中药抗肿瘤明星分子无载体和有载体超分子纳米体系研究进展

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摘要: 抗肿瘤中药具有悠久的临床应用史, 其中的明星分子一直是现代药物研究的热点, 但受限于中药单体成分溶解性、稳定性、靶向性、生物活性或毒性等成药性问题, 阻碍了中药抗肿瘤明星分子进一步临床转化应用。当前, 通过分子自组装、纳米材料包载等技术制备的纳米体系在改善中药活性成分抗肿瘤方面具有广阔的应用前景, 引起了国内外学者的广泛关注。本文系统概述了将中药抗肿瘤明星分子制备成超分子纳米体系的研究进展, 总结了目前报道的无载体和有载体两大类、10小类超分子纳米体系及其研究案例, 并对未来发展方向提出展望, 旨在为使用超分子技术改善中药抗肿瘤明星分子临床应用的研究及临床转化提供参考。

关键词: 抗肿瘤; 超分子; 无载体; 有载体; 中药明星分子

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Research progress on carrier-free and carrier-supported supramolecular nanosystems of traditional Chinese medicine anti-tumor star molecules

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Abstract: Anti-tumor traditional Chinese medicine has a long history of clinic application, in which the star molecules have always been the hotspot of modern drug research, but they are limited by the solubility, stability, targeting, bioactivity or toxicity of the monomer components of traditional Chinese medicine anti-tumor star molecules and other pharmacokinetic problems, which hinders the traditional Chinese medicine anti-tumor star molecules for further clinical translation and application. Currently, the nanosystems prepared by supramolecular technologies such as molecular self-assembly and nanomaterial encapsulation have broader application prospects in improving the anti-tumor effect of active components of traditional Chinese medicine, which has attracted extensive attention from scholars at home and abroad. In this paper, we systematically review the research progress in preparation of supramolecular nano-systems from anti-tumor star molecule of traditional Chinese medicine, and summarize the two major categories and ten small classes of carrier-free and carrier-based supramolecular nanosystems and their research cases, and the future development direction is put forward. The purpose of this paper is to provide reference for the research and clinical transformation of using supramolecular technology to improve the clinical application of anti-tumor star molecule of traditional Chinese medicine.

Key words: anti-tumor; supramolecular; carrier-free; carrier; star molecule of traditional Chinese medicine

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肿瘤是全球面临的重大健康问题, 随着人口基数上升、人口老龄化、生活节奏变快等因素, 肿瘤发病率、死亡率大幅度增长。中国在2022年便有约482万例新发癌症病例, 321万例癌症死亡病例, 我国的癌症负担正在日益加重[1]。中西医结合治疗肿瘤是我国应对该疾病挑战的特有模式。例如, 在中医药古籍中, 将肿瘤称为“积聚”、“癥瘕”、“瘵痛”、“噎膈”、“内痈”等。传统中药 (traditional Chinese medicine, TCM) 在肿瘤的治疗方面有着较长的历史, 中医药古籍中记载了大量治疗肿瘤的药物, 如:《神农本草经》中记载了71种治疗“癥瘕积聚”的药物[2],《本草纲目》中记载了214种经现代研究证明有抗肿瘤效果的药物[3]。此外, 在治疗肿瘤方面, 中药具有更广泛的适用性且不乏大量临床有效的治疗案例和方药。目前, 抗肿瘤中药注射液已经广泛使用, 如: 康艾注射液治疗食管癌, 白花蛇舌草注射液治疗卵巢癌, 鸦胆子油注射液抑制C6胶质瘤细胞, 康莱特注射液联合紫杉醇治疗胰腺癌等[4]。近年来, 已经有大量从中药中提取分离的抗肿瘤有效成分, 据统计, 具有抗肿瘤作用的代表性中药活性分子共有61种, 其中黄酮类17种 (芦丁、山柰酚、槲皮素等), 生物碱类15种 (苦参碱、喜树碱、石蒜碱等), 萜类9种 (熊果酸、紫杉醇、双氢青蒿素等), 皂苷类5种 (人参皂苷Rg3、黄芪皂苷II等), 酚类5种 (姜黄素、石斛酚等), 醌类4种 (大黄素、紫草素等), 苯丙素类3种 (毛蕊花糖苷、鬼臼毒素等), 有机酸类1种 (斑蝥素/去甲斑蝥素), 甾体类1种 (蟾酥灵), 也有部分暂未应用于临床的药物没有计入统计[5]。综上, 中药中存在许多被广泛研究且具有明确抗肿瘤活性的成分, 下文统称为中药抗肿瘤明星分子。部分中药抗肿瘤明星分子由于存在溶解度差、结构不稳定、毒性大、生物利用度低等成药性问题严重制约了其临床转化。例如: 木犀草素是一种具有抗肿瘤、抗氧化、逆转细菌耐药性等多种药理作用的黄酮类化合物, 由于木犀草素含有酚羟基, 且酚羟基之间的分子作用力导致其晶格能较高, 故木犀草素的水、脂亲和力均较差, 溶解度不佳[6]; 紫杉醇是一种从红豆杉中分离出的二萜类化合物, 具有抑制细胞复制作用和强抗肿瘤能力, 但水溶性低是限制其使用的重要因素, 现阶段将其与聚乙氧基化蓖麻油 (cremophor EL) 和乙醇混合形成潜溶剂给药, 在临床使用过程中, 该给药方式引发了明显的不良反应, 包括超敏反应、神经毒性等; 喜树碱 (camptothecin, CPT) 是一种从中国喜树中分离出的具有细胞毒性的天然生物碱, 具有强效抗肿瘤作用, 当喜树碱进入人体时, 由于人体内pH值不稳定, 喜树碱内酯环容易被打开, 从有效的内酯环形式转向无效的羧酸盐形式, 并且喜树碱的水溶性不高, 生物利用度有待提高。

