补益类中药治疗阿尔茨海默病作用及机制研究进展

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摘要 随着人口老龄化的加剧，阿尔茨海默病（AD）患者数量持续攀升，然其确切发病机制尚未完全明确，现有药物仅能缓解症状而无法根治。中医将AD纳入“痴呆”等范畴，认为其病机与肾精亏虚密切相关，多采用补益肾精治法，并在实践中重用补益类中药。随着现代科学方法的引入，补益类中药治疗AD的作用机制正逐渐被揭示。本文系统性回顾了近年来补益类中药为主的中药复方、单味药及活性部位、活性成分在AD治疗中的研究进展，重点梳理和总结了其复杂的作用机制，包括降低淀粉样蛋白β（Aβ）/tau蛋白、神经细胞保护和神经炎症抑制等。尽管补益类中药在AD治疗研究中取得了显著进展，但其临床转化应用仍面临着诸多挑战，未来我们需要更加专注于药效明确的补益类中药，进一步明晰其活性成分，阐明分子机制网络，以促进临床转化应用；同时，对尚未充分研究的补益类中药进行系统活性评价与活性部位筛选，以期发现新的治疗靶点，为AD治疗提供更多选择。

关键词 阿尔茨海默病；补益类中药；作用机制；研究进展

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Research progress on the effects and mechanisms of tonifying traditional Chinese medicine ingredients in the treatment of Alzheimer’s disease over the past five years

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Abstract With the intensification of population aging, the number of patients with Alzheimer’s disease (AD) continues to rise. However, the exact pathogenesis of AD remains unclear, and existing drugs can only alleviate

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symptoms without providing a cure. Traditional Chinese medicine (TCM) holds that the pathogenesis of AD is closely related to kidney essence deficiency. Treatment often involves tonifying kidney essence, with frequent use of tonifying TCM ingredients in practice. With the introduction of modern scientific methods, the mechanisms of action of tonifying TCM ingredients in treating AD are gradually being revealed. This article systematically reviews the recent research progress on the use of TCM ingredients, including formulas, single ingredient, active parts and active ingredients in the treatment of AD, focusing on summarizing their complex mechanisms of action, including reducing Amyloid-beta (Aβ)/tau protein, neuroprotection and inhibition of neuroinflammation. Although significant progress has been made in the research on tonifying TCM ingredients for the treatment of AD, there are still many challenges in their clinical translation and application. In the future, it is necessary to further focus on tonifying TCM ingredients with clear efficacy, delve into their active ingredients, and elucidate their molecular mechanism networks to facilitate clinical translation and application. Meanwhile, systematic activity evaluation and screening of active parts are carried out for the understudied tonifying TCM ingredients in order to discover new therapeutic targets and provide more options for the treatment of AD.

Keywords Alzheimer's disease; tonifying traditional Chinese medicine ingredients; mechanism; research progress

自1907年阿尔兹海默病(Alzheimer's disease, AD)被发现以来,尽管其多种病因已逐渐被揭示,但其确切的发病机制依然不清楚,且至今尚未开发出能够治愈该疾病的有效方法[1]。AD的病理特征主要表现为中枢神经系统的结构与功能受损,涉及蛋白质在神经系统中的异常沉积及神经退行性病变:一是由淀粉样蛋白β(Amyloid-beta, Aβ)在神经细胞外异常积聚形成的淀粉斑[2];二是由于tau蛋白过度磷酸化而在神经元内部形成的神经纤维缠结[3]。目前,被批准用于AD临床治疗的药物有4类,包括以多奈哌齐(Donepezil)、卡巴拉汀(Rivastigmine)、加兰他敏(Galanramine)等为代表的胆碱酯酶抑制剂[1];以美金刚(Memantine)为代表的谷氨酸受体拮抗剂[1];以仑卡奈单抗(Leqembi)和多纳单抗(Donanemab)为代表的抗Aβ药物[4];以布瑞哌唑(Brexpiprazole)为代表的抗精神病药物[5]。尽管这些药物在缓解AD患者症状方面确实展现出一定的疗效,但遗憾的是,它们仅能起到延缓病情发展的作用,而无法实现治愈或预防AD的目标。

AD属于中医"痴呆""迟钝病""健忘"等范畴[6]。中医认为,肾精亏虚是AD发病的根本,肾精不足则脑髓不充,记忆力衰退,中医临床上多采用补益类中药进行治疗[7]。补益类中药分为补气药、补阳药、补血药、补阴药四类,具有补益人体气血阴阳不足的功效,其在改善AD患者的认知功能和生活质量方面显示出巨大潜力。近年来,众多学者致力于探索补益类中药治疗AD的药效物质基础及分子作用机制,这些研究不仅深化了我们对补益类中药的认识,而且为AD的新药研发和临床应用提供了坚实的科学依据。本文旨在综合分析近年来补益类中药为主药的中药复方、单味药及活性部位、活性成分在治疗AD方面的作用及机制,以期能够为AD的药物研发和临床治疗提供有益的参考和启示。

