Journal of Clinical Personalized Medicine 临床个性化医学, 2026, 5(4), 427-435
Published Online August 2026 in Hans. https://www.hanspub.org/journal/jcpm
https://doi.org/10.12677/jcpm.2026.54267

基于现代药理学研究探讨延胡索治疗肝郁气滞证型失眠的可行性

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收稿日期：2026年7月18日；录用日期：2026年8月11日；发布日期：2026年8月20日

摘　要

本研究立足现代药理学研究，旨在探讨延胡索治疗肝郁气滞证型失眠的可行性。肝郁气滞证型失眠在临床上较为常见，而延胡索作为传统中药有着诸多药用价值。通过现有的关于延胡索的药理成分的研究进行总结归纳，以及根据延胡索在肝郁气滞证型中的临床疗效，探讨其能否有效干预肝郁气滞所致失眠，为临床应用延胡索治疗该证型失眠提供依据，进而拓展中医药在失眠治疗领域的应用思路，推动中医药现代化发展。

关键词

失眠，不寐，延胡索，病理机制，药理作用，肝郁气滞证，异病同治

Exploring the Feasibility of *Corydalis yanhusuo* in Treating Insomnia of the Liver-Qi Stagnation Pattern Based on Modern Pharmacological Research

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Received: July 18, 2026; accepted: August 11, 2026; published: August 20, 2026

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文章引用: 万子怡, 杨东东. 基于现代药理学研究探讨延胡索治疗肝郁气滞证型失眠的可行性[J]. 临床个性化医学, 2026, 5(4): 427-435. DOI: 10.12677/jcpm.2026.54267

Abstract

Grounded in modern pharmacological research, this study aims to explore the feasibility of using *Corydalis yanhusuo* (Yanhusuo) in the treatment of insomnia of the liver-qi stagnation pattern. Insomnia of the liver-qi stagnation pattern is commonly encountered in clinical practice, and *Corydalis yanhusuo*, as a traditional Chinese medicinal agent, possesses numerous therapeutic values. By synthesizing existing studies on the pharmacological constituents of *Corydalis yanhusuo* and evaluating its clinical efficacy in patients with the liver-qi stagnation pattern, this paper investigates whether it can effectively intervene in insomnia caused by liver-qi stagnation. The findings are intended to provide an evidence-based rationale for the clinical application of *Corydalis yanhusuo* in treating this pattern of insomnia, thereby broadening the therapeutic approaches of traditional Chinese medicine in insomnia management and promoting the modernization of Chinese medicine.

Keywords

Insomnia, Sleeplessness (Bumiao), *Corydalis yanhusuo* (Yanhusuo), Pathological Mechanisms, Pharmacological Actions, Liver-Qi Stagnation Pattern, Treating Different Diseases with the Same Method (Yibing Tongzhi)

1. 引言

失眠，中医又称不寐，是一种以入睡或保持睡眠困难、早醒或睡后感觉没有精神为特点的疾病，以致白天功能活动有障碍为特征的疾病[1] [2]，并对心理和身体影响能够导致情绪异常[3] [4]、记忆困难、工作效率降低增高，它甚至与心血管疾病[5]和死亡相关。一些研究[6]-[8]显示，全球约三分之一的成年人报告有失眠症状，仅以西方国家为例，临床明确诊断为失眠病的患者占总人口的 5.8%~19%。中医理论体系中，失眠其病因病机复杂多样，涉及多个脏腑，肝郁气滞型失眠较为常见，多因情志不遂，致使肝气郁结，日久则耗伤肝血，肝血不足进而影响心血，最终导致心神不安而发为失眠。延胡索，又称元胡，为罂粟科植物，具有悠久的药用历史，是中医临床常用药材。其性辛、苦，温，归心、肝、脾经，有活血、行气、止痛之功，常被用于治疗气血瘀滞、心腹疼痛等症。鉴于肝郁气滞型失眠与情志、气血不畅密切相关，因此基于现有研究成果探讨延胡索治疗肝郁气滞型失眠的可行性。

2. 西医失眠病理机制

现有研究应用多种现代研究手段从神经递质、神经－内分泌－免疫机制的不同角度对失眠的发展过程进行了分析。

一是神经递质 GABA 约占 RF 中所有神经元的三分之一，是促进睡眠的抑制性神经递质[9]，研究发现，失眠患者大多存在 GABA 分泌减少、对中枢神经抑制效应普遍下降，导致脑内睡眠启动的电活动紊乱[10]。胆碱能神经元通过乙酰胆碱(Ach)在大脑皮层弥漫性释放，影响细胞和突触生理，促进突触可塑性以及睡眠到觉醒的转换[11]。Han 等人[12]采用光遗传方法，在慢波睡眠期时激活小鼠 BF 脑区的胆碱能神经元，发现小鼠向觉醒及快动眼期的转变频次明显增加，其中以觉醒的转换为主。而 5-HT 能神经元能够促进下丘脑有催眠效应的肽类物质累积，同时与 NE、DA 等神经递质协同起效，诱导大脑进入睡眠

