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黑升麻在绝经女性健康管理中的研究进展

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摘　要

随着平均预期寿命的延长，女性有超过三分之一的生命处于绝经状态，围绝经期性激素水平波动及绝经后雌激素缺乏，引发机体诸多变化，引起令人困扰的更年期症状，亟需干预以提高女性福祉和生活质量。当前，激素补充疗法虽已被证实有效，但其存在适应症、禁忌症及慎用情况，不是所有患者都适用。因此需要更多可供选择的治疗方案，其中植物制剂黑升麻提取物被发现能有效缓解绝经症状，是激素补充治疗的合理替代药物。本综述旨在阐述和总结黑升麻提取物用于管理绝经女性健康的研究现状、有效性、安全性及作用机制。

关键词

黑升麻提取物，绝经后女性健康，作用机制，植物药

Research Progress of *Cimicifuga racemosa* in Menopausal Women's Health Management

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Abstract

With the increase of average life expectancy, women spend over one-third of their lives in the menopausal state. Fluctuations in sex hormone levels during the perimenopausal period and estrogen deficiency after menopause trigger numerous changes in the body, causing bothersome menopausal symptoms. There is an urgent need for intervention to enhance women's well-being and quality of life. Currently, although hormone replacement therapy has been proven effective, it has indications, contraindications and caution, and is not suitable for all patients. There is a need for more

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treatment options, among which the plant preparation black cohosh extract has been found to be effective in alleviating menopausal symptoms and is a reasonable alternative to hormone replacement therapy. This review aims to describe and summarize the research status, efficacy, safety and mechanism of *Cimicifuga racemosa* used to manage the health of menopausal women.

Keywords

***Cimicifuga racemosa* Extracts, Health of Postmenopausal Women, Mechanism of Action, Herbal Medicine**

1. 引言

绝经通常发生在 45~55 岁之间，本质是卵巢功能的衰竭[1]，目前中国女性的平均预期寿命已突破 80 岁[2]，不断升高的平均预期寿命使女性超过三分之一的生命在绝经状态下度过。围绝经期性激素水平的显著波动及绝经后雌激素的缺乏使机体发生一系列变化[3]，引起令人困扰和痛苦的更年期症状。除了自然绝经，因妇科良恶性疾病进行手术、内分泌治疗、化疗及放疗等医疗措施，导致卵巢功能抑制或衰竭[4] [5]，称为人工绝经。较之自然绝经，人工绝经者的症状出现更快、更严重[4] [5]。采取措施减轻更年期症状，会提高女性的福祉和生活质量。虽然激素补充疗法(*menopausal hormone therapy*, *MHT*)在控制更年期症状方面被充分证实有效[6]-[9]，但其存在适应症、禁忌症及慎用情况，不是所有患者都适用，尤其是存在激素补充禁忌证或错过治疗窗口期的(年龄 ＞60 岁或绝经 ＞10 年)。此外，部分患者对 *MHT* 顾虑大也不愿意使用。因此需要更多的替代选择方案，其中植物制剂已成为绝经女性健康管理的一种有效药物。黑升麻是一种被广泛开发和使用的草本植物，多项实验研究发现，黑升麻提取物可以有效缓解绝经症状[10]-[13]，尤其适用于上述不能或不愿用 *MHT* 的患者，是激素补充治疗的替代药物。本文结合近年文献，就黑升麻提取物在管理绝经女性健康中的研究现况进行综述。

