

# 天然产物抗皱活性研究进展

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## 摘要

皮肤老化是人体自然状态下不可避免的过程,分为生理状态下的内在老化和外部环境损伤下的外部老化。紫外辐射是致皮肤老化最严重的外部刺激因素,皮肤暴露在紫外线辐射下会引起晒伤、免疫抑制、光老化、突变、DNA和蛋白质变性、癌症等。皱纹是皮肤老化的典型症状,由弹性丧失引起,弹性丧失与皮肤真皮组织弹性相关的胶原蛋白和弹性蛋白减少有关。我国植物资源丰富,具有广阔应用前景。近年来大量研究证明,天然产物为抗皱活性的研究和相关产品的研发提供了新思路和新方法。本文就抗皱相关理论和多种具有抗皱活性的天然产物研究进展作一综述。

## 关键词

天然产物, 抗皱, UVB

# Research Progress of Anti-Wrinkle Activity of Natural Products

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## Abstract

Skin aging is an inevitable process in the natural state of a human body, which is divided into internal aging under physiological state and external aging under external environmental damage. Ultraviolet radiation is the most serious external irritant causing skin aging. Skin exposure to ultraviolet radiation will cause sunburn, immunosuppression, photoaging, mutation, DNA and protein degeneration, cancer, and so on. The wrinkle is a typical symptom of skin aging, which is caused

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by the loss of elasticity. The loss of elasticity is related to the reduction of collagen and elastin related to the elasticity of the skin and dermal tissue. China is rich in plant resources, which is a broad research field. In recent years, a large number of studies have proved that new ideas and methods for the research of anti-wrinkle activity and the research and development of related products which come from natural plants have been formed. The relevant theories of anti-wrinkle and the research progress of many natural drugs with anti-wrinkle activity were reviewed in the present study.

## Keywords

Natural Products, Anti-Wrinkle, UVB

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## 1. 引言

随着经济的快速发展和生活水平的不断提高,加之环境的恶化,现代社会对化妆品的关注度越来越高。据权威调查显示,“抗衰”已成为全球面部护肤产品中使用率增幅最快的三大产品宣传之一[1]。人体皮肤细胞完全更新一次需要历时三个月,在新更新的细胞还未到达皮肤表层时就已经被各种自由基氧化[2];此外,随着人体的衰老、基因、环境等的影响,胶原蛋白、弹性蛋白减少,最终导致皱纹产生。我国植物资源丰富,具有广谱生物活性、低毒性、自然、温和、不刺激等优点,随着提取技术、生物技术不断发展和优化,天然产物活性成分的稳定性不断提高,越来越多的植物提取物被用于抗皱等功效型化妆品中[3][4]。

## 2. 皮肤老化与皱纹形成

皮肤是构成人体最外层的组织,它由表皮、真皮和皮下组织构成。表皮是皮肤的最外层,主要由角质形成细胞、黑素细胞、朗格汉斯细胞和默克尔细胞组成。角质形成细胞是表皮中发现的最丰富的细胞,起到抵御外界环境的屏障作用[5]。真皮包括弹性蛋白、胶原蛋白和葡萄糖胺聚糖(Glucosaminoglycan)三个结构,是维持皮肤结构的细胞外基质(Extracellular matrix)[6][7]。皮肤老化表现为毛细血管扩张、色素沉着、面色蜡黄、干燥、松弛和深皱纹。根据作用机制的不同可分为内在老化和外在老化[8]。内在老化是生物体随时间的一种潜伏的退化过程,与遗传易感性和生理成分有关,是人体生理变化的必然结果。外在老化是外源性环境下损伤的结果,例如紫外辐射(UV)、环境污染和化学品等[3]。

在几种外部刺激因素中,致皮肤老化最严重的是紫外辐射,根据光子波长的不同,UV辐射分为长波紫外线UVA(320~400 nm)、中波紫外线UVB(280~320 nm)和短波紫外线UVC(200~280 nm)[9]。UVB可穿透表皮,直接导致DNA突变。UVA可深入真皮,诱导产生基质金属蛋白酶(MMPs)分解胶原和弹性蛋白纤维,导致皮肤老化和皱纹形成。皮肤暴露在紫外线辐射下会引起各种生理效应,如晒伤、免疫抑制、光老化、皮肤色素沉着、突变、DNA和蛋白质变性、癌症,以及活性氧(ROS)的产生[3][10][11]。

皱纹是皮肤老化的典型症状,由弹性丧失引起,弹性丧失与皮肤真皮组织弹性相关的胶原蛋白和弹性蛋白减少有关。胶原蛋白约占人类真皮细胞外基质(ECM)的90%,I型胶原蛋白是皮肤和结缔组织中最丰富的结构蛋白,占总胶原蛋白的80%,其结构变化被认为是皮肤老化和皱纹形成的主要原因[12]。暴