状态[13]。基因敲除实验发现，五羟色胺缺失会导致中枢神经系统的觉醒水平降低[14]。

二是神经－内分泌－免疫网络三者之间存在双向信息传递，通过激素、神经递质、免疫因子等调控睡眠节律，维持稳态。下丘脑－垂体－肾上腺轴(HPA 轴)是身体对各种外部压力反应的中枢系统。失眠患者常出现有 HPA 轴功能亢进，肾上腺皮质激素作为 HPA 轴活动的指标，也是研究睡眠－觉醒周期神经生物学的重要激素。通过短时间外源性的给予健康女性大剂量的 CHR，观察到用药后的夜间觉醒度提高，睡眠效率下降[15]；机体若长期处于应激状态时，会激活 HPA 轴，使轴上激素分泌增加，进而增加糖皮质激素的分泌与释放，睡眠从而表现出机体持续兴奋，快动眼期睡眠减少、觉醒增加等一系列失眠症状[16]。

3. 失眠中医病机分型

“不寐”病名虽首见于《难经·四十六难》。但在《灵枢·邪客》篇中就将不寐描述为“目不瞑”“不得眠”“不得卧”，并提出其重要病机为“卫气不得入于阴”，是中医学初步形成失眠相关理论的标志。《素问·逆调论》记载有“胃不和则卧不安”。李中梓提出：“不寐之故，大约有五：一曰气虚，一曰阴虚，一曰痰滞，一曰水停，一曰胃不和”。情志失常、饮食不节[17]、劳逸失调[18]、病后体虚[19]等均可能出现失眠，不寐的病机总属阳盛阴衰，阴阳失交，阳不入阴，阴不敛阳。《中国失眠症诊断和治疗指南》[20]则在中医诊疗方法中将不寐的证候划分为：心胆气虚、肝火扰心、痰热扰心、胃气失和、瘀血内阻、心脾两虚、心肾不交。其中，研究发现，失眠证型以肝郁气滞为主[21]。《素问·五脏生成篇》中记载“人卧血归于肝”，可见睡眠与肝关系密切。肝主疏泄，肝气郁结时，气机升降出入失常，气血上逆，扰动心神，心神不宁，进而导致失眠。肝郁气滞型失眠的表现为入睡困难，易醒再入睡困难，早醒，晨起头晕头痛，伴有情绪低落或烦躁易怒，善太息，胸胁胀痛，腹泻，舌红暗苔薄白或黄腻，脉弦。

4. 延胡索

4.1. 古籍追溯

延胡索是罂粟科紫堇属多年生草本植物，史载于《开宝本草》，性温，味辛苦，入心、脾、肝、肺，是活血化瘀、行气止痛之妙品，尤以止痛之功效而著称于世[22]。李时珍在《本草纲目》归纳延胡索有“活血，利气，止痛，通小便”四大功效[23]。《本草求真》有言：延胡索，不论是血是气，积而不散者，服此力能通达，以其性温，则于气血能行能畅，味辛则于气血能润能散。

4.2. 现代药理

现代药理研究表明，延胡索中含有生物碱类、甾体类等多种化学成分，主要包括原阿片碱、盐酸巴马汀、去氢紫堇碱、延胡索乙素、延胡索甲素等[24]，具有镇痛、抗炎、抗焦虑抑郁、神经保护等作用。其中生物碱是主要的生物活性成分[25]。来自延胡索的生物碱主要是原小檗碱(以四氢巴马汀(THP)、棕榈齿、四氢小檗碱为代表)、阿朴菲型生物碱(以 D-海罂粟碱为代表)、阿片类药物(以原阿片碱为代表)和其他。

4.2.1. 镇痛

延胡索的镇痛作用可归因于多种机制，包括调节神经递质系统、信号通路[26]、抑制炎症[27] [28]和电压门控钠通道[29] [30]等。Wang 等人[31]通过在不同的疼痛模式(即急性、炎症和慢性疼痛)中测试延胡索(RC)，来系统评价其抗伤害性，并探索机制，结果表明，RC 有效减轻了急性、炎症和神经性疼痛，而不会引起耐受性，同时在体外，RC 抑制了显着的多巴胺受体拮抗特性。Luo 等人[32]通过细胞膜固定层