2. 黑升麻提取物简介

2.1. 植物化学成分

黑升麻(*Cimicifuga racemosa*, CR)是一种原产于北美的植物药，在加拿大、中国也有所分布，并在欧洲被广泛种植[14]。黑升麻的根茎在以往被用于治疗风湿病、疟疾、喉咙痛、感冒和分娩相关并发症等疾病[15]。近几个世纪以来，黑升麻提取物通常用于缓解绝经妇女的更年期症状，如潮热、盗汗、睡眠障碍、眩晕、紧张、情绪波动和阴道干燥[16]。黑升麻的根茎富含多种成分，包括三萜苷、酚类、黄酮类化合物和生物碱，此外，还含有芳香酸、肉桂酸酯、树脂、植物甾醇和脂肪酸等次要化合物[17] [18]。目前的研究主要集中于三萜苷，三萜苷化合物在植物中积累并产生皂苷，三萜和皂苷已被证明具有一系列生物作用，如抗炎和抗癌作用，并可促进或诱导细胞凋亡[19]。迄今为止，从黑升麻提取物中已分离出多种三萜，其中 Actein (活性蛋白) and 23-epi-26-deoxyactein (23-epi-26-脱氧活性蛋白)是黑升麻根茎中含量非常丰富的三萜，常被用作黑升麻制剂的标准化标记[20] [21]。目前的研究认为三萜苷是黑升麻提取物中最主要的生物活性成分，发挥生物效应，可缓解绝经后症状。然而，由于缺乏对黑升麻提取物中的一种或多种活

性成分的标准化，大多数关于其疗效的研究都是针对它的全提取物或标准化提取物进行的，故虽然在提取物中发现了多种其他成分，但缺乏对这些成分的系统研究。

2.2. 作用机制

黑升麻的作用机制至今仍不明确，早先的研究发现黑升麻提取物不含雌激素，但在不同组织产生不同效果，在骨骼和阴道上皮等组织作为雌激素激动剂[22]-[24]，激活雌激素受体，表现出类似雌激素的作用；然而，在子宫和乳腺组织中作为雌激素拮抗剂[25]，表现出相反作用，抑制雌激素受体的活性。这种在不同组织中表现不同作用的特点，使黑升麻被视为一种选择性雌激素受体调节剂(*Selective estrogen receptor modulators*, SERMs)。后来的研究提示黑升麻提取物不与雌激素受体结合，对卵泡刺激素、黄体生成素、雌二醇、催乳素和皮质醇等水平没有影响[26] [27]，对靶器官安全，不增加乳腺密度，不刺激乳腺细胞增生，不影响子宫内膜厚度[28] [29]。最新研究认为，黑升麻含有类似神经递质的活性物质，通过调节下丘脑中枢神经系统发挥缓解绝经症状的作用[30]，主要有三个作用方式：(1) 5-羟色胺能的方式发挥作用，作用成分是 *N*-甲基-5-羟色胺[31]，并可能作用于 5-HT1A、5-HT1D 和 5-HT7 受体[32] [33]。(2) 直接与多巴胺 D2 受体作用。(3) 具有内源性阿片样活性，能与大脑中的 μ-阿片受体结合[34]。

3. 黑升麻药物在不同系统的作用

3.1. 对中枢神经系统

卵巢功能衰竭后雌激素的缺乏诱发一系列神经生化变化，引起中枢神经系统症状，如血管舒缩症状、睡眠障碍、焦虑和抑郁、偏头痛及认知能力的改变等。其中，体温调节的改变是引起血管舒缩症状的主要假设机制[35]，体温调节过程受到儿茶酚胺和/或血清素的调控，在这个过程中下丘脑扮演着重要角色，负责整合热信息并控制热调节反应[36]。有研究发现黑升麻提取物能与血清素受体结合，尤其是作为血清素受体 5-HT7 和 5-HT 1A 混合竞争配体[33] [36]，而这两种受体亚型都参与了下丘脑的体温调节，且可能在睡眠模式、情绪障碍中发挥作用[37] [38]。黑升麻提取物可能通过这种机制来缓解绝经后潮热、焦虑抑郁情绪[39]，并改善睡眠状况[40]。

