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口服疗法治疗黄褐斑的研究进展

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摘　要

黄褐斑是一种常见的获得性色素沉着性疾病，具有复发率高的特点，治疗难度大。发病机制涉及氧化应激、炎症反应、血管增生及黑素合成异常等多条通路。近年来，口服药物及膳食补充剂因其方便、安全及系统调节优势成为研究热点。本文综述了口服药物与膳食补充剂治疗黄褐斑的作用机制、临床疗效及安全性。氨甲环酸是目前证据等级最高的一线口服药物，通过抑制纤溶酶系统、抗炎、抗血管生成及竞争性抑制酪氨酸酶等多靶点发挥作用。谷胱甘肽、褪黑素等抗氧化剂通过清除自由基改善色素沉着，但证据等级较低。酮替芬、非那雄胺等其他口服药物疗效有限或存在争议，多作为辅助用药。松树皮提取物、番茄提取物等膳食补充剂主要通过抗氧化及光保护作用辅助治疗，临床证据尚不充分。

关键词

黄褐斑，口服疗法，膳食补充剂，氨甲环酸，疗效

Research Advances in Oral Therapies for Melasma

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Abstract

Melasma is a common acquired hyperpigmentation disorder characterized by high recurrence rates and therapeutic challenges. Its pathogenesis involves multiple pathways including oxidative stress, inflammatory response, angiogenesis, and abnormal melanin synthesis. In recent years, oral medications and dietary supplements have become research hotspots due to their convenience, safety,

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and systemic regulatory advantages. This review summarizes the mechanisms, clinical efficacy, and safety of oral medications and dietary supplements for melasma treatment. Tranexamic acid represents the first-line oral agent with the highest level of evidence, exerting therapeutic effects through inhibition of the plasminogen system, anti-inflammatory activity, anti-angiogenesis, and competitive inhibition of tyrosinase. Antioxidants including glutathione and melatonin improve hyperpigmentation by scavenging free radicals, though with lower evidence levels. Other oral agents such as ketotifen and finasteride show limited efficacy or remain controversial, serving primarily as adjunctive therapies. Dietary supplements including pine bark extract and tomato extract exert auxiliary effects mainly through antioxidant and photoprotective mechanisms, with insufficient clinical evidence to support their routine use.

Keywords

Melasma, Oral Therapy, Dietary Supplement, Tranexamic Acid, Efficacy

1. 引言

黄褐斑是一种常见的获得性色素沉着性疾病，好发于 Fitzpatrick III~V型皮肤类型的育龄期女性，全球患病率约为 1.5%~33% [1] [2]。其发病涉及遗传易感性、紫外线暴露及性激素紊乱等多种因素，发病机制复杂，涵盖氧化应激、炎症反应、血管增生、皮肤屏障受损以及酪氨酸酶介导的黑素合成等多条通路[3] [4]。口服药物和膳食补充剂可通过抗炎、抗氧化、抗血管生成等系统调节机制，同时干预上述多条通路，兼具用药便捷、安全性良好及协同增效等优势。近年来，以氨甲环酸为代表的口服疗法在黄褐斑治疗中积累了丰富的临床证据，口服治疗联合光电技术、外用制剂及微针等方案的研究不断涌现，不同联合方案可实现机制互补，为临床精准选择治疗方案提供了更多可能。本文就口服药物及膳食补充剂治疗黄褐斑的作用机制与临床疗效进行综述，并基于现有证据探讨联合治疗的协同机制与个体化选择策略。