析法从延胡索中筛选出 9 种调节 P2X3 受体的潜在活性成分，发现卡文定碱(CAV)能通过 P2X3 信号通路轴抑制小胶质细胞的激活，发挥镇痛作用。周梦媛等[33]采用免疫荧光和 western blotting 测定蛋白表达水平，并建立细胞体外研究，得出 RC 总生物碱(RC-TA)可显著缓解慢性缩窄性损伤(CCI)大鼠神经性疼痛、抑制脊髓中枢敏化的结果。

4.2.2. 抗焦虑和抗抑郁作用

金李莎 Jin 等人[34] [35]使用细胞模型和小鼠突触体研究发现，延胡索提取物中去氢延胡索素(DHC)可能通过抑制 uptake-2 转运体，改变大脑中单胺的含量并降低周转率，达到抗抑郁作用。Fang 等人[36]采用蔗糖偏好试验、悬尾试验和强迫游泳试验评价抑郁症模型小鼠的行为，用酶联免疫吸附测定和 PCR 技术检测抑郁相关因素，发现延胡索多糖(CYP)可能通过改善肠道菌群失调、促进短链脂肪酸(SCFA)的产生和激活 5-HT 信号表达来缓解抑郁症。Wu 等人[37]使用 1H-nmr 代谢组学研究了总生物碱(YHTA)在慢性不可预测的轻度应激(CUMS)大鼠模型中的抗抑郁作用，通过血浆代谢分析和多变量数据分析鉴定出抑郁样大鼠中的 13 个生物标志物，YHTA 治疗后，模型组和 YHTA 治疗组上述异常代谢物均表现出恢复正常水平的趋势，结果表明 YHTA 对抑郁症具有良好的治疗效果。Zhang 等人[38]基于酶固定化磁珠的方法快速从延胡索中筛选和鉴定出单胺氧化酶 A 抑制剂，用于抑郁症的治疗。

4.2.3. 抑制乙酰胆碱酯酶活性

最新研究[39]-[41]发现，根据高分辨电喷雾电离质谱(HRESIMS)、1D 和 2D 核磁振谱的广泛波谱数据分析阐明了异喹啉生物碱的结构，并通过 ECD 数据证实了它们的绝对构型，异喹啉生物碱与 IC 显示显著活性 $_{50}$ 与加兰他明(1.34 μM)相比，值为 0.78 (μM)，进一步支持 AChE 抑制活性。而根据胆碱能系统假说，阿尔茨海默病(AD)是大脑皮层乙酰胆碱能水平降低的结果。因此，抑制 AChE 活性是 AD 的常见治疗选择。Zhang 等人[42]研究了 THP 对氯胺酮诱导的小鼠学习和记忆障碍的神经保护机制，THP 处理后，氯胺酮诱导的小鼠 AChE 活性显著降低，而 ACh 水平的降低则逆转。Lyu 等人[43]通过使用 D-半乳糖和氢溴酸东莨菪碱诱导的 AD 小鼠模型，并口服延胡索(CR)，发现其改善了 AD 小鼠的焦虑样行为、空间和非空间识别以及记忆容量。

4.2.4. 神经保护

谷氨酸的过量释放可能导致神经系统的急性和慢性损伤(如缺血性脑卒中和神经退行性疾病)的兴奋性毒性[44] [45]。Lin 等人[46]的研究发现去氢延胡索素(DHC)通过抑制突触前电压依赖性 Ca^{2+}内流和 MAPK/ERK/突触素I信号通路来抑制大脑皮层突触体突触前谷氨酸的释放。多项研究[47]-[49]表明，延胡索所属的罂粟科紫堇属中药提取物，如季原小檗碱生物碱、异喹啉等，具有抗神经炎症和神经保护活性的作用。

4.2.5. 其他

有研究[29] [50] [51] [52]发现去氢延胡索素(DHC)能抑制动脉粥样硬化，软化血管，并通过上调 FoxO 信号通路以抑制细胞凋亡，发挥心脏保护作用。张永静等[53]通过高效液谱法发现延胡索提取物通过 PLC/PKC/STAT3 通路抑制肥大细胞活化，进而可缓解食物过敏。Wu 等人[54]发现延胡索提取物显示出在体内外均表现出不同程度的抗幽门螺旋杆菌、胃保护和抗炎活性。齐雅芝等人[55]研究发现延胡索的总生物碱可能通过调节肠道菌群，恢复肠道免疫稳态，抑制脑组织炎症级联反应，减少神经元铁死亡，从而改善糖尿病认知能力的下降。Wen 等人[56]发现四氢巴马汀(THP)可以通过抑制 TLR4/NF-κB/NLRP3 信号传导诱导 M1 巨噬细胞极化为 M2 以抑制炎症，来减弱急性肺损伤。Yu 等人[57]发现左旋四氢巴马汀(L-THP)通过体内和体外调节 PPARγ/NF-κB 和 TGF-β1/Smad 通路来抑制肝星状细胞(HSC)的活化和自噬，从而减少肝纤维蛋白病，降低肝纤维化的发生率。