3.2. 对骨骼系统

成年达骨量峰值后，骨形成与骨吸收之间良好的平衡对保持正常骨结构至关重要[41]。雌激素能促进成骨细胞的增殖与分化，也能抑制破骨细胞的分化与活性，帮助维护骨骼健康[42]。然而，绝经后雌激素水平降低，雌激素对破骨细胞的抑制作用减弱，骨吸收速度超过骨形成，绝经后骨量加速丢失。目前许多研究通过去卵巢骨质疏松大鼠模型探究了黑升麻提取物对绝经后骨质疏松的作用。其中有研究发现黑升麻所含的三萜苷能够抑制破骨细胞样细胞的形成和骨吸收活性，从而抑制破骨细胞的骨吸收，观察到骨密度的增加[43] [44]。另有研究发现，黑升麻可通过减少骨髓脂肪积累及抑制促炎细胞因子分泌来减缓骨质疏松的发展[45]。此外，一项为期 12 周的研究通过评估大鼠的骨密度、骨小梁结构，以及股骨和腰椎的生物力学参数等，对比戊酸雌二醇与黑升麻提取物在预防绝经后骨质疏松方面的效果，发现黑升麻能防止骨密度下降，并减少骨重吸收，从而保护骨骼结构[46]。许多研究支持黑升麻提取物及其所含三萜苷成分，可能延缓或改善绝经后骨质疏松和软骨退化[47]。有研究发现黑升麻提取物对骨标志物有利，在治疗后绝经妇女的血清中检测到骨吸收标志物(*N*-端肽)浓度降低，骨形成标志物(碱性磷酸酶)增加[48]。然而，在一项去卵巢骨质疏松大鼠试验中观察到，单独使用黑升麻提取物不会影响其骨密度或血清骨生物标志物水平，对改善骨质疏松的效果有限[49]。

3.3. 对生殖系统

绝经后雌激素的减退或缺乏，下生殖道组织受到影响，组织中的蛋白质含量降低，上皮细胞层变薄，平滑肌细胞形态和功能发生变化，阴道内血管数量及血流量显著减少及结缔组织的密度增加[50] [51]。这些变化导致阴道润滑度和弹性降低，阴道壁缩短、狭窄及更易受损[50]，引起生殖道不适症状。许多研究观察了黑升麻提取物对生殖道萎缩的疗效，如国外 Wuttke 等人的研究对比了激素治疗组与黑升麻提取物组的疗效，研究发现黑升麻在阴道粘膜发挥出有益的雌激素样作用，增加了阴道浅表细胞的数量，相较安慰剂组有效果，但逊色于激素治疗组[24]；国内也有许多临床研究显示在改善绝经期妇女生殖道萎缩症状方面，黑升麻提取物有良好的效果[52]-[54]，但需更多高质量的研究进行进一步验证。