20世纪80年代末, 纳米技术出现并迅速崛起, 旨在直接操纵原子或分子在纳米尺度上改变物质[7], 其关注于在改变物质过程中的一切化学键变化过程, 而超分子技术是将两种或两种以上的分子通过氢键、范德华力、二硫键等次级键联合形成多分子体系的技术, 关注于分子作用之间的非共价键作用。超分子技术作为另一种在纳米尺度 (0.1～100 nm) 对电子、原子和分子进行操作的方法, 在近年来获得众多关注。本文所述中药超分子是指将超分子技术用于研究非共价键驱动下中药药效成分通过分子自组装成具有纳米至微米尺度的分子聚集体, 例如, 将超分子技术应用于改善中药抗肿瘤明星分子的成药性等问题, 通过被动靶向或主动靶向直达肿瘤组织的方法, 可以增效减毒和提高生物利用度。目前, 超分子技术作为纳米制剂的有效制备手段, 已在临床得到使用, 例如紫杉醇白蛋白注射液[8]等。因此, 本文系统概述了中药抗肿瘤成分的超分子纳米化研究进展, 包括无载体和有载体两大类、10小类超分子纳米体系及其应用案例, 并对未来发展提出展望, 旨在为利用超分子技术改善中药抗肿瘤成分临床转化应用提供参考。

1 超分子纳米技术对中药抗肿瘤成分的纳米化研究进展

根据中药成分的理化特性有所不同, 使用超分子技术改善抗肿瘤活性的方式主要为两大类。其一为中药抗肿瘤明星分子本身纳米化, 通过无载体自组装的形式进行药物递送, 具体方法包括纳米混悬液、纳米共晶、纳米前药及超分子水凝胶。利用超分子技术将中药抗肿瘤成分纳米化后, 粒径大幅度减小, 表面积增大, 其物理、化学、药理学性质均发生较大变化。不仅可以增加水溶性、延长作用时间、减少毒不良反应, 还可以增加生物利用度。其二为通过超分子载体进行药物递送, 包括纳米脂质体、固体脂质纳米颗粒、超分子胶束、纳米乳、磷脂复合物和树枝状聚合物等。与无载体技术相比, 纳米载体技术拥有更强的靶向性, 在临床使用更为广泛[9]。

1.1 利用无载体超分子技术改善中药抗肿瘤成分

无载体超分子技术是一种药物自递送系统, 通过药物的自组装进行药物传递, 是诱导药物分子自发形成有序结构的一种技术。药物自组装的作用力主要是氢键、π-π键、疏水作用、静电作用和范德华力等非共价键作用力。制备方法包括体内制备和体外制备两种, 体内制备法借助原料药物的被动靶向, 利用进入体内的外源性小分子于特定位点发生自组装; 体外制备法于体外使药物进行自组装, 包括自上而下法、反溶剂沉

