

· 综述 ·

钩藤网络药理学多靶点效应价值研究进展

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摘要 中药钩藤为茜草科植物钩藤的干燥带钩茎枝, 所含化学成分包括生物碱类、萜类、黄酮类和有机酸类, 具有抗氧化、抗炎等多种药理活性, 对多种疾病具有潜在的治疗效用。网络药理学多成分、多靶点、多通路的特点能够分析中药活性成分群与疾病标志物之间的复杂作用机制, 阐明药物、靶点、疾病三者的关系。本文总结了基于网络药理学探究钩藤干预神经系统疾病、心血管疾病、炎症等疾病的研究进展, 为中药钩藤的临床应用提供理论依据。

关键词 钩藤; 网络药理学; 生物碱; 分子机制; 神经系统疾病; 心血管疾病

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Progress on the value of multi-target effect of Gouteng based on network pharmacology study

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Abstract *Uncaria rhynchophylla* (Miq.)Miq. ex Havil (Gouteng) is a dry and hooked stem branch of Rubiaceae, which contains chemical components including alkaloids, terpenoids, flavonoids and organic acids. It has antioxidant, anti-inflammatory, and potential therapeutic effects on various diseases. The characteristics of network pharmacology are multi-component, multi-target and multi-channel, which can analyze the complex mechanism of the active ingredient group of traditional Chinese medicine and the disease markers, and clarify the relationship between drugs, targets and diseases. This review summarises the research progress of the intervention of Gouteng in neurological disorders, cardiovascular diseases, inflammation, and other diseases based on network pharmacology and provides a theoretical foundation for the clinical application of Gouteng.

Key words *Uncaria rhynchophylla* (Miq.)Miq. ex Havil; network pharmacology; alkaloid; molecular mechanism; neurological disorder; cardiovascular disease

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钩藤化学成分包含生物碱类、萜类、黄酮类和有机酸类^[1], 对神经系统疾病、心血管疾病、炎症等均有抑制作用(表 1)。研究表明, 钩藤碱能够调节脑内超氧化物歧化酶、多巴胺和丙二醛的水平, 缓

解 α -突触核蛋白(α -synuclein, α -Syn)沉积^[2-3]; 柯诺辛碱 B 可加强 Beclin 1 与高迁移率族蛋白 B1/B2 相互作用, 促进 α -Syn 清除^[4]; 异钩藤碱可改善葡萄糖、乳酸和谷氨酸的异常代谢防治高血压^[5]; 槲皮素

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表 1 钩藤所含主要活性化合物信息

分 类	名 称	分子式	CAS号	化合物ID
生物碱类	钩藤碱	C ₂₂ H ₂₈ N ₂ O ₄	76-66-4	MOL008469(TCMSP数据库)
	异钩藤碱	C ₂₂ H ₂₈ N ₂ O ₄	6859-01-4	MOL008471(TCMSP数据库)
	去氢钩藤碱	C ₂₂ H ₂₆ N ₂ O ₄	630-94-4	MOL008477(TCMSP数据库)
	异去氢钩藤碱	C ₂₂ H ₂₆ N ₂ O ₄	51014-29-0	TCMC4211(TCMID数据库)
	毛钩藤碱	C ₂₂ H ₂₈ N ₂ O ₃	7729-23-9	MOL008487(TCMSP数据库)
	育亨宾	C ₂₁ H ₂₆ N ₂ O ₃	146-48-5	MOL008488(TCMSP数据库)
	四氢鸭脚木碱	C ₂₁ H ₂₄ N ₂ O ₃	6474-90-4	MOL008457(TCMSP数据库)
	柯诺辛碱	C ₂₂ H ₂₈ N ₂ O ₄	6877-32-3	TCMC5431(TCMID数据库)
	山柰酚	C ₁₅ H ₁₀ O ₆	520-18-3	MOL000422(TCMSP数据库)
黄酮类	槲皮素	C ₁₅ H ₁₀ O ₇	117-39-5	MOL000098(TCMSP数据库)
萜类	β-谷甾醇	C ₂₉ H ₅₀ O	83-46-5	MOL000358(TCMSP数据库)