1 补益类中药复方治疗AD作用及机制

中药复方是中药治疗AD的主要形式,因其多样的药理作用和多途径调节机制,在AD治疗中展现出了一定的优势。在临床实践中,以补益类中药为主的中药复方为AD治疗的常用方剂,在改善认知功能、缓解AD症状方面显现出显著疗效。近年来,大量研究聚焦于临床确有疗效的抗AD中医经典方剂,旨在深入剖析其具体作用机制,促进其临床转化应用。

1.1 补气类中药复方 以补气类中药如人参、黄芪、山药为主药的中药复方包括七福饮、开心散、生慧汤、四君子汤、洗心汤、黄精丸、塞络通等中医经典方剂,通过多机制协同作用,有效缓解AD症状并改善认知功能。研究发现,七福饮可通过改善肠道菌群结构[8]和抑制tau蛋白磷酸化过程[9]等途径发挥抗AD作用。开心散可减少Aβ的沉积及抑制tau蛋白的过度磷酸化[10],通过PTEN诱导的假定激酶1(PTEN induced putative kinase 1, PINK1)/帕金蛋白(Parkin)通路促进线粒体自噬[11],上调线粒体中去乙

酰化酶3（silent information regulator 3, SIRT3）表达以减少NLR家族Pyrin域蛋白3（nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3, NLRP3）激活[12]和激活Wnt/β-连环蛋白（β-catenin）信号通路以促进神经元存活与再生[13]等多种分子机制协同作用发挥抗AD作用。生慧汤及其颗粒剂通过调节神经递质[14]，经磷脂酰肌醇3激酶（phosphatidylinositol 3-kinase, PI3K）/蛋白激酶B（protein kinase B, AKT）/哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin, mTOR）信号通路激活自噬，促进Aβ和磷酸化tau蛋白的清除，改善AD学习记忆能力[15]。四君子汤通过调节中枢海马能量代谢及线粒体功能，改善AD症状[16]。洗心汤通过调节PI3K/AKT/糖原合成酶激酶-3β（glycogen synthase kinase-3β, GSK-3β）信号通路以减轻AD症状及其诱导的损伤[17]和降低炎症相关因子及其受体表达[18]等机制发挥抗AD作用。黄精丸能增强脑内抗氧化系统功能、降低神经炎症反应和氧化应激引发的$A\beta_{1\text{-}42}$沉积、维持APP蛋白表达水平，以发挥防治AD的作用[19]。塞络通可提高血管内皮生长因子（vascular endothelial growth factor, VEGF）表达，促进血管增殖，上调低密度脂蛋白受体相关蛋白1（low-density lipoprotein receptor-related protein-1, LRP-1）表达，促进Aβ清除，改善认知功能障碍等[20]。

1.2 补血类中药复方 以当归为主药的补血类中药复方如当归芍药散通过调节Toll样受体4（toll-like receptor 4, TLR4）/髓样分化初级应答蛋白88（myeloid differentiation primary response protein 88, MyD88）/核因子κB（myeloid differentiation primary response protein 88, NF-κB）信号通路抑制神经炎症反应[21]，调节肠道微生物群[22]，发挥神经递质调节和雌激素样作用[23]，促进小胶质细胞极化，增强Aβ清除能力[24]，调节脂蛋白受体表达，减轻脑内淀粉样变性和神经元变性[25]，调节二十二碳六烯酸代谢[26]等多种机制发挥抗AD的作用。

1.3 补阳类中药复方 以肉苁蓉为主药的补阳类中药复方如苁蓉散在临床展示良好的抗AD治疗效果，其通过增强下丘脑—垂体—性腺轴功能，提高血清雄激素水平，进而减少$A\beta_{1\text{-}42}$诱导的神经元丢失，以改善AD学习和记忆能力[27]。

1.4 补阴类中药复方 以女贞子和熟地黄为主药的补阴类中药复方包括二至丸、六味地黄汤、地黄饮子等。研究发现，二至丸通过直接调控组织蛋白酶D，发挥抗AD的作用[28]。六味地黄汤抑制神经胶质细胞活化及炎症因子的表达，以减轻神经炎症，保护神经元免受损害，从而改善AD症状[29]，其丸剂可激活AMP依赖的蛋白激酶（adenosine 5'-monophosphate-activated protein kinase, AMPK）/沉默信息调节因子1（sirtuin 1, SIRT1）信号通路以改善中枢神经线粒体功能，修复神经元损伤[30]。地黄饮子通过调节胰岛素受体底物1（insulin receptor substrate 1, IRS1）/PI3K/AKT/葡萄糖转运蛋白4（glucose transporter 4, GLUT4）信号通路减轻AD脑胰岛素抵抗，以改善AD认知功能障碍[31]。此外，地黄饮子还可通过靶向调控miR-34a-5p表达，进而影响PI3K/AKT/B淋巴细胞瘤-2基因（B-cell lymphoma-2, Bcl-2）信号通路以抑制大鼠神经细胞凋亡，同时影响TLR4/MyD88/NF-κB信号通路以抑制海马胶质细胞炎性反应[32]。