淀法、模板辅助沉淀法等。与利用纳米载体的方法相比, 自组装药物除拥有传统纳米药物的优点, 还具有更高的药物负载能力和传递效率[10]。药物的自组装分为单一药物自组装和多种药物自组装, 单一药物自组装易受到药物本身的结构限制, 部分药物无法独立完成自组装。多种药物自组装通过利用特定分子间的作用力进行偶联, 拥有更广阔的发展前景[11]。

1.1.1 纳米混悬液 纳米混悬液, 又称为纳米混悬剂或纳米晶体药物, 是在助悬剂帮助下使固体颗粒稳定悬浮存在于介质之中, 再通过粉碎形成的稳定纳米级分散体系。纳米混悬液可用自上而下 (top-down) 技术、自下而上 (bottom-up) 技术及联用技术3种方法完成。top-down技术是指直接将药物粒子物理粉碎, 包括球磨法、高压介质法等; bottom-up技术是使药物分子凝结为沉淀和结晶的方法, 包括沉淀法、乳化法等; 联用技术是将二者联合使用以得到稳定的混悬液[12]。以上为常用的纳米制剂技术, 而利用超分子技术获得稳定纳米混悬液的方法也有着广泛应用, 通过将药物分散后自组装可获得所需要的超分子。诸多萜类化合物由于拥有不同数量的羟基和羧基, 更易进行自组装。例如雷公藤红素又名为南蛇藤素, 是一种五环三萜类化合物, 除了有抗炎、抗风湿作用外, 还具有高效的抗肿瘤活性, 是在临床广泛使用的化疗增敏药物[13]。反溶剂法是指在药物溶液体系内加入反溶剂 (通常为水或者水性介质) 混合后促进水相过饱和, 促进纳米晶体析出的方法。反溶剂法是沉淀法的分支, 属于bottom-up技术。Xiao等[14]通过反溶剂法制作了雷公藤红素−多柔比星自组装无载体药物, 此自组装无载体药物不仅可以提升雷公藤红素的抗肿瘤能力, 还能增加雷公藤红素溶解度, 提高生物利用度, 减弱其全身毒性。利用PBS缓冲液模拟肿瘤环境, 研究表明药物经过超分子纳米化后抗肿瘤作用大大提升, 肿瘤平均直径从100%降低至11.8%。

1.1.2 纳米共晶 纳米共晶是药物活性成分 (active pharmaceutical ingredient, API) 的分子或者离子和1个及以上的中性分子 (cocrystal former, CCF) 通过氢键或其他非共价键的作用而形成的超分子晶体化合物, 其在常温状态下为固态。形成纳米共晶可以改善药物成分的物理化学性质。在形成纳米共晶后, 表面刚度降低, 溶解度、溶出速率、熔点、光稳定性、引湿性等方面有着较大的变化[15]。部分药物活性成分易发生构型转变, 纳米共晶的形成可增加药物稳定性, 提升水溶性、安全性和生物利用度。制备纳米共晶有2种方法: 溶剂合成法和固体合成法。溶剂合成法需要药物活性成分和中性分子在溶剂中相互作用力大于各物质分子间和溶剂分子间作用力, 具体方法有: 蒸发溶液、降温析晶等。固体合成法需要两种分子间拥有结构互补性并可以进行相互位移, 在此基础上加入增塑剂等提高分子的移动, 核心是利用固体研磨。与溶剂合成法相比, 固体合成法不需要使用有机溶液, 更为环保[16]。Zhang等[17]利用溶剂合成法首次合成了木犀草素-4,4'-联吡啶药物共晶, 形成共晶后, 药物本身的药效活性和分子结构没有发生很大变化, 而溶解度、溶出速率却大大提高。Liu等[18]研究发现, 木犀草素-4,4'-联吡啶药物纳米共晶可提高细胞的增殖活性并且提升药物原有的抗炎作用。Liu等[19]使用固体研磨的方法, 成功制备出杨梅素−烟酰胺纳米共晶, 制备出的共晶具有更强的溶解速率。同时, 该组也通过溶剂合成法制备了杨梅素−烟酰胺纳米共晶, 和固体研磨法所制备出的共晶相比, 溶剂合成法制备得到的晶体具有更多的溶出量, 而研磨法对共晶的溶解度改良程度有限。