能下调糖原合成酶激酶-3β(GSK-3β)/Fyn 信号通路,降低氧化应激水平,抑制心肌细胞纤维化^[6];绿原酸通过调节 nuclear factor kappa-light-chain-enhancer of activated B cells(NF-κB) 通路治疗类风湿关节炎^[7]。现有研究着重于单个活性化合物的作用机制,但多种活性成分协同作用的药效物质基础尚不明确。网络药理学的分析流程为:通过数据库获取药物与疾病的交集靶基因,对交集基因进行富集分析,得到中药活性成分群干预疾病的潜在机制,强调多成分、多靶点、多通路,不仅可以整合生物学与药物活性成分网络,推测中药活性成分群与疾病靶点之间的关系,阐明中药的复杂作用机制,还能解释中药复方组合规则,为揭示中药的药效学基础提供方向。

1 基于网络药理学研究钩藤治疗疾病的潜在机制

1.1 神经退行性疾病

钩藤及其所含活性化合物能够抑制阿尔茨海默病(Alzheimer’s disease, AD)、帕金森病(Parkinson’s disease, PD)等神经退行性疾病,延缓疾病进程,基于网络药理学研究揭示了以上抑制效果的潜在作用机制。

1.1.1 阿尔茨海默病 AD 的主要病理改变为淀粉样斑块(amyloid beta, Aβ)沉积和 tau 蛋白过度磷酸化^[8-9]。基于 AD 病理改变的研究结果揭示 angustoline, angustidine 和异去氢钩藤碱可减少 Aβ 产生,而柯诺辛碱、异去氢钩藤碱、毛钩藤碱等成分能够抑制 tau 蛋白过度磷酸化^[10]。Zeng 等^[11]通过 Gene Ontology(GO)生物学过程富集分析揭示了柯诺辛碱、柯楠因、异钩藤碱等多种生物碱成分通过

作用于 Aβ 和 tau 蛋白异常病变、突触功能失衡等靶点治疗 AD,潜在作用靶点或为丝氨酸/苏氨酸激酶 1(AKT1)、胱天蛋白酶 3(CASP3)、基质金属蛋白酶 9(MMP9)等。现代药理学研究证明,钩藤所含生物碱能够显著抑制 Aβ 沉积和 tau 蛋白磷酸化,缓解认知障碍^[12-13]。因此,阿尔茨海默病通路或为预防和治疗 AD 的重要通路。Jiang 等^[14]通过 Kyoto Encyclopedia of Genes and Genomes(KEGG)富集分析得出神经活性配体-受体相互作用、钙信号通路等也与 AD 发生发展密切相关。钩藤所含非生物碱成分对 AD 也具有潜在疗效^[15]。

1.1.2 帕金森病 PD 的主要病理改变为中脑黑质内多巴胺能神经元变性坏死,纹状体内多巴胺含量减少及黑质神经元胞质内路易小体异常聚集^[16]。李浩然等^[17]研究发现天麻-钩藤药对可干预 p53 信号通路、白细胞介素-17(IL-17)信号通路等细胞凋亡和炎症相关的通路从而对 PD 发挥抑制作用,在 TCMSP, TCMID 等数据库中筛得天麻-钩藤药对中有效成分共 58 种,包含山柰酚和槲皮素,为钩藤所含黄酮类化合物。尹茜茜^[18]通过构建蛋白质-蛋白质相互作用(PPI)网络模型发现,钩藤所含槲皮素、β-谷甾醇、山柰酚等成分通过作用于 AKT1、白细胞介素-6(IL-6)、肿瘤坏死因子-α(TNF-α)、血管内皮生长因子 A(VEGFA)等核心靶点抑制炎症因子聚集,发挥神经保护作用,潜在作用机制涉及肿瘤坏死因子(TNF)信号通路、hypoxia-inducible factor 1(HIF-1)信号通路及丝裂原活化蛋白激酶(MAPK)信号通路等。除黄酮、萜类化合物外,钩藤碱^[19]、异钩藤碱^[20]等生物碱成分也可抑制 PD 进程。

