马钱子及其活性成分临床应用研究进展

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摘要　马钱子中可以提取出士的宁、马钱子碱、环烯醚萜苷等多种具有生物活性的化合物。综述了马钱子主要提取物在神经系统、免疫系统、肌肉骨骼系统、抑制病原微生物和抗肿瘤方面的药理机制,并分析了其活性成分的临床应用价值。结果发现马钱子活性成分具有可兴奋中枢神经系统,提高感觉器官的功能,有效减轻炎症反应,有较强的镇痛抗炎功能,此外还对多种肿瘤具有抑制效果,未来有望开发成为抗血管增生和抗癌治疗药物。

关键词　马钱子;士的宁;马钱子碱;药理机制

马钱子别名番木鳖,是中国的传统中药,为马钱科植物马钱 *Strychnos nuxvomica* L. 的成熟种子[1],其性苦、寒,在《本草纲目》中有"治伤寒热病,咽喉肿痛,消痞块"的记载。马钱子最先在亚洲被认识,并广泛应用于治疗各种疾病,例如消化不良、神经系统疾病、慢性风湿病、尿失禁、阳痿等[2-3]。17世纪,马钱子被引入美国,随后在欧洲国家也有使用。大约2个世纪前,研究人员分别从化学和药理学2个层面对马钱子进行深入研究后发现:士的宁和马钱子碱是马钱子的主要毒性成分[4],合理使用时则具有很高的临床医用价值,由此衍生出多种药物制剂,如粉末、酊剂和液体提取物[5-6]。包括美

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国药典、英国药典、爱丁堡和都柏林药典在内的多个药典中都有关于其制剂的记载[7-8]。由于马钱子在世界各国临床上的广泛应用,马钱子在中医药走向国际的过程中,成为备受各国专家关注的药物之一;也是迄今为止,研究最详细的中药之一。本文综述了目前马钱子在神经、免疫、肌肉骨骼系统以及抗肿瘤、抑制微生物方面的研究进展。

1 马钱子临床应用研究

1.1 马钱子在神经系统中的研究

马钱子组方在神经系统疾病中的应用有记载于《医林改错》的"龙马自来丹"、记载于《解围元薮》卷三的"仙花膏"等方剂。现代医学研究指出士的宁是马钱子的主要成分,可以兴奋整个中枢神经系统,其中大脑皮质感觉中枢和脊髓对士的宁具有高度的敏感性,可以提高各感觉器官的功能,还能兴奋血管运动中枢和咳嗽中枢[2,9-10]。马钱子是自然界提供的经典神经活性化合物,寻找士的宁所作用的神经递质受体一度成为研究热点。甘氨酸受体(glycine receptors,GlyRs)属于五聚体"Cys-loop"受体一族,是脊髓和脑干中分布广泛的一种调节运动行为的受体,在中枢神经系统中发挥重要作用,GlyRs的功能障碍将引起严重的神经系统疾病[11]。在同聚和异聚GlyRs的高分辨率晶体结构被发现之后,得以根据士的宁在这些受体结合囊中的特定相互作用,对士的宁的构效关系做更深入的探索[12]。研究发现,士的宁结合位点在GlyRs中高度保守,在同源和异源受体中有着相同的方向和结合模式[13]。作为一种天然产物,士的宁已通过进化选择优化为与生物靶点的强相互作用。因此,几乎所有对士的宁的结构修饰都会导致GlyRs拮抗剂活性降低。

然而探索通过修饰士的宁来设计配体,是一种有效减少其毒副作用,增加其治疗效果的一种策略。基于冷冻电镜技术不断进步,最近GlyRs的高分辨率结构为未来基于结构的配体设计提供了机会[14]。在过去使用的基于配体的策略中,新配体是通过士的宁的结构修饰来设计的,而在基于结构的方法中,配体是使用来自结合位点的结构信息来生成的,包括所有残基作为配体-受体相互作用的潜在结合伙伴[15]。基于结构的方法可能会发现GlyRs配体具有与士的宁不同的简单结构和支架。与GlyRs/士的宁结构类似,完全有可能在可预见的未来获得士的宁与其某些其他靶点复合物的高分辨率结构并有助于配体设计[16]。此外,虽然新一代的神经递质mAChRs变构调节剂的特点是靶向效价、亚型和靶向/非靶向选择性远远高于马钱子碱/马钱子碱衍生物,因此对这些受体来说,它们构成了比马钱子碱衍生物更有吸引力的线索,但马钱子碱所表现出的强大的乙酰胆碱受体(acetylcholine receptor,AChR)拮抗作用为开发新型镇痛药物提供有价值的前景[17]。此外,还有研究表明,马钱素可改善东莨菪碱诱导的小鼠学习和记忆障碍[18-19]。