1.1.3 纳米前药 纳米前药是前药策略和纳米颗粒给药系统的有机结合, 通过平衡药物分子−水分子或药物分子之间的作用力, 提高目标药物的自组装能力, 获得所需的超分子药物。通过前药策略, 能够改善抗肿瘤药物的溶解度、稳定性和药物动力学特性。和传统纳米技术相比, 纳米前药在载药率、靶向性等方面有较大优势。纳米前药作为自组装纳米颗粒, 主要分为4种类型: 两亲单体前药、疏水单体前药、同二聚体前药和异二聚体前药。不同类型的纳米前药自组装机制不同: 两亲性单体前药通过将药物分子和亲水性侧链偶联提高药物在水中的溶解性, 具有表面活性剂样特点; 疏水单体前药通过修饰线性链、芳香链和支链等疏水侧链, 平衡药物间作用力, 减少药物沉淀; 同型二聚体前药通过引入缺陷结构, 让两种相同的药物偶联达到自组装目的; 异型二聚体前药是通过低溶解药物和高溶解药物偶联, 平衡药物间作用力, 完成自组装过程[20]。Qing等[21]将紫杉醇和二羧酸链偶联, 获得了紫杉醇同型二聚体, 溶解度比游离紫杉醇提升2 500倍, 加入甲氧基聚乙二醇后, 紫杉醇同型二聚体载药量高达85%, 且在体内、体外试验中都表现出强抗肿瘤能力。Xu等[22]将喜树碱和亲水型肽链通过酯键结合, 设计出智能自组装纳米前药, 显著提高了喜树碱的稳定性和水溶性, 并且, 通过使用前列腺特异性膜抗原响应肽链, 可以明显提高药物的靶向性, 实现了药物的高效转运。

1.1.4 超分子水凝胶 水凝胶是一种具有三维网络结构的亲水型聚合物网络, 分为高分子凝胶和小分子凝胶。超分子凝胶即两种或两种以上的小分子所制成的水凝胶, 可用于局部给药和微创给药, 可持续释放药物, 具有良好的溶胀性、生物相容性, 可做腔体植入物,

防止癌症复发[23]。芫花作为一种传统中药, 在长期临床中证明了其抗肿瘤效果, 其中脂溶性成分瑞香型二萜被明确证明具有良好的抗肿瘤功效[24]。甘草–芫花配伍属于“十八反”内容, 现代药理表明, 二者共用会增强芫花毒性, 影响大鼠体内酶活性, 造成肝损伤[25]。Yang 等[26]将甘草酸和芫花进行处理得到了芫花萜类成分–甘草酸超分子水凝胶, 在正电离模式下获得了58 种成分信息, 揭示了甘草酸对芫花毒性增强的本质。同时, Yang 等[27]证明芫花萜类成分–甘草酸水凝胶能够通过促进乳腺癌细胞线粒体凋亡和 CXCL1/2-S100A8/9 途径抑制肿瘤的生长, 并且阻止癌细胞肺转移。Pi 等[28]研究发现甘草酸和金属 Cu^{2+}之间首先通过配位作用进行组装, 随后甘草酸和去甲斑蝥素之间通过分子间氢键作用共组装形成水凝胶。该超分子水凝胶不仅具有良好的机械稳定性, 还具有光介导–类芬顿效应, 实现了肿瘤的化学动力学疗法, 系统阐释了复杂多元成分中药胶体的形成机制。从中药源头发现新型多基源共组装无载体抗肿瘤水凝胶, 克服了水凝胶在既往研究中多需要高分子材料的瓶颈, 也拓展了国际超分子凝胶研究的新认识。