2. 黄褐斑发病机制

黄褐斑的发病机制错综复杂，各因素相互交织。传统上认为，其核心环节主要包括黑素合成异常、炎症反应、血管异常及激素水平紊乱，依据核心病理改变可将黄褐斑分为色素型、血管型及混合型。其中，黑素合成异常是核心病理环节。紫外线照射可诱导自由基生成，激活 α-促黑素细胞激素/黑皮质素 1 受体(α-MSH/MC1R)信号通路，上调小眼畸形相关转录因子(MITF)表达，进而激活酪氨酸酶家族，促进黑素合成。同时，氧化应激可直接损伤黑素细胞与基底膜带，进一步加剧黑素颗粒的生成与沉积[4] [5]。炎症与血管因素也深度参与其中。炎症反应释放的前列腺素 E2 会招募肥大细胞、T 细胞浸润，释放组胺、IL-17 等炎症介质。组胺可通过组胺受体 2 直接刺激黑素细胞，并导致基底膜损伤；肥大细胞分泌的血管内皮生长因子(VEGF)及角质形成细胞分泌的内皮素-1 (ED-1)则加剧血管增生[6]。此外，纤溶酶可通过成纤维细胞生长因子、前列腺素 E2 及白三烯等多条信号通路刺激黑素细胞活化；还可降解皮肤基底膜成分，使基底膜完整性受损，导致黑素细胞及黑素颗粒坠入真皮，形成难治性黄褐斑[7]。激素方面，雌激素可激活黑素细胞的雌激素受体 2 及角质细胞中的 Wnt/β-链蛋白通路，同时上调 VEGF 及 ED-1 水平，通过增加血管数量来维持色素沉着[8]。上述不同通路的异常激活为治疗提供了靶点。

3. 黄褐斑评估工具与指标

黄褐斑的诊断虽以临床为主，但伍德灯、皮肤镜及反射式共聚焦显微镜等无创辅助工具在病情评估、分型和疗效判定中发挥着重要作用。伍德灯可通过色素荧光特征区分表皮型、真皮型及混合型色素沉着，是临床简易分型的重要手段。表皮型黄褐斑在口服药物治疗后荧光对比度减弱，可作为初步疗效观察的简便手段[9]。皮肤镜则可清晰显示皮损区色素形态及血管结构，通过色素网络、点状/线状血管的分布特征分型。治疗后常见色素网络变浅、血管直径减小，可用于动态监测治疗对黑素细胞及血管生成的双重抑制作用[10]。皮肤 CT 实现了皮肤黑素含量的无创定量评估，同时可观察真皮层血管密度及炎症细胞浸润情况，治疗后黑素颗粒密度下降、分布范围缩小，血管密度降低，提示治疗有效[11]。近年来，新型成像技术进一步聚焦黑素与血管的定量分析，并尝试区分弹性纤维与胶原纤维，以更全面评估黄褐斑严重程度及光老化状态[12]。

在黄褐斑的疗效评估中，黄褐斑面积严重程度指数(MASI)及其改良版(mMASI)是目前国际通用的核心工具[13]。MASI 通过评估面积、色素沉着程度和均匀性三个维度，分别对面部四个区域(额头、左右颧颊及下巴)进行计分，最终得出综合评分。但由于其计算过程较为繁琐，临床上更常用简化后的 mMASI，总分 0~24 分，分值越高提示皮损越重。在临床试验中，MASI 或 mMASI 的变化率常作为判定疗效的主要指标。此外，借助皮肤 CT 或色度计测得的黑素指数(Melanin Index)与红斑指数(Erythema Index)，可分别定量反映色素型、血管型黄褐斑的核心病理改变，指数下降往往提示治疗对相应分型的靶向作用有效。除了客观评分，黄褐斑生活质量量表(MELASQoL)则从患者主观感受出发，衡量疾病对社交、娱乐、情绪等方面的心理社会影响[14]。上述指标共同构建了黄褐斑严重程度、分型与疗效评价的客观体系，为治疗方案选择及疗效判定提供了支撑。

4. 口服药物

4.1. 氨甲环酸

口服氨甲环酸是目前唯一获得广泛专家共识的口服治疗选择，尤其适用于外用治疗效果不佳或需要联合治疗增效的患者，是血管型、混合型黄褐斑口服治疗的首选药物，也可通过抑制黑素合成辅助改善色素型黄褐斑[15]。氨甲环酸靶向纤溶－血管－炎症等多环节发挥治疗作用，使其成为与多种联合方案的核心口服药物。氨甲环酸抑制纤溶酶/纤溶酶原途径，阻断紫外线诱导的纤溶酶激活，进而干扰黑色素细胞与角质细胞的相互作用，下调表皮黑色素细胞酪氨酸酶活性，抑制黑素细胞增殖及黑素合成。它可下调 VEGF、ED-1 的表达，减轻皮损区毛细血管扩张，降低血管通透性，这一作用是其针对血管型黄褐斑的核心机制。此外，氨甲环酸还可减少皮损区前列腺素 E2 等炎症介质释放，从而减轻慢性炎症对黑素细胞的刺激，缓解炎症介导的色素沉着。其抗黑素生成作用还与分子结构相关，因与酪氨酸结构相似，氨甲环酸可竞争性抑制酪氨酸酶活性，直接阻断黑素合成过程，减少黑素颗粒的生成与沉积[16] [17]。