随着冷冻电镜等新技术不断进步,对马钱子结构及其在神经系统中作用的认识不断加深,很可能会发现马钱子新的结构和功能。

1.2 马钱子在免疫系统中的研究

马钱子组方在免疫系统疾病中的应用有记载于《外科证治全书·卷四》的"祛风逐湿散"等方剂。现代医学研究指出马钱子具有免疫调节作用。在一项小鼠迟发性超敏反应研究中,马钱子碱可以有效降低免疫T细胞增殖,减轻炎症反应,降低模型鼠的耳廓肿胀程度,但对脾脏和胸腺指数没有明显影响。以上研究提示,马钱子碱主要作用于T淋巴细胞,发挥免疫抑制作用,尚无对免疫器官有影响的证据[20]。为揭示马钱子的免疫调节机制,有一项研究构建了实验性自身免疫性重症肌无力大鼠模型,试验发现马钱子可以降低模型大鼠的乙酰胆碱受体抗体(acetylcholine receptor antibody,AChRAb)水平,从而能够维持免疫抑制和免疫活化之间的动态平衡[21]。此外,马钱子叶中含有的萜类化合物也表现出调节巨噬细胞和脂肪细胞介导的炎症过程能力[22]。

因此,马钱子在治疗多种自身免疫性疾病和过敏性疾病中,很有可能是通过T淋巴细胞,稳定免疫反应,发挥免疫调节作用。

1.3　马钱子在肌肉骨骼系统中的研究

马钱子组方在肌肉骨骼系统中的应用有记载于《慈禧光绪医方选议》的“九分散”,记载于《卫生总微·卷五》的“四圣散”,记载于《串雅补·卷一》的“小元门”等方剂。现代医学研究认为马钱子有镇痛抗炎的功能,适用于治疗关节损伤、肌肉痛和风湿性骨病等[23-24]。中医药的很多止痛处方中可以见到马钱子的配伍,如九分散、四圣散、八里散和小元门等方剂。马钱子具有通络止痛、散结消肿的功效。近现代中医学张锡纯曾盛赞其功效说“其开通经络,透达关节之力,实远胜于它药也”。

现代实验研究进一步证实了马钱子的镇痛和抗炎作用。在大鼠佐剂性关节炎(adjuvant arthritis,AA)模型中,马钱子能显著抑制AA大鼠的足肿胀[25]。主要表现为延缓AA进展的速度,降低足肿胀程度,减轻关节病理损伤,改善相关炎症指标水平[26-27]。马钱子干预后的AA大鼠体内相关炎症因子(如IL-1、PGE2、IL-6、TNF-α等)表达水平降低,因此推测其发挥抗炎作用的机制可能与抑制炎症因子的释放有关[24, 28-29]。

马钱子叶提取物在小鼠扭体试验、热板试验和大鼠尾部浸没试验中显示出有效的镇痛作用。Yin等[30]研究发现,在人为构建的多种动物疼痛和炎症模型中,马钱子碱能有效缓解相关刺激引起的疼痛,同时可对抗机体的脂质过氧化。

马钱子碱与马钱子碱N-氧化物的镇痛、抗炎机制不完全相同[31]。二者都能作用于中枢和外周神经,抑制炎症组织中前列腺素E2(PGE2)的释放,降低血管通透性以及关节炎大鼠血浆中5-羟色胺(5-HT)的含量,增加5-羟基吲哚-3-乙酸(5-HIAA)的含量发挥抗炎功能[32]。Patel等[31]的研究发现,马钱子碱N-氧化物抑制对角叉菜胶诱导的大鼠足肿胀的效果优于马钱子碱。

马钱子是肌肉骨骼系统疾病的常用药,近年来的细胞和动物实验发现其不仅可以抑制免疫细胞因子,还可以抑制花生四烯酸信号通路,从而发挥抗炎作用。

1.4　马钱子抑制病原微生物的研究

马钱子组方在抑制病原微生物中的应用有记载于《外科大成·卷四》的“合掌丸”和记载于《串雅补·卷一》的“神惠小灵丹”等方剂。现代医学研究认为马钱子抑制病原微生物的功能主要体现在抗疟原虫活性[33-34]。马钱子的主要成分士的宁及其各种士的宁单体类似物抗疟疾活性不明显。但是,士的宁二聚体类似物双去甲二氢毒素、士的宁、松古辛、异松古辛,尤其是羟基异松古辛具有显著的体外抗疟原虫活性,因为这些化合物在各种恶性疟原虫菌株中显示出高纳摩尔/低微摩尔范围内的细胞的半数抑制浓度(inhibitory concentration 50,IC50)[35]。双吲哚生物碱士的宁A和B在体外对这些恶性疟原虫菌株也显示出强大的抗疟原虫活性,具有中到高纳摩尔IC50值,在vinckei petteri疟原虫和berghei疟原虫小鼠模型中显示出体内抗疟疾活性[36-37]。因为疟原虫对当前抗疟药物的耐药性有所上升,二聚士的宁类似物的新型支架,将成为开发新型抗疟疾药物的潜在线索。然而,应注意的是,由类似物(如松古辛、士的宁和异松古辛)介导的抗疟原虫活性的浓度明显高于目前大多数抗疟药物所需的浓度。因此,除了上述要求在所有假定的非靶点对此类新型衍生物进行更严格的药理学分析外,将二聚士的宁衍生物开发成抗疟疾药物的关键目标之一必须是大幅提高其抑制效力[38]。