3.4. 对心血管系统

绝经后女性更易发生高血压[55]及脂质代谢紊乱，其特征是更易发生动脉粥样硬化：低密度脂蛋白胆固醇(LDL-C)和甘油三酯(TG)升高，高密度脂蛋白胆固醇(HDL-C)降低[56]，同时雌激素缺乏使绝经后女性体重更易增加并发展为腹部肥胖，腹腔内脂肪积累与糖耐量异常、胰岛素抵抗和 2 型糖尿病风险增加有关[57] [58]。观察性和临床试验结果都清楚地表明，在绝经窗口期内开始激素补充治疗对绝经后女性的心血管系统有益[59]。然而随着绝经时间的增加，尤其当年龄 ≥ 60 岁或绝经>10 年后开始激素补充治疗可能会增加罹患中风、冠心病等心血管疾病的风险[60] [61]。因此，探究替代选择药物-黑升麻提取物对心血管系统的影响变得重要。在血压方面，Wang Z 等人的研究利用蟾蜍心力衰竭体外模型，发现黑升麻中的有效成分对 β-肾上腺素能受体(β-AR)具有非选择性活化作用，能激活 β1 和 β2 肾上腺素受体，这种活化作用可能产生有益的心血管效应[62]；Lilian Brites Campos 等人的研究利用高血压去卵巢大鼠模型验证了黑升麻在降低平均动脉压方面的有益作用[63]。在血糖代谢方面，去卵巢大鼠模型和临床随机双盲对照实验均表明黑升麻对血糖、胰岛素没有明显影响[63] [64]。在对血脂的影响上，不同试验有不同的结论。Leslie Spangler 等人的一项为期 3 个月的随机双盲安慰剂对照试验观察到，与安慰剂组相比，激素替代疗法组患者的低密度脂蛋白(LDL)水平相比基线有统计学意义的降低，然而，黑升麻治疗组患者的血脂水平(包括总胆固醇、低密度脂蛋白和高密度脂蛋白)并无统计学意义上的显著变化，且无统计学意义上的治疗效果。因此，该研究结果不支持黑升麻对血脂具有任何短期影响[64]。然而，另一项针对去卵巢大鼠的研究发现，摄入黑升麻提取物能够延缓体重增加、减少腹部脂肪积累，并降低空腹血清胰岛素水平，治疗后动物的血浆甘油三酯水平有所下降，但低密度脂蛋白水平却有所上升，但需考虑到啮齿类动物的血脂谱和脂蛋白与人类存在差异，这可能会对实验结果产生影响[65]。Nappi 等人的临床研究发现，绝经后女性在连续使用黑升麻提取物三个月后血脂变化为：高密度脂蛋白胆固醇水平略有上升，而低密度脂蛋白胆固醇水平有所下降，而血清甘油三酯水平没有受到治疗的影响[26]。

4. 黑升麻药物的临床应用范围

4.1. 围绝经期及绝经后女性

黑升麻药物在临床上被广泛应用于治疗更年期症状，黑升麻提取物可有效缓解围绝经期妇女的绝经症状，症状开始出现时即可应用[11]，对仍有月经或月经紊乱、雌激素水平不低的绝经过渡期患者，黑升麻药物尤为适用[66]。研究表明黑升麻提取物用于缓解绝经后女性的症状，疗效优于安慰剂，对应用激素顾虑较大、不愿或不能使用 *MHT* 的，可使用黑升麻药物治疗其绝经症状。目前认为黑升麻提取物在降低更年期症状评分和潮热方面有效[67] [68]，但不优于 *MHT*。同时，在改善生殖道萎缩症状，管理骨骼健康、心血管代谢及健康相关生存质量(HRQoL)方面，相较于激素补充治疗，黑升麻药物的有益作用尚没有

足够的高质量证据来确定。

4.2. 存在绝经症状的乳腺癌患者

在乳腺癌治疗过程中，他莫昔芬、促性腺激素释放激素激动剂(GnRH-α)、芳香化酶抑制剂及化疗可诱发或加重乳腺癌患者的绝经症状，由于雌激素替代是禁忌的，替代方案如黑升麻提取物已被证实可应用于乳腺癌患者，并表现出有益治疗作用[29] [69]-[73]，它不促进乳腺癌细胞系的细胞生长，对雌激素浓度没有影响，因此不会对乳腺组织产生不良影响，不会增加乳腺癌风险及复发。因而推荐有绝经症状的乳腺癌患者选择黑升麻提取物进行治疗。

4.3. 存在绝经症状的妇科肿瘤患者

宫颈腺癌、I 型子宫内膜癌、卵巢内膜样癌、子宫内膜间质肉瘤等激素依赖性肿瘤是雌激素治疗的相对或绝对禁忌证，这些患者对激素补充治疗心理负担更重，治疗风险更难把控，黑升麻不含雌激素成分，不与雌激素受体结合，对性激素、子宫及子宫内膜没有影响[28] [29]，适用于这类不能或需慎用 *MHT* 的人群。