1.2 纳米载体技术

纳米载体技术旨在利用载体运载药物, 是利用多个单分子组成多分子结构运载药物, 能够达到表面修饰、提高靶向作用、加速生物膜转移等目的。

1.2.1 纳米脂质体 纳米脂质体 (nanoliposomes, NL) 是用脂质双分子膜对药物进行包裹, 形成一种类似于囊泡的具膜微粒, 属于典型的超分子载体。脂质双分子膜结构类似于生物膜, 处于动态, 利用该特点可以增加药物溶解度, 改善药物在体内的跨膜吸收情况, 提高药物的生物利用度。同时, 通过对脂质体表面的电荷进行控制或使用聚乙二醇、配体等聚合物进行表面修饰后, 可以实现主动靶向, 对药物体内分布, 作用部位和作用时间进行控制[29]。Masato 等[30]通过添加双苯甲酸 (3,5-bis (dodecyloxy) benzoic acid, DB) 作为脂质转运体, 并且在脂质体表面涂布人血清白蛋白 (human serum albumin, HSA) 获得喜树碱的纳米脂质体, 大幅度提高了喜树碱在小鼠体循环的稳定性和储存稳定性。同时, 喜树碱纳米脂质体的静脉注射毒性比修饰前喜树碱的毒性降低了 600%, 且在肿瘤处富集程度提升, 增强了抗肿瘤作用。Zhu 等[31]制备了一种具有热敏磁性的脂质体, 可保护羟基喜树碱的内酯环, 使其保持活性状态。通过药代动力学和体内外实验证明, 该脂质体通过磁性定向交付和热敏释放作用, 可实现羟基喜树碱的靶向释放和抗肿瘤功效。天然抗肿瘤成分紫杉醇, 有着外周神经毒性, 由于紫杉醇的神经毒性有剂量依赖性, 在高剂量下会造成近端肢无力、急性疼痛综合征、急性脑病等, Yang 等[32]提出使用含聚乙二醇类柔性亲水性聚合物修饰脂质体表面, 使紫杉醇的药代动力学性质发生改变, 降低了毒性。

1.2.2 固体脂质纳米颗粒 固体脂质纳米颗粒 (solid lipid nanoparticles, SLN) 是一种用固态的、天然的或者合成的类脂为载体, 将药物包裹或者吸附在脂质核中, 与脂质体相比, 其动态性较差。固体脂质纳米颗粒作为一种小粒径物质, 在胃肠道的附着作用增强, 增加胃肠道停留时间, 提高口服生物利用度[33]。同时, 固体脂质颗粒也可以用于缓释或者定点运输, 进行表面修饰达到主动靶向作用。制备固体脂质纳米颗粒的方法有高压均质法、乳化–超声法、微乳液法、溶剂乳化–蒸发法等。Chen 等[34]使用聚氧乙烯-20-硬脂基醚制备了含有紫杉醇的固体脂质纳米颗粒 (paclitaxel-loaded solid lipid nanoparticles, PL-SLNs)。与未修饰的紫杉醇相比, 拥有更长的聚乙二醇链和更多的亲水链, 排斥血浆蛋白的能力更强, 拥有较长的半衰期。Li 等[35]利用大豆卵磷脂、单硬脂酸甘油酯乳化制备槲皮素固体脂质颗粒 (quercetin-loaded solid lipid nanoparticles, QT-SLNs), 对大鼠进行灌胃给药后, 发现 QT-SLNs 的胃肠道吸收率升高, 其中肠道 (回肠和结肠) 是最主要的吸收部位, 并且口服给药条件下, QT-SLNs 的生物利用度提升 5 倍有余。

1.2.3 纳米胶束 纳米胶束是一种由具有亲水性外壳及疏水性内核物质 (即表面活性剂) 溶于水后, 自发形成的聚合物胶束。该胶束对药物进行包裹, 以达到改性的目的。纳米胶束是一种新型的高分子药物控释系统, 有载药量高的优点。与其他纳米载体技术相比, 纳米胶束可以使药物逃离单核巨噬细胞的吞噬作用, 有效减少由于自身免疫而导致的药物损失[36]。载药胶束的制作较为简单, 一般用透析法进行制作。在制作过程中, 可以通过对纳米胶束表面进行修饰以获得主动靶向作用。Wang 等[37]制备了一种基于左旋聚乳酸-*b*-聚赖氨酸和右旋聚乳酸-*b*-甲氧基聚乙二醇之间的空间立构复合作用的载喜树碱的空间立构复合胶束, 拥有 pH 敏感性和长循环功能。该载药胶束在常温 (25 ℃) 下水溶性为未修饰喜树碱的 9.37 倍, 渗透性大幅提高, 抗肿瘤活性明显提高。Yin 等[38]用透析、沉淀、聚合获得了两亲性的甲氧基聚乙二醇–聚己内酯嵌段的姜黄素纳米胶束, 通过体外实验发现该纳米胶束可以促进人肺癌细胞对姜黄素的摄取, 对肺癌细胞的 72 h 的 IC_{50} 值为 34.5 μmol·L^{-1}, 小于未修饰姜黄素的 IC_{50} 值 53.0 μmol·L^{-1}, 拥有更高的抗肿瘤能力。本文所述的纳米胶束, 多为自聚集胶束, 广义的纳米胶束还有