综上所述，补益类中药复方通过调节免疫功能、改善神经炎症、减轻脑内淀粉样变性和神经元变性，以及调节神经递质和激素水平等方面，对AD的治疗展现出多维度的疗效。

2 单味补益类中药及其活性部位治疗AD作用及机制

《中国药典》目前收录多种中药提取物，可作为中药新药的原料，深入开展补益类中药提取物的活性评价和作用机制研究可能为AD治疗提供新的药物选择。

2.1 补气药活性部位 人参及其炮制品提取物通过多途径发挥抗AD作用。研究显示，人参蛋白通过调节肠道微生物多样性以激活脑源性神经营养因子（brain-derived neurotrophic factor, BDNF）/酪氨酸激酶B（tropomyosin receptor kinase B, TrkB）信号通路，进而抑制APP、磷酸化tau蛋白表达[33]。人参炮制品——红参提取物可降低活性氧水平，抑制线粒体功能障碍、NF-κB活化和促凋亡基因的表达[34]，改善Aβ诱导的线粒体功能障碍，减少AD相关的Aβ沉积，改善神经胶质增生和神经元丢失[35]。此外，红参多糖可减少tau蛋白的沉积及过度磷酸化和Aβ的沉积[36]，同时，红参多糖非皂苷部位可减轻Aβ的蓄积、神经炎症、神经元丢失和线粒体功能障碍[37]。人参另一炮制品——黑参低聚物可抑制胆碱能功能障碍，调节肠道微生物群进而激活Kelch样

ECH相关蛋白1(Kelch-like ECH-associated protein 1, Keap1)/核因子红细胞2相关因子2(nuclear factor erythroid-2-related factor 2, Nrf2)途径以缓解氧化应激[38]。党参提取物可调节胆碱能功能、提高抗氧化和抗炎作用[39]。大枣乙醇提取物通过提高纤溶酶水平和活性从而改善突触缺陷[40]。红景天提取物可通过调节脑内甘油磷脂代谢[41]、亚油酸代谢、α-亚油酸代谢、鞘脂代谢、醚脂代谢[42]、谷胱甘肽代谢、花生四烯酸代谢[43],色氨酸代谢、鞘脂代谢和甘油磷脂代谢[44]等代谢紊乱,以发挥抗AD的作用。

2.2 补阳药活性部位　研究显示,菟丝子提取物可抑制神经细胞凋亡,激活GSK-3β和抑制tau磷酸化,防止Aβ过度蓄积后发生的突触丢失[45]。锁阳提取物可保护AD模型大鼠线粒体超微结构[46],通过激活PI3K/AKT/GSK-3β信号通路介导的自噬作用改善AD认知功能障碍[47],其总黄酮提取物具有激活BDNF/TrkB信号通路和抑制凋亡通路的作用[48]。益智仁提取物能调节氨基酸代谢、脂类代谢和能量代谢[49],神经递质的功能以及神经元网络的可塑性[50],其多糖提取物可抑制神经炎症[51]。核桃仁提取物可抑制胆碱酯酶[52],其蛋白降解产物可激活AKT和调节肠道菌群通路[53],脱脂核桃仁粉能调节神经细胞能量代谢和抗氧化能力密切相关的氨基酸代谢[54],核桃仁油则可促进神经细胞线粒体生物合成,增加基础三磷酸腺苷(adenosine triphosphoric acid, ATP)水平[55]。

2.3 补血药活性部位　研究显示,当归多糖可激活BDNF/TrkB/环磷酸腺苷反应元件结合蛋白(cyclic AMP response element-binding protein, CREB)信号通路发挥抗AD作用[56]。当归挥发油通过调节胆碱能神经递质、自由基氧化等介导的Aβ代谢有关,有效改善AD学习记忆能力[57]。楮实子提取物可特异性降低细胞凋亡信号转导,增加AKT和β-catenin信号转导从而发挥神经保护作用[58]。熟地和生地混合提取物通过降低血脑屏障通透性、保护血脑屏障完整性,减少脑内Aβ沉积,提高日常活动能力及记忆功能[59]。