露于急性紫外辐射下的皮肤, 活性氧(ROS)和基质金属蛋白酶(MMPs)会被上调, 核因子- $\kappa$ B (NF- $\kappa$ B)也被激活[13]。基质金属蛋白酶是锌依赖性内肽酶, MMP 酶家族负责结缔组织的降解和多种 MMPs 的转录, 主要受核因子- $\kappa$ B (NF- $\kappa$ B)和激活蛋白 1 (AP-1)的调控, 后者特异性上调 MMP-1 (间质胶原酶)、MMP-3 (基质分解酶-1)和 MMP-9 (明胶酶 B), 直接参与胶原的降解[10] [13]。ROS 可以与 DNA、蛋白质、脂肪酸和糖类反应, 造成氧化损伤[14]。ROS 是多种 MAPK (丝裂原活化蛋白激酶)通路的必需参与者, MAPK 信号通路包括 ERK、p38 和 JNK 三条通路, 负责激活蛋白(AP-1)和核因子- $\kappa$ B (NF- $\kappa$ B)的激活, 而上调 MMP 的表达。JNK 主要由 ROS 激活, 参与 AP-1 转录因子的产生。此外, MAPKs 通过 ERK 和 p38 的磷酸化使 NF- $\kappa$ B p65 (Ser276)磷酸化, 最终诱导 MMP 产生, 致皮肤老化和皱纹产生[15]。此外, 紫外辐射还会下调转化生长因子  $\beta$  (TGF- $\beta$ ), 这是一种多功能细胞因子, 它诱导下游蛋白 Smad 2/3 与 Smad 4 形成异二聚体复合物, 并转移到细胞核中, 激活前胶原启动子, 从而诱导胶原蛋白和弹性蛋白的产生, 并阻断 MMP-1 和 MMP-3 的生成[9]。

### 3. 抗皱天然产物

我国植物资源丰富, 具有广谱生物活性、低毒性、自然、温和、不刺激等优点[1]。运用极广的绿茶、人参和山楂等均被证明有抗皱和延缓衰老的功效[16] [17] [18]。

#### 3.1. 植物提取物

绿茶富含植物多酚, 大量研究表明, 绿茶多酚具有抗紫外线加速皮肤衰老的保护作用, 包括抗皱、抗黑素、抗氧化、抗炎等[16]。动物实验证明, 绿茶提取物可促使胶原和弹性纤维含量增加, 抑制 MMP-3 的表达, 从而防止皱纹的形成[19]。山楂多酚提取物主要包含绿原酸、原花青素、表儿茶素等酚类化合物, 体外实验表明可上调 I 型前胶原和下调 MMP-1; 体内实验表明可逆转 UVB 诱导的表皮增厚和真皮损伤, 可逆转 UVB 辐射引起的活性氧产生增加、抗氧化剂酶活性降低以及核因子  $\kappa$ B 活性和丝裂原活化蛋白激酶(MAPK)磷酸化的增加, 并抑制 MMP38 的表达, 诱导 UVB 辐射小鼠背部皮肤 I 型前胶原的产生[18]。发酵黑参是以新鲜人参为原料, 经反复蒸煮、烘干后, 用酿酒酵母发酵而成, 可产生活性较高的人参皂苷。显著增加人成纤维细胞中 I 型前胶原蛋白的表达水平, 并降低 MMP-1、3、9 的表达水平[20]。红参乙醇提取物使 UVB 辐射所致皮肤增厚、皮肤弹性降低的小鼠 MMP-1 的 mRNA 和蛋白水平显著降低, 通过抑制胶原降解来发挥抗皱作用[21] [22]。桑黄是蘑菇的一个种类, 其甲醇提取物和热水提取物的抗胶原酶和弹性蛋白酶活性均较好, 可用于开发皮肤抗皱药物[23]。刺槐叶乙醇提取物中酚类化合物含量非常高, 可显著抑制胶原酶和弹性蛋白酶的活性, 还可促进人真皮成纤维细胞中胶原蛋白的合成和降解[12], 在预防或缓解紫外线引起的皮肤皱纹方面颇有潜力。松叶是被用作抗炎的民间药物, 落下的松叶会保持两年的绿色, 直到颜色变成棕色, 可制得褐松叶提取物, 能减弱 UVB 诱导的 AP-1 反式激活和蛋白激酶 B(Akt)磷酸化, 抑制经 UVB 诱导的角质形成细胞 MMP-1 的表达[24]。积雪草被描述为一种抗衰老的植物, 可用于草药化妆品中, 以改善皮肤的粘弹性和水合性能。其提取物对透明质酸酶、弹性蛋白酶和 MMP-1 均有较强的抑制活性[25]。