5. 延胡索在肝郁气滞证型中的运用

“证”是由证候与病机组成的统一体，即证候是证之外候，是病机的证据，病机是证的内在本质，是证候的根源[58]。中医“治病求本”，本于病机，因此中医以辨证为主，病机相同即病证同，治法亦相同，即异病同治。延胡索经研究发现在辨证为肝郁气滞证的疾病中疗效显著。

5.1. 失眠

中医认为肝郁气滞型失眠应治以疏肝解郁，行气活血，养心安神。基于数据挖掘国医大师张震论治不寐经验[59]，发现延胡索、香附是最常用的第二对药对，疏肝行气解郁，针对病机治疗的同时改善伴随症状，提高生活质量。王琦院士[60]用交合安魂汤、血府逐瘀汤，喜加用延胡索通畅气血，《本草纲目》曰：“延胡索能行血中气滞，气中血滞”。刘吉善[61]擅从肝论治失眠，常用酸枣仁–延胡索治疗不寐。国医大师禤国维教授[62]认为治理失眠应法以滋补肾阴、养心安神为主，佐以理气活血，运用六味地黄丸合天王补心丹加减，方中重用延胡索理气活血，使血脉通、营卫调和，魂归于肝。

5.2. 抑郁/双相情感障碍等

肝郁脾虚证是双相情感障碍、抑郁症的核心病机，也是治疗之本[63] [64]。根据仝小林院士提出的态靶辨治，周流畅等人将抑郁症“瘀态”病机定为肝气郁结，气滞血瘀，治以疏肝解郁、活血化瘀，代表靶药为郁金、延胡索[65]。赵婉璐[66]等人通过中医传承辅助平台发现延胡索–川楝子药对常用于气滞血瘀证、肝郁气滞证、肝郁血虚证等主治证侯中应用广泛。

5.3. 其他

基于现代临床数据挖掘发现，诸多疾病如胆结石、恶性肿瘤、消化性溃疡等，在疾病的某些阶段均可辨证为肝郁脾虚证，临床经验用药多在香砂六君子汤的基础上加以金铃子散(川楝子、延胡索)疏肝行气止痛[65] [67]-[70]。

6. 讨论与结果

延胡索在《中国药典》中记载归肝、脾经，辛、苦，温，用以活血，利气，止痛。而现代药理学研究表明，延胡索主要作用于心脑血管、神经递质等方面，具有镇痛、抗焦虑抑郁、抗血管软化、神经保护等作用，与其传统医学作用相呼应。同时现代众多中医大家的临床经验表明，延胡索在辨证为肝郁气滞证、肝郁化火证、肝郁脾虚证等证型的疾病治疗中发挥着关键作用。综上所述，延胡索在治疗肝郁气滞型失眠方面具有明确而有效的作用，但其具体成分通过哪些机制达到发挥改善睡眠的作用，还需要进一步的研究。

7. 展望

结合现有研究短板，未来可继续开展相关研究方案，建议如下：

第一，构建贴合中医病机的复合失眠动物模型。现有单一造模方法难以完整复刻肝郁气滞情志郁滞、气机失调、睡眠紊乱复合特征，是否可联合慢性不可预知应激、五羟色胺耗竭复合造模，从行为学、HPA轴激素、脑内神经递质多维度完成模型验证，为机制研究提供可靠载体。

第二，结合网络药理学与分子对接预测延胡索活性成分、疾病交集靶点及调控通路，筛选四氢巴马汀、去氢延胡索素等核心生物碱，通过分子对接评估化合物靶点结合能力，再开展细胞与动物体内实验，验证预测通路，阐明延胡索多成分协同安神、疏肝的分子机制。

第三，开展小规模随机对照临床预试验，纳入肝郁气滞型失眠患者，设置延胡索有效部位制剂组与安慰剂组，以 PSQI、肝郁证候积分为核心疗效指标，同步监测肝肾功能与不良反应，初步明确药物有效剂量、疗程及安全性，为大样本临床试验奠定循证基础。

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