引起的明胶酶活化，显著改善皮肤弹性，减少角质层中明胶酶的含量，促进真皮-表皮交界处基底膜成分沉积，有效防止皱纹形成。以上研究表明，姜黄素可通过抗氧化、抗炎、抗凋亡、调节胶原代谢和激活Nrf2信号通路等，改善UV导致的皮肤光老化。

2.6 羟基酪醇

羟基酪醇(hydroxytyrosol，HT)是一种主要存在于橄榄果实和枝叶中的多酚类化合物，具有较强的抗氧化活性[42]。Avola等[43]研究发现，HT能抑制ROS产生，清除蓝光照射产生的自由基，减少8-羟基-2′-脱氧鸟苷的形成，减少DNA损伤，抑制MMP-1和MMP-12的表达，增加Col Ⅰ的表达。Zwane等[44]通过制备的HT二聚体显著提高了UVB辐射后HaCaT细胞的存活率，减轻细胞炎症反应，显著减少UVB辐射引起的DNA损伤标记物环丁烷嘧啶二聚体(cyclobutane pyrimidine dimers，CPDs)的形成，效果优于HT。这些研究表明，HT在改善皮肤光老化方面具有重要的应用潜力。

2.7 丁香酚

丁香酚(eugenol)是一种具有强烈香味的天然酚类化合物，广泛存在于丁香等多种植物的挥发油中[45]。Tong等[46]发现，口服丁香酚能剂量依赖性地促进光老化小鼠的皮肤屏障修复、皮肤组织再生、减轻氧化应激损伤、增加细胞外基质(extracellular matrix，ECM)的生成，调节皮肤微环境。转录组测序分析发现，丁香酚可能通过调节细胞因子-细胞因子受体相互作用和ECM-受体相互作用等信号通路来缓解皮肤光老化。Hwang等[47]发现，丁香酚能抑制UV诱导的NHDF细胞中MMP-1和MMP-3的表达及AP-1的磷酸化，激活Nrf2/抗氧化反应元件(antioxidant response elements，ARE)信号通路，抑制NF-κB和IL-6的表达，抑制活化T细胞C1(NFATc1)的核因子，抑制NFATc1协同TGF-β和NF-κB参与钙调神经磷酸酶调节的转录过程，通过多种分子途径发挥抗氧化和抗炎作用，具有保护皮肤细胞免受UVB引起的损伤及衰老效应的潜力。

2.8 鞣花酸

鞣花酸(ellagic acid)是一种广泛存在于各种软果、坚果等植物组织中的多酚类化合物[48]。Hong等[49]对主要成分为没食子鞣酸和鞣花酸的锐齿栎果实提取物的活性进行了研究，发现其能有效减轻UVB对HaCaT细胞的毒性，抑制细胞内ROS的产生，抑制ERK/AP-1信号通路的激活，降低MMP-1表达，抑制胶原蛋白降解。Duckworth等[50]将鞣花酸和视黄酸联合干预HSF细胞，可观察到弹性蛋白和胶原蛋白显著增加。Moon等[51]将鞣花酸与二氢杨梅素联合应用，可减轻UVB引起的小鼠皮肤晒伤、发红和起泡，表现出较好的协同作用，显著降低ROS水平，减少TNF-α和IL-6等炎症因子的产生，抑制UVB诱导的MMP-1和MMP-9表达，促进TGF-β1表达，帮助修复皮肤损伤，增加胶原合成，激活Wnt/β-catenin信号，有效防止细胞核等细胞结构损伤，促进细胞再生和组织修复，增强皮肤结构和功能。

2.9 绿原酸

绿原酸(chlorogenic acid)是一种在植物中广泛分布的酚酸类化合物[52]。Xue等[53]发现，CGA能上调HDF细胞中Col Ⅰ的mRNA和蛋白质表达水平，下调MMP-1和MMP-3的表达，减少ROS积累，减轻DNA损伤，并促进细胞修复，抑制UVA照射引起的HDF凋亡。Wang等[54]对小鼠进行了为期56 d的口服绿原酸处理，发现绿原酸可显著减轻UVB诱导的表皮厚度减少，提升胶原蛋白含量，抑制MMP过度表达，增强SOD和CAT活性，降低MDA及炎性细胞因子IL-1β、IL-6和TNF-α的水平。同时，绿原酸的抗糖基化作用能减少晚期糖基化终产物(advanced glycation endproducts，AGEs)的生成，减少AGEs与晚期糖基化终产物受体结合引起的炎症和氧化应激反应，改善皮肤光老化。

2.10 紫檀芪

紫檀芪(pterostilbene)是一种来源于紫檀、蓝莓、葡萄和花榈木等植物的Res类似物[55]。Li等[56]研究发现，在UVB照射前对HaCaT细胞采用紫檀芪预处理，可有效预防光损伤，紫檀芪可激活磷