近年来，多项研究为氨甲环酸的临床应用提供了有力支撑。一项平均随访时间为 12.7 个月的观察性研究中，42 名患者每日两次服用 325 mg 氨甲环酸，73.8%报告皮损改善，且无改善者中 90.9%患者用药不足 1 个月。与安慰剂相比，一项针对中重度黄褐斑患者的 RCT 发现，每日两次 250 mg 氨甲环酸，持续 3 个月，mMASI 评分下降 49%，而对照组仅下降 18% [18]。另一项为期 24 周的 RCT 显示，口服氨甲环酸相比于安慰剂可改善黄褐斑相关红斑，进一步验证其针对血管成分的靶向治疗作用[19]。为确定有效剂量，一项随机开放标签试验对 50 名黄褐斑患者进行了为期 12 周的治疗和共 24 周的随访，发现每日两次 250 mg 与每日两次 500 mg 在改善 mMASI 评分、复发率及安全性方面效果相当[20]。与其他给药方式对比，在治疗中重度黄褐斑方面，口服给药可能更具前景[21]。一项前瞻性、随机、开放标签研究发现口

服氨甲环酸相比病灶内注射显著减少了 MASI 值[22]。另一项针对 40 名黄褐斑患者的 RCT 研究比较了每日两次 250 mg 氨甲环酸对比两周一次氨甲环酸溶液滚轮微针经皮给药的疗效，口服组和经皮溶液组分别有 70%和 45%达到 75%整体改善，但 MASI 评分无显著差异[23]。另一项采用相同剂量方案的研究发现口服和皮内氨甲环酸效果相同[24]。与其他疗法的直接比较中，发现口服氨甲环酸单药疗效优于富血小板血浆(PRP)治疗。一项纳入 60 名患者的研究发现，口服氨甲环酸 3 个月后 MASI 下降 65.7% ± 24.6%，而每月皮内 PRP 者下降 54.6% ± 20.7% [25]。

口服氨甲环酸与其他疗法联合应用亦是近年研究热点。三联乳膏(TCC)是黄褐斑外用治疗的首选，其主要成分为氢醌、糖皮质激素、维 A 酸，分别对应直接抑制黑素合成、抗炎、促进角质代谢作用，对于表皮型黄褐斑有效，但对于真皮或混合型黄褐斑则效果有限。一项针对重度黄褐斑患者的 RCT 研究发现口服氨甲环酸与 TCC 的联合治疗对于降低 MASI 值优于单独口服[26]。另一项同类 RCT 疗程仅 8 周，未报告患者的分型与严重程度，则发现 MASI 分数未显著下降[27]。一项针对 120 名黄褐斑患者的研究显示，每日两次 250 mg 氨甲环酸联合 TCC 治疗 12 周后，mMASI 改善幅度显著优于单用 TCC 组，分别有 65.6%和 11.9%的患者达到 75%以上的改善；治疗 24 周后，联合组复发率为 18.03%，对照组为 64.4% [28]。该研究进一步证实氨甲环酸与 TCC 的联合协同作用，且联合治疗可通过抑制血管增生减少色素沉着的维持因素，降低复发率。另一项 RCT 发现口服氨甲环酸联合 4%氢醌存在协同效应，但复发率无改善(联用组对单外用组为 30%对 26%) [29]。富血小板血浆(PRP)可促进皮肤修复、改善微循环，与氨甲环酸联合适用于血管型及伴屏障损伤的混合型黄褐斑。一项 RCT 发现联合口服氨甲环酸与 PRP 皮内注射治疗 12 周后，mMASI 评分中位数变化(2.90)显著大于单 PRP 组(0.90) [30]。4 名患者(15.4%)出现短暂的红斑和肿胀，联合组中有 1 名参与者(7.7%)在治疗后出现短暂的轻度胃肠道不适[30]。物理治疗(如激光、微针)直接作用于皮损局部，靶向清除黑素或诱导真皮重塑并修复基底膜。一项研究发现口服氨甲环酸联合 Q 开关 Nd:YAG 激光对真皮/混合型黄褐斑疗效显著优于表皮型(mMASI 改善：真皮型 64.44%、混合型 60.95%、表皮型 37.17%)，联合治疗组疗效显著优于单药组。12%患者出现反常性色素沉着，表皮型疗效有限且风险较高。停药 6 个月后两组复发率相当(联合组回升 32.40% vs 单药组 28.13%)，提示联合激光虽能提高短期疗效，但未能显著延长缓解期，表皮型需谨慎选择[31]。另一项研究显示，口服氨甲环酸联合氢醌治疗混合型黄褐斑疗效最佳(改善率 77.5%)，优于单口服氨甲环酸(35.9%)或联合低能量激光(24.9%)，且复发率最低(20%)，但局部刺激反应较常见[32]。一项临床及组织学研究显示，TCC 联合口服氨甲环酸和微针可显著减少表皮黑素、修复基底膜、改善光老化，且干细胞因子仅在微针组增加，而联合组未增加，提示口服氨甲环酸可能抑制干细胞因子分泌[33]。