1.1.3 癫痫 癫痫发作通常伴有免疫紊乱, 认知障碍和精神异常, 治疗主要以西药为主, 但药物的不良反应多, 且停药易复发。临床研究显示, 钩藤复方制剂抗痫煎剂能够调节免疫紊乱, 改善患者的临床症状, 而钩藤单味药剂能够预防实验性癫痫^[21]。网络药理学研究结果显示, 钩藤及其复方制剂可通过作用于晚期糖基化终末产物-受体 (AGE-RAGE) 信号通路、HIF-1 信号通路、NF- κ B 信号通路等干预癫痫进程, 揭示其抑制癫痫的潜在机制或为降低炎症因子水平及介导神经递质传递等生物学过程^[22–23]。已有研究证实钩藤碱可通过抑制 I_{NaP} 和 *N*-甲基-D-天冬氨酸受体干预癫痫发生发展^[24]。

网络药理学研究表明, 山柰酚、槲皮素、 β -谷甾醇等黄酮及萜类化合物针对 PD 和癫痫展现出潜在的抑制效应; 生物碱类化合物则通过干预阿尔茨海默病通路及神经活性配体-受体相互作用通路抑制 AD 进程。

1.2 儿童期常见神经系统疾病

抽动障碍 (tic disorder, TD)、高热惊厥可归属于神经系统疾病, 常见于儿童。钩藤及钩藤复方制剂对 TD、高热惊厥均表现出较好的抑制作用。

1.2.1 抽动障碍 TD 以快速、重复和非节律性的不自主运动或发声为特点, 临床表现复杂。临床多用钩藤复方制剂治疗 TD^[25], 但具体机制不明。PPI 网络与成分-靶点网络揭示了钩藤中 β -谷甾醇、育亨宾、钩藤碱、槲皮素等成分通过干预磷脂酰肌醇 3-激酶-蛋白激酶 B (PI3K-Akt) 信号通路、钙信号通路及神经活性配体-受体相互作用途径发挥治疗作用^[26]; 研究表明钩藤复方制剂可通过干预 PI3K-Akt 信号通路改善大鼠抽动障碍^[27], 可验证网络药理学的研究结果。除此之外, 李建荣^[28] 构建调肝健脾方成分-TD 靶点-作用通路网络, 揭示调肝健脾方治疗 TD 的潜在机制为钩藤所含多种生物碱成分与毒蕈碱型胆碱受体 M1 (CHRM1)、肾上腺素能受体 α 1B (ADRA1B)、阿片受体 mu 1 (OPRM1) 等靶点相互作用从而抑制 TD 进程。

1.2.2 高热惊厥 高热惊厥常伴有意识错乱, 甚至可能引起癫痫发作, 造成脑损伤。治疗药物多为镇静剂和抗癫痫药, 不良反应多且预后差。蔡小其等^[29] 基于网络药理学研究发现钩藤中活性成分通过影响 AGE-RAGE、IL-17、TNF、HIF-1 等信号通路, 达到抑制炎症发生, 减少细胞凋亡的效果。临床常用羚角钩藤汤治疗高热惊厥, 该制剂能降低神

经元特异性烯醇化酶和髓鞘碱性蛋白的水平, 对中枢神经系统起到保护作用^[30]。

网络药理学研究结果表明, 钩藤及钩藤复方制剂干预 TD 和高热惊厥的潜在机制在于影响神经活性配体-受体相互作用、AGE-RAGE、TNF 等信号通路, 主要活性作用靶点或为 AKT1、IL-6、VEGFA、CHRM1 及 OPRM1 等。