#### 3.2. 化合物

人参皂苷是人参中具有主要药理活性的物质。现有研究表明, 20-O- $\beta$ -D-葡萄糖基-20(S)-原人参二醇(GPPD)、人参皂苷 Rb1、Rb1 代谢物的苷元衍生物 20(S)-原人参二醇(20(S)-PPD)和化合物 K 均有具有抗皱作用[26]。20(S)-PPD 通过抑制 MEK1/2-ERK1/2/p90RSK 和 MEK3/6-p38 通路, 从而降低 MMP-1 的主要转录因子激活蛋白(AP)-1 活性, 实现 HaCaT 细胞中具有抑制太阳紫外线诱导的 MMP-1 的表达[17]。

人参皂甙 Rb1 的代谢产物化合物 K 可降低经 UVB 辐射的 NIH3T3 细胞 MMP-1 和环氧合酶(COX)-2 的产生, 恢复 I 型胶原的表达水平[27]。阿魏酸是一种酚酸, 存在于多种植物中。可诱导 UVB 辐射的人成纤维细胞 CCD-986sk 合成前胶原、透明质酸、金属蛋白酶抑制剂, 抑制 MMP-1 和 MMP-9 的表达[28], 具有抗皱潜力。紫玉甙 I 是地榆根提取物中分离的活性物质, 体外实验证明其可降低人成纤维细胞中 MMP-1 的表达。同时, 在使用视觉评估和图像分析进行测量的临床试验中, 也证实了作为抗皱化妆品活性成分潜力[29]。咖啡酸是一种天然存在的酚类化合物, 广泛存在于蔬菜、水果、油脂、葡萄酒和咖啡等植物产品以及蜂胶等农产品中, 3,5-二咖啡酰表奎宁酸是咖啡酰奎宁酸的生物活性衍生物。可使经 UVB 辐射的人 HaCaT 角质形成细胞抑制了 MMP-1、-2 和 -9 的 mRNA 和蛋白质的过表达, 同时增加 I 型原胶原的产生[30] [31]; 同时通过阻断 MAPK 级联调控的 AP-1 转录活性, 还可改善经 UVA 照射的人真皮成纤维细胞 HDFS 中 MMP-1、MMP-3 和 MMP-9 的表达[9]。单宁酸是天然存在的植物多酚, 具有较强的抗氧化、抗胶原酶和抗弹性蛋白酶活性, 并能抗紫外线吸收、防止氧化应激和氧化损伤, 可抑制经 UVB 照射的 L929 成纤维细胞的氧化应激、氧化损伤和 MMP-1 表达[32]。此外, 运用极广的白藜芦醇也是多酚类化合物, 在抗光老化方面作用显著。它通过下调 MMP、上调血管内皮生长因子-B (VEGF-B), 并发挥抗炎、抗氧化和抗凋亡特性治疗光老化[33]。熊果酸是从酸枣中提取的一种五环三萜类化合物, 通过抑制 ERK 和 c-Fos 信号通路, 降低 HaCaT 角质形成 MMP-1 的 mRNA 水平[34]。(±)-丁香树脂醇是木脂素类物质, 通过抑制 UVA 诱导的 p38 和 JNK MAPKs 及其下游效应因子 c-Fos 和 c-jun 的磷酸化, 从而抑制由 AP-1 激活的 MMP-1 的表达[35]。大豆异黄酮具有抗皱、美白和保湿的功效, 研究证明其代谢物 6,7,4'-三羟基异黄酮和香豆素也具有较好的抗皱功效。6,7,4'-三羟基异黄酮是蛋白激酶抑制剂, 可抑制紫外线诱导的 MMP-1 产生[36]; 香豆素则通过抑制 FLT3 激酶的活性来抑制 UVB 诱导的 MMP-1 的表达[37]。1,4-二羟基-2-甲氧基-7-甲基蒽醌是巴戟果实提取物中分离出的一种具有 I 型胶原刺激作用的单体化合物, 可增加人真皮成纤维细胞 I 型胶原和糖胺聚糖的产生, 并下调 MMP-1 的表达[38]。人皮肤单细胞转录组学研究表明[39], 黄酮类化合物槲皮素作用于 HES1 敲除的真皮成纤维细胞, 促进衰老真皮成纤维细胞的年轻化。

#### 4. 小结

综上所述, 天然产物具有自然、温和、不刺激、安全性高等优点, 随着提取技术、生物技术不断发展和优化, 天然植物活性成分稳定性的不断提高, 植物原料被用于抗皱、美白等功效性化妆品中。我国人口众多, 植物资源丰富, 抗衰老化妆品市场和研发潜力巨大。环保、健康、安全的天然组分化妆品的开发是众望所归, 回归天然逐渐成为一种趋势。因此, 开发更安全、更有效的对抗皮肤皱纹的天然产品已成为医疗、食品和化妆品行业的研究重点, 具有重要意义。

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