氨甲环酸的安全性已在多项长期研究中得到验证。其常见不良反应以轻度胃肠道不适为主，包括恶心、腹胀、腹泻等，发生率约为 5%~10% [24]。这些症状多见于用药初期，通常随着用药时间延长而自行缓解，无须停药[34]。严重不良事件较为罕见，临床中最需警惕的是血栓形成风险，尤其对于有血栓病史、高血压、糖尿病或长期服用避孕药等高危人群。因此，用药前应详细询问血栓相关病史并检测凝血功能；用药期间需定期监测凝血指标，并避免与其他抗纤溶或抗凝药物联用。最新研究数据显示，常规剂量下氨甲环酸相关血栓发生率低于 0.5%，明显低于其他抗纤溶药物。通过规范筛查与监测，这一风险还可进一步降低，显示出良好的安全性优势，适合长期规范使用。对于高危患者，治疗前还应进行基线评估，包括凝血功能、血常规及肝肾功能检查[35]。

4.2. 谷胱甘肽

谷胱甘肽因其抗氧化特性而被用作美白剂，近年来在黄褐斑治疗中的潜在价值逐渐受到关注，其核心作用为抗氧化、直接抑制黑素合成，是色素型黄褐斑的口服辅助药物，也可作为氨甲环酸禁忌者的替

代选择。研究发现，黄褐斑患者血清及红细胞中谷胱甘肽水平与病情严重程度呈显著负相关，其缺乏可能加重氧化应激反应并促进黑素合成，这为补充谷胱甘肽治疗黄褐斑提供了理论依据[36] [37]。目前临床研究多采用每日 500 mg 的剂量。与安慰剂相比，连续 4 周口服谷胱甘肽可显著降低患者的 mMASI 评分，其疗效亦优于外用谷胱甘肽乳膏，亚组分析提示年龄 < 40 岁、黄褐斑病程 < 5 年、Fitzpatrick III型及表皮型更优，进一步验证其对表皮型黄褐斑的靶向改善作用[38]。但另一项针对 90 名黄褐斑患者的随机对照试验显示，每日 500 mg 谷胱甘肽的疗效不及同等剂量的氨甲环酸，耐受性良好[39]。谷胱甘肽无出血相关禁忌，无抗血管、抗炎作用，对血管型、混合型黄褐斑的改善效果有限，因此，谷胱甘肽更适合作为氨甲环酸存在禁忌(如凝血功能异常)时的替代选择，尤其适用于合并凝血功能异常的色素型黄褐斑患者。