1.3 心血管疾病

高血压发病原因复杂, 肥胖、炎症、糖尿病均有可能引发高血压, 且高血压持续发展易增加心力衰竭、慢性肾病、动脉粥样硬化等其他疾病发生的风险。网络药理学研究^[31] 表明, 中药钩藤所含 11 种有效成分通过协同作用于 29 个高血压相关靶点发挥治疗效用, 其中前列腺素内过氧化物合酶 1 (PTGS1) 和前列腺素内过氧化物合酶 2 (PTGS2) 为 11 种有效成分的共同作用靶点, 揭示 PTGS1 和 PTGS2 或为高血压的核心靶点。PTGS1、PTGS2 也是动脉粥样硬化的核心靶点, 槲皮素、山柰酚等黄酮类化合物可与 PTGS1、PTGS2 稳定结合, 干预动脉粥样硬化进程^[32]。槲皮素、山柰酚还可与 IL-6、AKT1、VEGFA 等核心靶点相互作用, 抑制炎症反应与氧化应激, 调节脂质代谢, 从而治疗糖尿病合并高血压^[33]。

网络药理学研究结果表明, 含钩藤的中药药对也可用于抑制多类高血压。黄晓纯^[34] 通过分子对接验证了天麻-钩藤药对中钩藤碱可与 AKT1、CASP3、甘油醛-3-磷酸脱氢酶 (GAPDH)、表皮生长因子 (EGF) 等多个肝阳上亢型高血压的核心靶点稳定结合, 说明钩藤碱可作为治疗肝阳上亢型高血压的潜在药物。祝娜等^[35] 利用 FunRich 临床表型富集分析得到钩藤-杜仲药对的最优适应证为妊娠高血压, 同时构建成成分-靶点-通路网络模型揭示该药对治疗妊娠高血压的关键靶点为 AKT1、一氧化氮合酶 2 (NOS2)、肾上腺素能受体 β 2 (ADRB2) 等, 涉及肾素-血管紧张素作用通路、AGE-RAGE 信号通路等。

钩藤复方制剂也可多成分多靶点多通路抑制高血压。清眩降压汤中 β -谷甾醇、山柰酚等活性成分可影响 MAPK、TNF、HIF-1 等多个信号通路, 干预细胞凋亡、炎症及氧化应激多个生物学过程^[36]。复方钩藤降压片中钩藤碱、异钩藤碱等生物碱成分通过作用于肾上腺素能信号转导通路、钙信号通路、血管平滑肌收缩通路调控高血压病理过程^[37]。

药物-成分-靶点-通路网络揭示了天麻-钩藤-牛膝-葛根复方治疗高血压的核心活性成分或为槲皮素、山柰酚、 β -谷甾醇、毛钩藤碱、育亨宾等, 这些核心活性成分通过调控 PI3K-Akt 信号通路、MAPK 信号通路及 rat sarcoma protein(Ras) 信号通路干预高血压的发生发展^[38]。p38 MAPK 通路为 MAPK 信号通路的主要组成部分, 有研究表明天麻钩藤饮治疗自发性高血压的潜在机制可能为干预 p38 MAPK/heat shock protein 27(HSP27) 通路^[39]。

基于网络药理学研究发现, 钩藤、含钩藤的中药药对与钩藤复方制剂干预多类型高血压的活性成分包含黄酮类、萜类和生物碱类化合物, 作用机制或为干预信号转导、脂质代谢、炎症等通路。现代药理学研究揭示了钩藤含有的生物碱成分或为发挥降压作用的主要活性成分^[40-41]。相关临床研究也可证实钩藤复方制剂对高血压具有较好疗效^[42-43]。

1.4 炎症

器官病变大多与炎症的不受控发展相关。基于网络药理学研究表明, 钩藤对哮喘、炎症性肠炎 (inflammatory bowel disease, IBD)、肺纤维化等疾病均存在一定的抑制作用。钩藤中多个活性成分可协同作用于 IL-6、VEGFA、MAPK8、JAK、雌激素受体 α (ESR1) 等靶点从而干预炎症进程。