单分子胶束和交联的胶束两种。单分子胶束形式上类似于自聚集胶束, 由单一的聚合物分子构成, 可形成树枝状大分子。树枝状大分子聚合物 (dendrimers) 是一种可以捕获疏水分子的高稳定性水溶性分子, 拥有较高的溶出度和药物释放速率的物质。目前, 使用树枝状聚合物构建疏水性药物的递送系统, 可有效提升口服生物利用度[39]。Kulhari 等[40]通过将多西紫杉醇 (docetaxel, DTX) 和树枝状聚合物偶联获得载药聚合物, 乳腺癌细胞属于的人表皮生长因子受体2型 (human epidermal growth factor receptor 2, HER2) 阳性细胞, 载药聚合物和DTX相比, 针对HER2阳性细胞的IC_{50}值大幅度降低, 针对HER2阴性细胞的毒性并没有显著增加, 证明了载药聚合物具有主动靶向性。

1.2.4 磷脂复合物 磷脂复合物是药物通过电荷迁移作用和磷脂分子紧密结合形成的化合物, 由于其制备简单、成本低廉、稳定性高、对药物的理化性质有较大的改变, 可以大幅度提升口服生物利用度。磷脂复合物的制备环境为非质子传递溶剂, 通过加热、搅拌、回流等手段制成, 也可用冷冻干燥法和溶剂沉淀法分离获得[41]。淫羊藿苷源自小檗科草本植物淫羊藿、朝鲜淫羊藿、柔毛淫羊藿、箭叶淫羊藿的干燥叶。淫羊藿苷磷脂化合物同淫羊藿苷作用类似, 均可用于膀胱癌和食管癌的治疗[42]。Jiang 等[43]通过恒温磁力搅拌的方法获得了淫羊藿磷脂复合物, 该类复合物使淫羊藿苷的亲脂性有效提升, 从而促进了淫羊藿苷的生物利用度。

1.2.5 纳米乳 纳米乳 (nanoemulsion) 是由油相、水相、乳化剂共同组成, 部分纳米乳需要助乳化剂。纳米乳为大小均匀的乳滴, 粒径在10～100 nm。纳米乳有水包油型 (O/W 型)、油包水型 (W/O) 型及双连续型3种。W/O型在实验和临床中多用于药物缓释, O/W型多用于增加亲脂性药物的溶解度。纳米乳不能自发形成, 需要外界能量转化为表面能, 制备方法一般有高能乳化法、低能乳化法、相转变法和自动乳化法等[44]。槲皮素 (quercetin) 是一种广泛存在于槐花、山豆根等植物中的黄酮类化合物, 具有抗氧化、抗病毒、抗肿瘤等作用, 对于肿瘤治疗疗效良好且无毒性, 近些年在抗肿瘤方面引起了广泛关注。槲皮素对肺癌、肝癌、宫颈癌、胰腺癌、结肠癌、食管癌、膀胱癌等癌症细胞均有效。但槲皮素的低水溶性、低稳定性和低口服利用度限制了其使用[45]。Das 等[46]开发制备了纳米级槲皮素负载纳米乳液 (quercetin-loaded nanoemulsion, QNE) 系统, 并对其进行了秀丽隐杆线虫和人类癌细胞等活性探究, 发现其具有较槲皮素更好的神经保护作用和抗癌细胞活性, 同也使槲皮素的生物利用度得以提升。

