·综述·

钩藤提取物及钩藤碱的药理研究进展

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摘要：钩藤是一味具有息风定惊、清热平肝功效的中药材。近年来，研究发现钩藤提取物及钩藤主要有效成分钩藤碱具有保护神经、降压、保护心肌、抗癌、抗炎、平喘等多种药理作用，且对多种疾病，包括心脑血管、癌症、哮喘等均具有潜在的治疗作用。该文概述了钩藤提取物及钩藤主要有效成分钩藤碱的药理作用研究进展，可为钩藤的临床应用提供依据。

关键词：钩藤提取物；钩藤碱；药理作用；研究进展
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Research Progress on Pharmacological Effects of Uncaria Extract and Rhynchophylline

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Abstract: Uncaria is a traditional Chinese medicine that has the effects of dispelling wind, calming shock, clearing heat and calming liver. In recent years, studies have found that Uncaria extract and rhynchophylline, the main active ingredient of Uncaria, have multiple pharmacological effects such as nerve protection, blood pressure reduction, myocardial protection, anti-cancer, anti-inflammatory, and anti-asthmatic. Moreover, Uncaria extract and rhynchophylline have potential therapeutic effects on cardiovascular and cerebrovascular diseases, cancer, asthma. This article summarizes the research progress of the pharmacological effects of Uncaria extract and rhynchophylline, the main active ingredient of Uncaria, and provides a basis for clinical medication.

Keywords: Uncaria extract; rynchophylline; pharmacological effects; research progress

钩藤为茜草科植物钩藤[*Uncaria rhynchophylla*（Miq.）Miq.ex Havil]、大叶钩藤（*Uncaria macrophylla* Wall.）、毛钩藤（*Uncaria hirsuta* Havil.）、华钩藤[*Uncaria sinensis*（Oliv.）Havil.]或无柄果钩藤（*Uncaria sessilifructus* Roxb.）的干燥带钩茎枝，具有息风定惊、清热平肝之功效。临床上钩藤多与天麻构成药对，仅用于心脑血管疾病的治疗，很少用于治疗其他疾病。近些年的药理研究发现，钩藤提取物及钩藤主要有效成分钩藤碱具有多种药理作用，不仅对神经系统疾病、心血管系统疾病有治疗作用，还对癌症、哮喘、代谢综合征、骨质疏松等多种疾病均具有潜在的治疗作用。本文系统阐述了钩藤提取物及钩藤主要有效成分钩藤碱的药理作用，以期为临床用药提供依据。

1 保护神经作用

阿尔茨海默病（Alzheimer's disease，AD）、帕金森病（Parkinson's disease，PD）、抑郁症、癫痫、脑

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缺血损伤等神经系统疾病发病的具体机制尚未完全阐明[1]。但研究发现，这些疾病均与氧化应激、炎症、衰老等所引起的神经损伤有关[2-4]。研究证实，钩藤提取物可有效地透过血脑屏障[5]，通过抗氧化、抗炎、抗衰老等机制，发挥保护神经的药理作用[6-7]，进而防治AD、PD、抑郁症、癫痫、脑缺血损伤等神经系统疾病[8]。

1.1 抗AD作用 AD的病理特征之一是β淀粉样蛋白(amyloid-β，Aβ)的异常聚集。体外实验表明钩藤碱能够抑制Aβ的聚集[9]。在AD小鼠动物模型中，钩藤水醇提取物能有效地改善AD小鼠的学习和记忆功能障碍[10]，有效抑制大鼠Aβ在大脑皮质和下丘脑的聚集和积累[11]，减轻AD大鼠下丘脑和皮层的神经胶质增生和神经变性[12]，改善小鼠海马神经损伤[13]。用现代技术制备的钩藤碱纳米颗粒可以有效穿过血脑屏障，并表现出有效的神经保护作用，有望成为AD治疗的替代药物[14]。另外，乙酰胆碱酯酶(acetylcholinesterase，AChE)是治疗AD的关键靶标，研究也证实钩藤水提取物能够有效抑制AChE活性[15]。

1.2 抗PD作用 PD是最常见的进行性神经退行性疾病，其特征是黑质纹状体组织中的多巴胺(dopamine，DA)神经元大量丢失。研究表明，钩藤水提取物可改善PD动大鼠模型纹状体DA水平[16]。在1-甲基-4-苯基-1,2,3,6-四氢吡啶(MPTP)诱导的小鼠PD动物模型中发现，钩藤乙醇提取物能够明显改善小鼠的行为障碍，增加DA及其代谢产物的含量。在1-甲基-4-苯基吡啶离子(MPP+)诱导的人神经母细胞瘤(SH-SY5Y)细胞模型中，钩藤乙醇提取物呈剂量依赖性地增强细胞活力，增加B细胞淋巴瘤/白血病-2(B cell lymphoma/leukemia-2，Bcl-2)、细胞周期素D1、磷酸化的细胞外调节激酶(phos-extracellular signal regulated kinase，p-ERK)、磷酸化丝氨酸苏氨酸蛋白激酶(p-serine-threonine kinase，p-AKT)的表达，显著降低线粒体跨膜电位，来减少细胞凋亡[17]。另外，在PD细胞模型中，钩藤碱能够通过调控磷脂酰肌醇-3激酶(phosphoinositide-3-kinase，PI3K)/蛋白激酶B(proteinkinase B，Akt)/糖原合成酶激酶3β(glycogen synthase kinase 3β，GSK-3β)途径，实现对神经细胞的保护作用[18]。