脂酰肌醇-3-激酶(phosphoinositide 3-kinase，PI3K)信号通路诱导Nrf2磷酸化，进而激活Nrf2/ARE通路，增强内源性防御机制，清除ROS，促进DNA修复。Hseu等[57]发现，紫檀芪可剂量依赖性地抑制黑素瘤细胞(B16F10)中α-促黑素细胞激素(α-melanocyte-stimulating hormone，α-MSH)刺激的黑色素生成，降低酪氨酸酶(tyrosinase，TYR)等黑色素生成相关蛋白的表达，抑制PI3K/AKT/mTOR通路，使自噬相关蛋白Beclin-1与Bcl-2比例失调，上调促自噬蛋白LC3-Ⅱ和p62的表达。Sirerol等[58]发现，给予SKH-1无毛小鼠皮肤涂抹紫檀芪可减轻UVB诱导的皮肤红肿、增厚等损伤，减轻与光老化相关的皮肤皱纹和增生。使用HaCaT细胞进一步发现，紫檀芪皮肤光保护作用的机制涉及调节Nrf2依赖性抗氧化反应。Majeed等[59]评估了含有0.4%紫檀芪的面霜对38名健康志愿者的抗衰老和美白效果，结果显示，受试者的皮肤纹理显著改善，皱眉纹和鱼尾纹面积显著减少，表明紫檀芪可抑制皮肤衰老。

3 多酚类化合物的皮肤递送

多酚在具有较好抗氧化能力的同时，具有较低的结构稳定性，且皮肤外用需考虑提高其透皮吸收生物利用度。将多酚负载于适当的载体中可增强其稳定性，提高其渗透能力，从而增强其抗氧化和抗衰老功效。

3.1 纳米囊泡

纳米囊泡(nanovesicle)通常由磷脂和蛋白质构成，其类似细胞膜的结构能共包封疏水性和亲水性成分，促进其与细胞膜融合，实现有效地传递药物、基因或其他生物活性物质，并能保护多酚成分免受外界环境因素引起的氧化或降解，确保其稳定性[60]。Abd-Elghany等[61]制备了包载鞣花酸的壳聚糖涂层纳米囊泡，可减少药物降解，提高生物利用度，改善UV暴露下衰老相关*Col* Ⅰ*A1*、*Timp 3*和*TERT*等基因的表达，优于鞣花酸单独应用的效果。Abbas等[62]通过薄膜水合法制备纳米囊泡，并将水不溶性药物Res包封在内，可提高Res的皮肤渗透性和稳定性，有效减轻UV照射动物模型中的皮肤红斑和氧化应激反应，并调节皮肤中CAT、GSH和SOD等因子的水平。

3.2 纳米颗粒

纳米颗粒(nanoparticle)是一种直径介于1~1 000 nm的微小粒子，包括生物可降解聚合物以及金属或无机材料制成的纳米载体。这些纳米颗粒可将多酚分子包裹其中，同时其尺寸有利于穿透皮肤屏障进入皮肤细胞，改善多酚的渗透性和生物利用度[63]。Adusumilli等[64]使用乳化-溶剂蒸发法等技术制备姜黄素纳米颗粒(Cur-NPs)，解决了其水溶性差和稳定性差的问题，对UV诱导皮肤损伤的保护作用优于姜黄素单体。Nisar等[65]制备了负载槲皮素的氧化锌纳米颗粒Quercetin@ZnO，槲皮素的羟基官能团可与铁离子形成配位键，从而实现对铁离子的螯合作用，减少铁离子在生物体内可能与氧自由基发生的氧化应激反应。Quercetin@ZnO颗粒不仅能反射UVA，还能消散高能光子，释放出槲皮素分子，抗氧化的同时螯合游离铁并降低IL-1β、IL-6、NF-κB、TNF-α等炎症因子的表达。

3.3 微针

微针(microneedle)可穿透皮肤角质层，将多酚直接递送至真皮层，避免经皮递送过程中的屏障问题[66]。Puri等[67]通过微针技术有效递送了EGCG，相比传统涂抹方式，微针显著提升了EGCG在深层皮肤的含量，长期使用微针递送EGCG未发现显著的皮肤毒性或不良反应。Chen等[68]报道了一种双层PLGA/HA微针，同时负载姜黄素和没食子酸两种多酚类化合物，皮肤应用后可发挥两者协同抗氧化和抗炎的作用。Chiu等[69]将EGCG包封到γ-聚谷氨酸微针中并利用L-抗坏血酸作为稳定剂，可显著提高EGCG的稳定性。

4 总结

多酚类化合物在对抗皮肤光老化方面展现出巨大的应用潜力，是预防和治疗皮肤光老化的重要天然资源。由于传统天然提取分离等制备工艺复杂、环境污染严重，有必要开发更为绿色环保的酶法转化等生物制备技术，以批量获得高品质的多酚类化合物。多酚的稳定性和生物利用度是影响其效果的重要因素，微针等制剂技术的进步为其提供了重要的解决方案。同时，有必要深入研究其机制，进一步阐明多酚改善皮肤光老化的分

子调控网络。随着技术的不断进步，多酚类化合物在皮肤光老化防治方面的作用将得到更深入的挖掘和应用。

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