4.3. 褪黑素

褪黑素是一种主要调节昼夜节律的激素，同时具有较强的抗氧化活性，适用于伴屏障损伤、氧化应激显著的色素型黄褐斑。其在黄褐斑治疗中的潜在作用机制可能与减少自由基损伤、抑制 α-MSH 的刺激作用以及维持皮肤屏障功能有关[40]。近年来的临床研究为其应用提供了初步证据。一项针对 50 名女性中重度黄(mMASI > 5)褐斑患者的 RCT 显示，每日口服 5 mg 褪黑素，连续治疗 8 周，可使黄褐斑 mMASI 改善 22%，显著优于安慰剂且未观察到不良反应[41]。一项针对 7 例顽固性黄褐斑(既往对多种治疗无效)的病例系列研究发现，口服褪黑素(3 mg/日，共 12 周)联合广谱防晒，所有患者均报告色素沉着减轻，mMASI 评分较基线下降，为口服褪黑素在顽固性黄褐斑中的应用提供了初步临床证据[42]。另一项 RCT 显示，口服褪黑素(3 mg/日)联合氨甲环酸治疗黄褐斑，疗效显著优于单用氨甲环酸，且起效更快，安全性良好[43]。上述结果表明，褪黑素作为抗氧化剂在黄褐斑治疗中具有一定潜力。

4.4. 酮替芬

酮替芬作为一种肥大细胞稳定剂，理论上可通过减少组胺等炎症介质的释放、减轻氧化应激及基底膜损伤，发挥抗炎作用并稳定皮肤微环境，从而间接辅助色素淡化，用于炎症主导型血管型及混合型黄褐斑的辅助治疗。一项纳入 74 名女性的 RCT 显示，口服酮替芬联合法莫替丁可使黄褐斑获得适度改善，初步提示其在联合治疗中可能具有一定的辅助价值[44]。该联合方案通过双重抗炎、抑制组胺作用治疗黄褐斑，但该研究未对不同分型做分层分析。在另一项联合口服氨甲环酸的随机对照试验中，酮替芬未能体现出统计学意义上的增效作用[45]。其辅助效果可能被氨甲环酸较强的抑黑素效应所掩盖，且氨甲环酸本身已具备抗炎、抗血管作用，与酮替芬的作用靶点重叠，二者联合未实现机制互补。总体而言，酮替芬尚未成为黄褐斑的常规治疗选择，需进一步研究验证其是否在特定亚型黄褐斑(如炎症主导型或血管增生型)患者中存在差异化获益，在联合治疗时需评估靶点重叠性。

4.5. 非那雄胺

非那雄胺在黄褐斑治疗中的作用尚存争议。作为一种 5α 还原酶抑制剂，非那雄胺常用于治疗脱发和前列腺癌。体外实验显示非那雄胺可抑制 MC1R 表达，从而降低酪氨酸酶和酪氨酸相关蛋白表达，减少黑素细胞中的黑色素生成，对色素型可能存在潜在改善作用[46]。然而，一项以氢醌乳膏为背景治疗的 RCT 显示，与安慰剂相比，非那雄胺未能显著改善治疗结局，因此尚无法对其疗效得出明确结论[47]。另一方面，部分临床病例报告及药物警戒研究提示，非那雄胺可能通过影响皮肤局部雌、孕激素水平，诱发或加重黄褐斑，尤其可能通过激素紊乱促进血管增生，加重血管型、混合型[48] [49]。总体而言，非那雄胺治疗黄褐斑的证据有限，暂不推荐作为黄褐斑的常规治疗药物。在因斑秃等其他适应症使用非那雄胺时，应告知患者潜在的黄褐斑诱发风险，尤其对于有黄褐斑病史的血管型、混合型患者，需谨慎使用。

5. 膳食补充剂

天然植物提取物主要通过抗氧化及光保护作用改善黄褐斑，核心靶向黑素合成的氧化应激诱因，适用于色素型黄褐斑的口服辅助治疗，但目前临床证据相对有限。

松树皮提取物(碧萝芷，Pycnogenol)在体外实验中显示出抗酪氨酸酶活性、抗氧化、抗炎及抗血管生成特性，可通过下调酪氨酸酶、减少 ED-1 等色素沉着相关介质，并抑制血管内皮生长因子，靶向色素型及轻度血管型混合型黄褐斑[50]。一项临床针对 44 名女性的 RCT 研究显示，每日两次口服 75 mg 碧萝芷作为外用 TCC 的辅助治疗，60 天时试验组和对照组的 mMASI 评分分别降低 49%和 34%，显著提升 TCC 疗效，且安全性良好[51]。