1.3 抗抑郁作用 研究表明，钩藤具有抗抑郁作用[19]。在抑郁小鼠动物模型中，钩藤碱能显著改善小鼠的抑郁样行为。进一步研究表明，钩藤碱的抗抑郁机制包括：①提高单胺神经递质水平，增强单胺氧化酶A的活性[20]；②升高神经生长因子和脑源性神经营养因子水平，减少肿瘤坏死因子α(tumor necrosis factor-α，TNF-α)和白细胞介素(interleukin，IL)-6的释放；③抑制核转录因子-κB(nuclear factor kappa Bp65，NF-κBp65)从细胞质到细胞核的转运，减弱NF-κB的结合活性[21]。

1.4 其他神经保护作用 研究表明，钩藤碱对癫痫具有潜在的治疗作用[22]。在癫痫大鼠动物模型中，钩藤碱可有效地降低大鼠癫痫发作程度，保护内侧内嗅皮质(medial entorhinal cortex，mEC)Ⅲ层神经元免受凋亡并终止mEC Ⅱ层神经元的自发癫痫样放电，通过抑制持续钠电流和N-甲基-D-天冬氨酸(NMDA)受体电流来抑制神经元的过度兴奋[23]。此外，研究[24-25]发现钩藤碱能够通过抑制氧化应激、抑制炎症反应、抑制凋亡来防治脑缺血损伤。

2 降压、保护心肌作用

高血压、冠心病心肌梗死是常见的心血管疾病。长期的高血压会引起心肌肥大，导致心脏重构[26]。而缺血再灌注损伤是冠心病心肌梗死治疗中存在的不容忽视的难题[27]。

研究表明，钩藤具有降压作用[28-29]。在自发性高血压大鼠中，钩藤水提取物治疗6周后，大鼠收缩压明显下降[30]。机制研究显示，钩藤降压机制复杂，首先与其能改善维生素和氨基酸代谢有关[31]，其次能通过改善下丘脑中的神经递质失衡并抑制肾素-血管紧张素系统和交感神经系统的过度活化[32]；再次可显著抑制氧化型低密度脂蛋白(oxidized low density lipoprotein，ox-LDL)诱导的氧化应激，缓解由ox-LDL诱导内皮细胞的自噬损伤，并改善内皮依赖性血管舒张功能[33]。另外，钩藤发挥血管舒张作用的信号传导途径包括一氧化氮/可溶性鸟苷基环化酶/环鸟苷单磷酸、前列腺素I2(prostaglandin I2，PGI2)、G蛋白偶联的M3和β2受体[34-35]，以及钙通道和钾通道[36-37]等。

此外，钩藤碱能够抑制心肌肥大，其机制与抑制体内心房利钠肽(atrial natriuretic polypeptide，ANP)、脑钠肽(brain natriuretic peptide，BNP)、β-肌球蛋白重链和相关的纤维化基因[包括转化生长因子-β1(transforming growth factor-β1，TGF-β1)、胶原蛋白Ⅰ、胶原蛋白Ⅲ和结缔组织生长因子(connective tissue growth factor，CTGF)]表达有关[38]。同时，钩藤

碱还能缓解心脏重构，其机制与调节核因子E2相关因子2(nuclear factor E2 related factor 2，Nrf2)核易位和调控促分裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)通路有关[39]。在心肌细胞缺血再灌注细胞模型中，钩藤碱呈剂量依赖性地增加心肌细胞的活力，并抑制缺血再灌注诱导的心肌细胞凋亡[40]。此外，钩藤碱还能够调节缺血再灌注心肌细胞中Ca^{2+}和基质金属蛋白酶(matrix metalloproteinase，MMP)的水平，抑制氧化应激和凋亡相关蛋白的表达，调节线粒体相关基因的表达，从而保护心肌细胞免受缺血再灌注损伤[41]。

3 抗肿瘤作用

在体实验表明，钩藤碱能有效抑制A549异种移植小鼠模型中的肿瘤生长[42]。进一步研究发现，钩藤碱能调控Rho相关卷曲蛋白激酶1(Rho-associated coiled-coil containing protein kinase 1，ROCK1)/磷酸酶-张力蛋白基因/PI3K/Akt信号通路，调节糖原合成酶激酶3β(glycogen synthase kinase-3β，GSK3β)去磷酸化和线粒体通透性转换孔的开放，最终导致半胱氨酸天冬氨酸蛋白酶(cystein-asparate protease，caspase)-3的活化，从而引起癌细胞凋亡[43]。