2.4 补阴药活性部位　研究显示,石斛酚提取物可抑制蛋白水解过程和自噬—溶酶体途径,维持蛋白质稳定,减轻Aβ和tau蛋白的毒性和减少多聚谷氨酰胺的聚集[60]。石斛生物碱可调节PI3K/AKT/GSK-3β信号通路降低tau过度磷酸化[61],减少异常蛋白质/基因表达以保护神经细胞[62],通过脱氧核糖核酸(deoxyribonucleic acid, DNA)甲基化途径减轻高蛋氨酸饮食诱导的AD样症状[63],通过靶向Wnt/β-Catenin信号通路改善$A\beta_{25-35}$诱导的突触缺陷[64]。黄精多糖可重塑肠道微生物群减少肠道炎症发生从而改善认知功能[65]。枸杞提取物可激活Skinhead-1(SKN-1)介导的抗氧化系统和卵泡刺激素受体1(follicle-stimulating hormone receptor 1, FSHR-1)介导的线粒体未折叠蛋白反应以减低Aβ的生成[66],其多糖提取物可减少脑内tau蛋白的磷酸化水平[67],降低神经细胞$A\beta_{1-42}/A\beta_{1-40}$的比值[68],影响Aβ的加工,降低Aβ水平,修复海马CA 3-CA 1通路的突触功能障碍,恢复突触可塑性[69]。桑椹提取物可降低脑内肿瘤坏死因子-α(tumor necrosis factor-alpha, TNF-α)含量以减轻神经炎症反应[70],诱导Aβ寡聚体解离为单体和抑制Aβ单体聚合以减弱Aβ寡聚体的毒性[71],促进Aβ的清除和抑制神经炎症[72]。

3　补益类中药活性成分治疗AD作用及机制

补益类中药蕴含众多活性成分,针对不同病理环节发挥作用,展示了潜在的AD治疗效果。研究显示,人参皂苷Rg3通过改善线粒体功能障碍保护神经细胞[73],虫草素则通过抗氧化,抗凋亡保护神经细胞[74]。在调节Aβ方面,女贞子活性成分3-O-顺式或反式对香豆酰马斯林酸(3-*O*-*cis*- or 3-*O*-*trans*-*p*-coumaroyl maslinic acid, OCMA)通过抑制γ-分泌酶以降低Aβ水平[75],枸杞子活性成分羟基肉桂酸酰胺二聚体可促进Aβ聚集体的解聚[76],甘草查耳酮B可抑制Aβ的聚集和沉积[77]。在抗炎方面,人参皂苷CK显著降低海马内NLRP3炎症小体的激活和下游炎症因子的释放[78],肉苁蓉活性成分苯乙醇苷则通过抑制TLR4/NF-κB炎症信号通路减轻氧化应激损伤[79]。在调节胆碱能功能方面,肉苁蓉活性成分松果菊苷和毛蕊花糖苷能促进神经递质乙酰胆碱合成[80]。核桃五肽PW5可改变肠道微生物群群落,改善肠道生态失调发挥抗AD作用[81]。

4　小结与展望

基于中医理论及已有的研究报道,补益类中药已被证实在治疗AD方面具有广阔的研究前景和实际应用价值。对于已有报道且疗效确切的补益类中药,因其活性成分多样、作用机制复杂,后续有必

要进一步探索其药效物质基础及分子层面的网络调控机制；而对于提取物或活性部位在抗AD作用尚未得到充分研究的补益类中药，则有必要采用经典且可靠的体内外实验模型，系统性地进行活性评估与活性部位的筛选，并在此基础上进一步阐明其药效作用机制。

此外，系统开展补气药、补阳药、补血药及补阴药治疗AD的对比研究显得尤为迫切。这不仅能够有效缩小研究范围，集中探讨不同类型的补益中药在治疗AD中的作用特点，并筛选其标志性的活性成分，从而为补益类中药在AD治疗中的应用提供更加明晰的科学内涵解释。同时，通过对比分析也能够发掘出不同类别补益药物之间可能存在的相似作用机制与共有活性成分，这不仅丰富我们对补益类中药治疗AD机制的综合理解，也为后续研究提供宝贵参考，有助于完善和丰富中医药治疗AD理论框架。

当前，补益类中药治疗AD的研究仍主要停留在体外实验和动物模型阶段，高质量的临床研究相对较少。未来需要更多设计严谨、样本量充足的临床试验来验证补益类中药在治疗AD中的疗效和安全性。尤其是中药复方作为中医治疗的重要手段，在AD治疗中可能具有独特的优势。然而，目前对于中药复方多成分、多靶点的作用机制研究尚不深入。未来研究应引入新的研究方法和技术，如人工智能、大数据等，以更全面地揭示补益类中药及其复方在AD治疗中的复杂作用机制。利用这些先进技术对补益类中药进行更深入的数据挖掘和分析，将有助于我们发现新的候选药物和治疗策略。

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