1.2.6 MOFs药物传递系统 金属有机骨架 (metal organic framework, MOFs) 是一种高度多孔的、具有生物相容性和极大表面积、可定制的金属有机混合结构, 多孔性是其运载“货物” (如: 药物、基因、蛋白质等) 的重要条件。将药物封装在MOFs多孔中, 由MOFs进行准确靶向, 逐渐成为了纳米药物递送的新方向和新态势。对比其他技术, MOFs拥有更强的靶向能力, 可通过内部有机链形成pH响应和氧化还原响应, 进行被动靶向, 还可通过表面修饰配体、抗体或前药可以实现纳米药物的主动靶向。在温和条件下MOFs也更易进行表面修饰和合成, 众多优势使其在癌症治疗方面占有一席之地[47], 如通过被动靶向优先在肿瘤细胞处积累, 使其封装的抗癌药物具有更高的稳定性, 从而实现纳米药物在体内的循环和靶向作用[48]。甘草次酸 (glycyrrhetinic acid, GA) 是从甘草中提取的活性成分, 具有抗炎、抗病毒、抗纤维化和降低转氨酶活性的作用。Li等[49]将GA放入修饰后的MOFs中, 使用1,4-丁二胺对GA-MOFs载体进行修饰, 成功构建了活性肝癌靶向的MOFs药物载体, 而这种药物载体有良好的纳米颗粒尺寸, 细胞MTT实验分析显示, MOFs作为抗癌药物有纳米载体, 有较高的生物相容性, 并且具有较低的心脏毒性和肾脏毒性, 在临床上有很高的治疗潜力。

2 近10年超分子纳米技术改善中药抗肿瘤成分的案例研究

超分子纳米技术已经在世界范围内获得了学者的广泛关注, 本文对近10年来使用无载体及有载体超分子纳米技术对中药抗肿瘤成分改良改进的文章进行归纳、提炼, 具体案例见表1[50-100]。

3 超分子纳米技术对中药抗肿瘤成分纳米化的研究展望

超分子纳米技术是当前国际纳米药物研究热点领域, 但在大量的基础研究和临床使用过程中其负面作用逐渐暴露。例如: 纳米药物会在肝脏蓄积, 并且对肝细胞、Kupffer细胞、肝窦内皮细胞、肝星状细胞等产生肝毒性, 通过氧化反应、炎症反应、细胞器损伤等形式表现[101]。这种肝毒性可以减缓, 但并不能根除。此外, 许多类型的纳米颗粒会透过血睾屏障、胎盘屏障和上皮屏障, 破坏生殖细胞和支持细胞, 导致生殖活动障碍[102], 但不同的纳米颗粒所造成的组织和细胞的具体损伤仍由纳米颗粒制剂的组成确定。超分子纳米技术制备的纳米药物, 由于其独特的颗粒性, 其毒理学特征和原型药物有很大的不同。未来需要对纳米药物和非纳米药物的毒性进行归纳总结, 以期对超分子纳米药物的毒理学特性有更为清晰的认识。

此外, 中药的临床使用, 从来不是让一味药物中的某种活性成分单打独斗, 中药的精髓在于配伍, 在于君

Table 1 Research on the improvement of anti-tumor activity of traditional Chinese medicine by carrier-free or carrier-supported supramolecular nanotechnology