这些研究显示,马钱子在抗疟原虫的疗效优于传统药物,为抗疟原虫的治疗提供新的治疗选择。

1.5　马钱子抗肿瘤作用的研究

马钱子的活性成分马钱子碱、马钱子碱N-氧化物、异番木鳖碱等可以通过多种机制抑制肿瘤细胞的生长增殖[39-42],对多种肿瘤均有抑制效果,如多发性骨髓瘤、肝癌、乳腺癌、宫颈癌、肺癌、胃癌和结肠癌[43]。

肿瘤的生长、侵袭和转移进程需要借助血管内皮生长因子(VEGF)在体内诱导血管生成。VEGF受体在血管内皮和多种免疫细胞上都有表达,VEGF作用于VEGF受体可直接或间接抑制机体免疫功能,因此减少VEGF的表达可以达到抑制肿瘤的目的[44-46]。研究表明,马钱子碱引起的VEGF水平下降,使得小鼠海绵植入模型的微血管密度降低,且明显抑制乳腺癌裸鼠骨转移模型中的血管生

成,能有效阻止乳腺癌向骨组织扩散转移[39,47-50]。

研究表明马钱子的水提取物可上调细胞周期蛋白A、肿瘤抑制因子p53和p21,抑制G2/M调节蛋白表达,从而诱导人体胃癌AGS细胞G2/M期阻滞[51];同时乙醇提取的马钱子根能够诱导人体多发性骨髓瘤细胞群聚集[52-53]。马钱子碱可以诱导人体结肠癌细胞系LoVo细胞G1期阻滞[48,53-54],还可以导致肝癌HepG2细胞的G0/G1期阻滞[55-59]。马钱子碱对体外结肠癌SW480细胞也可发挥抑制作用。

马钱子诱导细胞凋亡的另一机制是改变细胞形态,如造成不同程度的细胞整体收缩、染色质和细胞膜的破坏,以及细胞核凝结。马钱子根乙醇提取物处理人多发性骨髓瘤细胞系U266B1时,可以使细胞形态发生改变[60],并对人体肝癌SMMC 7721细胞有相似的抑制作用。已有研究指出其凋亡效应的可能机制是下调Bcl-2蛋白的表达和上调Bax蛋白的表达,同时半胱氨酸蛋白酶-3(caspase-3)和环加氧酶-2(cyclic oxygenase-2)也可能参与到马钱子诱导的细胞凋亡中[57,61-63]。此外,Rao等研究发现,破坏肿瘤细胞线粒体诱导凋亡也是马钱子抗癌机制之一[52]。

现阶段西药抗肿瘤药物的疗效并不稳定,且疾病谱窄,马钱子可作为新型抗肿瘤等药物的潜在靶点。未来马钱子碱有望开发成为抗血管增生和抗癌治疗药物。

2 结论

马钱子味苦性温,具有通络止痛、散结消肿的功效,但生品有大毒。目前诸多研究显示其在治疗神经系统、免疫系统、肌肉骨骼系统疾病以及抗肿瘤药物的研发中都有很大的潜力,随着对其药理机制的深入研究,其主要化合物在神经系统、肌肉骨骼系统等组织和细胞的靶点不断被鉴定。

随着《"十四五"中医药发展规划》的发布,针对马钱子碱和士的宁类似物的药理基础将会有更为深入的研究,这也正是对发展规划中"传承精华、守正创新,实施中医药振兴发展重大工程"和"推进中医药和现代科学相结合"的全面落实。

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Research progress on clinical application of nux-vomica

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Abstract *Strychnos nuxvomica* L. is a traditional Chinese medicine, which has the effect of relieving pain and reducing swelling. Modern pharmacological studies have found that strychnine, brucine, iridoid glycosides and other bioactive compounds can be extracted from Semen Strychni. To understand the clinical value of nux vomica and its active ingredients, we collected relevant research results, explored the pharmacological mechanisms of its main extract in nervous system, immune system, musculoskeletal system, inhibiting pathogenic microorganisms and anti-tumor, respetively, and then analyzed the clinical application value The results show that the active components of nux vomica can excite the central nervous system, improve the function of sensory organs, reduce inflammation effectively, ease pain, and reduce inflammation, in addition to playing a role of inhibiting a variety of tumors. Possibly, it can be developed as anti-angiogenic and anticancer drugs in the future. With the in-depth study of the pharmacological mechanism of nux vomica, more confirmed evidences of pharmacology and experiment will be mastered to guide the clinical application.

Keywords Strychnos nux-vomica; strychnine; brucine; pharmacological mechanism

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