在细胞实验中，钩藤碱对正常细胞无细胞毒性，但对人类肝癌细胞HepG2表现出实质性的细胞毒性作用，可增加癌细胞中的活性氧(reactive oxygen species，ROS)的生成，降低还原型谷胱甘肽水平，激活caspase-8、caspase-9和caspase-3，诱导癌细胞凋亡。此外，钩藤碱可抑制人类肝癌细胞HepG2的增殖和迁移，抑制趋化性细胞受体因子4、MMP-9和MMP-2的表达，切断ERK、c-Jun氨基末端激酶(c-Jun N-terminal kinase，JNK)、环磷腺苷效应元件结合蛋白、Akt和信号转导和转录激活因子3(signal transduction and transcriptional activator 3,STAT3)等多个信号途径[44]。

在MDA-MB-231乳腺癌细胞中，钩藤水提取物呈剂量依赖地显著抑制癌细胞的活力和迁移能力，增加癌细胞ROS的产生，促进线粒体膜电位的丧失，升高Bcl-2相关X蛋白(Bcl-2 associated X protein，Bax)/Bcl-2的比值，进而诱导癌细胞凋亡[45]。另外，钩藤碱也可以诱导乳腺癌细胞发生DNA损伤，并抑制其转移，进而促进其凋亡[46]。

其余研究也表明，钩藤水提取物呈剂量和时间依赖性地增加鳞状癌细胞、前列腺癌细胞ROS的产生，降低癌细胞活力[47-48]。另外，通过比较发现，钩藤水提取物可不同程度地调节癌细胞和正常细胞的氧化代谢，增强化疗对癌细胞的细胞毒性[49]，减轻癌细胞的多重耐药性[50]，同时增加正常细胞对化疗的耐药性[51]。

4 抗炎、平喘作用

在哮喘小鼠动物模型中，钩藤水提取物腹膜内注射小鼠，可减轻小鼠支气管肺泡灌洗液中嗜酸性粒细胞的募集，减少肺组织中的胶原蛋白沉积，并抑制IgE和促炎细胞因子的产生，抑制NF-κB的转录，减少TNF-α的产生，减少呼吸气道阻力，显著减轻支气管周围炎症反应[52]。气道平滑肌细胞(airway smooth muscle cell，ASMC)的增生是哮喘进展的关键，研究[53-54]发现，钩藤碱能够通过抑制叉头框转录因子C1/NF-κB信号通路和Smad/MAPK信号通路，进而抑制AMSC的增殖并诱导其凋亡。

另外，在急性肺损伤的细胞模型中，钩藤碱可抑制炎性细胞因子的产生，抑制诱导型一氧化氮合酶和环氧合酶-2的表达，同时还能通过抑制Toll样受体4(Toll-like receptor 4，TLR4)/NF-κB/核苷酸结合寡聚结构域样受体蛋白3炎症小体途径来发挥抗炎作用[55]。

5 其他药理作用

钩藤碱对粪肠球菌具有抗菌作用[56-57]，同时可以明显减弱金黄色葡萄球菌的毒性[58]。钩藤乙醇提取物与特比萘芬或氟康唑具有协同作用，可减少真菌对抗菌药物的耐药性[59]。最近研究发现钩藤水醇提取物对登革热病毒具有抗病毒和免疫调节作用[60-61]，而钩藤甲醇提取物具有α-葡萄糖苷酶抑制活性[62]。在小鼠肥胖动物模型中，钩藤粗提物能显著降低小鼠的肝脏脂肪变性，增强胰岛素敏感性[63]。

在大鼠氯胺酮依赖性动物模型中，钩藤碱可以逆转氯胺酮引起的行为偏好[64]，对甲基苯丙胺和氯胺酮成瘾具有积极的戒断作用[65]。近年发现钩藤水提取物能够抑制核因子-κB受体活化因子配体诱导的鼠骨髓巨噬细胞和RAW264.7细胞向破骨细胞的分化，抑制NF-κB的活化，抑制成熟破骨细胞的骨吸收活性，显著改善骨小梁的微结构[66]。

6 讨论

在临床上，钩藤常与天麻构成药对，仅用于治疗

心脑血管疾病，而钩藤很少用于治疗其他疾病。通过对文献的分析总结，发现钩藤提取物及钩藤主要有效成分钩藤碱除了具有保护神经、降压、保护心肌药理作用外，还具有抗癌、抗炎、平喘、杀菌、抗病毒、改善糖脂代谢、戒断毒品成瘾、抗骨质疏松等作用。这提示临床上除了心脑血管疾病外，钩藤还能够用于其他疾病的治疗。

目前，临床上所用钩藤多为水煎剂，而药理研究为钩藤的多种提取物或钩藤的主要有效成分钩藤碱，二者存在一定的区别。因此，需要以水煎剂为研究重点，进一步明确钩藤的组分及药理作用。虽然钩藤的主要有效成分钩藤碱的药理作用研究比较深入，但是还没有相应的临床试验，临床上也无钩藤的相关注射剂。因此，应用现代科学技术，加大钩藤的开发力度，提取有效成分，进一步深入挖掘钩藤的现有药理作用，开发新药品对推广中药的临床应用具有重要的价值和意义。

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