1.4.1 哮喘 哮喘与气道炎症、遗传、微生物菌群等因素有关, 发作时易出现呼吸短促、困难、意识模糊等情况。钩藤复方制剂在临床上可被用来治疗哮喘^[44]。用 String 数据库构建成分-机制-靶点网络, 揭示了加味升降散治疗哮喘的核心靶点与 TNF、PI3K-Akt 等通路显著相关, 说明其治疗哮喘的潜在机制或为抑制炎症及气道平滑肌细胞增殖^[45]。钩藤所含生物碱成分也可作为治疗哮喘的潜在药物^[46-47]。王国玉等^[48]通过分子对接实验揭示了育亨宾可与 CASP3、MAPK8 等哮喘相关靶点稳定结合。

1.4.2 炎症性肠炎 IBD 包含结肠、直肠黏膜层及黏膜下层的病理改变^[49]。相关研究显示钩藤碱可作为 Janus 激酶 (JAK) 抑制剂与 JAK1、JAK2 等靶点稳定结合, 下调 JAK1 及 JAK2 蛋白, 治疗 IBD^[50]。

1.4.3 肺纤维化 异常的炎症反应会导致肺组织皱缩变硬, 氧气弥漫入血能力降低。异钩藤碱能够减少促炎因子形成, 抑制胶原产生, 该抑制过程涉及上皮细胞增殖与迁移、炎症以等生物学过程及 PI3K-Akt 通路^[51]; 钩藤碱也可抑制 receptor tyrosine kinase

(TEK)-PI3K/Akt 信号通路来限制肺纤维化^[52], 揭示了 PI3K-Akt 通路或为治疗肺纤维化的关键通路。

1.5 其他疾病

钩藤复方制剂在临床上可用于治疗绝经综合征, 调节激素水平^[53]。中药-活性成分-核心靶点-通路网络显示, 清心滋肾方的核心有效成分包含长春花苷内酰胺、缝籽嗪甲醚、槲皮素、芦丁、绿原酸等, 多种有效成分通过调节 MAPK、PI3K-Akt 等 19 条信号通路干预绝经综合征^[54]。

Zhang 等^[55]应用双维网络药理学及体内外实验揭示 GSK-3 β 是脱发的潜在靶点, 钩藤所含槲皮素和四氢鸭脚木碱通过促进 GSK-3 β 磷酸化, 激活 Wnt/ β -连环蛋白信号通路治疗脱发。

2 结 语

基于网络药理学对活性化合物及疾病靶点的结合位点进行深度分析, 筛选钩藤活性成分与疾病靶点相互作用的药效基团, 有助于快速确定活性官能团, 为新药开发、制剂研发与临床应用提供依据。临床多用钩藤单味药剂或钩藤复方制剂治疗高血压、炎症及神经系统疾病, 但整体作用机制尚不明确。网络药理学研究强调中药复杂体系的整体作用机制, 因而网络药理学研究结果与临床研究结果可相互补充。本文基于网络药理学对钩藤治疗疾病的潜在机制进行综述, 从客观角度揭示了钩藤中槲皮素、山柰酚、 β -谷甾醇、钩藤碱、异钩藤碱、毛钩藤碱、育亨宾等黄酮类、萜类及生物碱类化合物发挥治疗作用的潜在机制。钩藤所含活性成分通过干预炎症、细胞凋亡与自噬等信号通路抑制神经退行性疾病; 钩藤及钩藤复方制剂抑制儿童期常见神经系统疾病的潜在机制在于影响脂质和动脉粥样硬化途径、神经活性配体-受体相互作用通路以及 AGE-RAGE 信号通路; 干预脂质合成与代谢、炎症通路以及信号转导途径则是钩藤及其复方制剂治疗高血压的潜在机制; 炎症、细胞凋亡与生长等信号通路则为钩藤干预炎症相关疾病的主要途径。

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