PLE (Polypodium leucotomos)来源于热带蕨类植物，具有光保护和抗氧化作用，可减少紫外线诱导的黑素合成，是色素型黄褐斑的辅助治疗选择[52]。一项 40 名黄褐斑患者的 RCT 中，每日两次 240 mg 口服 PLE 组，治疗 12 周，PLE 组和安慰剂组的黑色素指数改善分别 28.8%和 13.8%，但 MASI 和 MelasQoL 组间无显著差异，认为 PLE 对黄褐斑的改善不足以证明其成本和使用价值[53]。另一项试验探究作为外用氢醌乳膏的辅助治疗，PLE 组第 28 天治疗反应显著增强，表明临床反应更快，第 56 天 mMASI 减少了 49.4%，而安慰剂组下降了 32.6%，差异具有统计学意义，PLE 组和安慰剂组分别有 31.3%和 6.3%达到 mMASI 值 75%改善，但未达到统计学显著性；此外 MelasQoL 的改善也相当，提示其可改善和加速外用氢醌乳膏的疗效，耐受性良好[54]。

番茄提取物富含番茄红素，有助于减轻紫外线诱导的氧化应激。作为氢醌乳膏的辅助治疗，补充番茄提取物可提高血清超氧化物歧化酶水平，改善黄褐斑严重程度，二者联合通过系统及局部抗氧化、抑黑素，协同改善色素型黄褐斑[55]。基于羟基酪醇的橄榄提取物口服后，与安慰剂相比可降低黑素指数及 mMASI 值，提示其在黄褐斑控制方面具有一定潜力，适用于色素型黄褐斑的辅助治疗[56]。白藜芦醇具有抗炎及抵御紫外线损伤的作用，与谷胱甘肽的抗氧化作用互补，二者联合可使黄褐斑患者 mMASI 评分显著降低，该方案对经氢醌、维 A 酸类外用药物治疗后的患者仍显示明确疗效[57]。

总体而言，尽管上述膳食补充剂因其抗氧化作用在黄褐斑治疗中显示出一定潜力，但其核心作用靶点为氧化应激、黑素合成，仅适用于色素型及轻度血管型混合型黄褐斑的辅助治疗。但现有证据尚不充分，仍需进一步研究以明确其临床价值。

6. 总结与展望

口服氨甲环酸是目前黄褐斑单药治疗的一线选择，尤其适用于血管型、混合型黄褐斑，疗效确切、安全性良好。其他口服药物单用疗效有限，多作为辅助治疗或特定人群的替代选择：抗氧化剂(谷胱甘肽、褪黑素)适用于色素型黄褐斑；抗炎类药物(酮替芬)可作为炎症主导型血管型黄褐斑的潜在辅助。新兴药物仍处于研究阶段，需要更多高质量研究验证其疗效与安全性。联合治疗通过机制互补，靶向黄褐斑不同病理环节，进一步优化了治疗策略。与外用制剂、微针及激光等技术联用，在提高疗效、降低复发率及提升患者满意度方面优于单药治疗。临床实践中需结合皮肤镜、Wood 灯及皮肤 CT 分型动态调整联合方案，明确协同机制、避免靶点重叠：色素型黄褐斑以强化抑黑为核心，可选口服氨甲环酸联合外用 TCC/氢醌，谷胱甘肽可作为不适宜氨甲环酸时的安全替代；血管型黄褐斑以控血管因素为先，以氨甲环酸为基础，肥大细胞稳定剂、抗组胺药及具轻度抗血管作用的植物提取物可作为辅助或替代；混合型黄褐斑序贯或联合上述策略，伴皮肤屏障受损者需联用微针、PRP 修复基底膜，为后续治疗奠定基础。全程规范使用防晒是维持疗效、预防复发的基石。未来研究应聚焦于黄褐斑分型，推动精准个体化联合治疗方案的发展。同时，需关注新靶点的药物研发，如黑素合成通路相关因子(MITF、酪氨酸酶家族)、血管生

成标志物(VEGF、ED-1)、炎症因子(IL-17、PGE2)及氧化应激指标(谷胱甘肽、ROS 水平)等，以期开发出高效、低副作用的新型口服药物，丰富治疗选择。此外，开展大样本、多中心、特定亚组的长期随访研究，验证远期疗效、复发率及安全性，将为临床实践提供更可靠的循证依据。

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