4.4. GnRH-α 使用中有绝经症状的患者

子宫内膜异位症和/或子宫肌腺病患者在接受促性腺激素释放激素激动剂(GnRH-α)治疗时，由于体内激素水平降低，可能会引发围绝经期症状，从而限制了 GnRH-α 的使用。反向添加疗法常被用于减轻由 GnRH-α 引起的不良影响，但该法需要个体化地把控给药时机和剂量，且存在原疾病复发、血栓形成等潜在风险。试验发现 GnRH-α 与黑升麻提取物联合用于治疗子宫内膜异位症时，因 GnRH-α 引起的绝经症状得到了显著改善[74] [75]。GnRH-α 对卵巢功能的抑制作用通常在第 1 针注射后约 1 个月出现。鉴于黑升麻的药理学特性，建议从 GnRH-α 第 1 针即开始使用黑升麻提取物，联合治疗 3~6 个月[66]。

4.5. 合并严重肝功能不全的患者

一项采用去卵巢大鼠模型的实验发现，黑升麻会对肝脏的氧化还原状态产生不良影响，表现为实验动物的肝脏出现了氧化损伤，肝脏线粒体活性氧生成增加，同时过氧化物酶体过氧化氢酶活性降低，这一变化可能使肝脏更容易受到药物引发的肝毒性影响[63]。然而，另一项研究在大鼠模型上评估了高剂量黑升麻提取物的肝毒性，结果显示，黑升麻提取物并未对大鼠的肝脏形态及各项肝功能指标造成影响[76]。根据至今黑升麻肝毒性的病案报道[77]，对于有严重肝功能异常或肝病史的患者，应依据患者的具体健康状况谨慎选用黑升麻药物。

4.6. 在其他的 MHT 慎用群体

黑升麻不含雌激素，对卵泡刺激素、黄体生成素、雌二醇、催乳素和皮质醇，孕激素等水平没有影响[28] [29]，因此它对雌孕激素敏感的靶器官是安全的，在激素补充治疗慎用的群体中展现出良好的替代作用。同时黑升麻在绝经晚期，尤其是对于那些已错过激素补充治疗窗口期但仍有相关症状的绝经女性，仍然表现出较好的治疗效果。

5. 黑升麻药物临床应用的安全性

5.1. 不良反应

大量的临床前和临床研究表明，黑升麻有良好的安全性，副作用是罕见、轻微和可逆的。在已记录的不良反应中，胃肠道症状和皮疹最为常见，且随着时间的推移，这些症状会逐渐减轻，黑升麻引发的

整体不良事件发生率与使用安慰剂相当[76] [77]。

5.2. 药物相互作用

研究显示，黑升麻提取物与他莫昔芬和 GnRH-α 药物联合使用时，不会影响它们的疗效。同时，当与改善骨质疏松、血糖、血压及血脂的药物合用时，黑升麻提取物既没有抑制这些药物的有效性，也没有产生任何负面影响，甚至表现出一定的积极作用。

6. 总结

黑升麻提取物作为一种适用范围更广、更安全的植物制剂，能有效改善绝经女性血管舒缩症状，在不同程度上改善更年期相关症状。然而，相较于激素补充治疗，黑升麻提取物对绝经后女性健康的多方面影响尚无明确结论，如它对改善认知功能、情绪障碍，缓解生殖泌尿道萎缩症状，维护骨骼和心血管健康方面的效果尚需进一步验证。同样，尚不清楚黑升麻提取物的具体作用机制，特定化学成分与药理作用的联系。因此，亟需开展更多、更深入的研究，以全面揭示其作用机制，并探讨其对全身各器官系统可能产生的作用。值得注意的是，目前尚无研究结果支持黑升麻提取物含有雌激素，因此，它可安全地用于乳腺癌、雌激素依赖性肿瘤患者及其他激素补充治疗禁用及慎用的群体。专科医生在制定治疗方案时，可结合患者的自身情况及意愿考虑应用黑升麻提取物，以期为绝经后女性，尤其是那些不适用激素补充疗法的群体，提供安全、有效的治疗选择。

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