Active molecule	Applied technology	Improvement of molecule′s properties	Targeting	Ref
Paclitaxel	Nanoparticles	Enhancing transmission of immunomodulator to tumor and reshaping tumor microenvironment	Passive	[50]
	Nanoparticles	Improving water solubility and achieving sustained specific release of paclitaxel	Active	[51]
	Nano-eutectic	Increasing solubility in water and targeting ability, decreasing hemolytic toxicity	Active	[52]
	Nano-prodrugs	Reducing the toxicity of normal cells, targeting delivery and improving effectiveness	Active	[53]
	Nanoliposomes	Increasing solubility, bioavailability and targetability	Active	[54]
	Solid lipid nanoparticles	Prolong the half-life of drugs and increasing the tumor inhibition rate	Passive	[55]
	Nano micelles	Enhancing treatment effectiveness, and reducing toxic side effects	Active	[56]
Triptolide	Nanosuspension	Reducing systemic toxicity and promoting the entry of drugs into tumors	Passive	[57]
	Nanoparticles	Reducing the nephrotoxicity of rat and toxicity to digestive system, urinary system and reproductive system	Passive	[58]
	Nanoliposomes	Enhancing the transdermal property of drug and achieving active targeting	Active	[59]
	Solid lipid nanoparticles	Reducing the side effect in digestive system and increasing the drug loading capacity	Passive	[60]
Rutin	Solid lipid nanoparticles	Increasing the stability and prolonging the half-life of drug	Passive	[61]
	Metal organic framework (MOFs)	Improving the ability of cancer inhibition and antibacterial properties, reducing cyto-toxicity of normal cells	Passive	[62]
Dihydromyricetin	Nano-eutectic	Improving water solubility and reduce solubility differences between drugs	Passive	[63]
	Nanoliposomes	Improving antibacterial ability and pH-stable release performance	Passive	[64]
	Phytosome	Improving loading drug capacity, solubility, and bioavailability	Passive	[65]
Luteolin	Nanoliposomes	Increasing water solubility and targetability	Active	[66]
	Solid nanoparticles	Improving drug synergy, increasing uptake of nanoparticles, and reducing side effects	Active	[67]
	Nanomicelles	Enhancing drug hydrophilicity and oral availability	Passive	[68]
	Phospholipid complex	Improve bioavailability and cancer cell permeability to drugs	Passive	[69]
	MOFs	Enhancing anticancer activity	Active	[70]
Naringenin	Nanoliposomes	Enhancing the activity of anticancer	Passive	[71]
	Solid lipid nanoparticles	Improving the bioavailability and sustained releasing, prolonging half-life period	Passive	[72]
	Nano micelles	Improving cell permeability and reducing toxicity	Passive	[73]
Quercetin	Nanoliposomes	Reducing the vitality of cancer cells and enhancing the passive targeting effect	Passive	[74]
	Solid lipid nanoparticles	Improving drug efficacy, extending drug half-life, and reducing drug toxicity	Passive	[75]
	Solid lipid nanoparticles	Making it easier for drugs to cross the blood-brain barrier	Active	[76]
	Nano micelles	Improving the water solubility and bioavailability of drugs	Passive	[77]
	Phospholipid complex	Improving cell uptake ability and combating cancer cell proliferation	Passive	[78]
	Nano emulsion	Improving oxidative damage induced by chemotherapy drugs	Passive	[79]
	MOFs	Improving water solubility, enhancing ability to scavenge free radicals and anti-tu-mor properties	Passive	[80]
	Dendritic polymer	Prolonging blood circulation time and lifespan	Active	[81]
Icariin	Solid lipid particles	Enhancing bioavailability and oral availability, promoting vascular production in fi-brotic tissues	Passive	[82]
	Nano micelles	Enhancing water solubility, reducing cell apoptosis, and improving anti-cancer ability	Active	[83]
	Phospholipid complex	Enhancing water solubility and lipid solubility, improving drug dissolution	Passive	[84]
Matrine	Nano emulsion	Improving stability and skin permeability	Passive	[85]
Camptothecin	Nanoliposomes	Regulating immunity and synergistic anti-tumor potential	Active	[86]
	Solid lipid nanoparticles	Enhancing the drug's ability to penetrate the blood-brain barrier, reducing maximum inhibitory concentration and side effects	Passive	[87]
	MOFs	Improving water solubility and specificity, and reducing cytotoxicity	Active	[88]
	Dendritic polymer	Overcoming drug resistance and promoting cell uptake rate	Active	[89]
Berberine	Nanoeutectic	Increasing melting point, improving drug solubility and dissolution rate	Passive	[90]
	Nanoliposomes	Improving oral availability, reducing toxicity, and enhancing bioavailability	Passive	[91]
	Solid lipid nanoparticles	Improving bioavailability and reducing cardiac toxicity	Passive	[92]
	Nano micelles	Improving oral bioavailability and stability	Passive	[93]
	Phospholipid complex	Improving the safety and bioavailability of drugs	Passive	[94]
	Nano emulsion	Improving oral utilization, enhancing cell metabolism and cell permeability	Passive	[95]
	Dendritic polymer	Reducing the toxicity of berberine, slowing release the drug	Active	[96]
Resveratrol	MOFs	Inhibiting the proliferation of cancer cells and reducing drug toxicity	Passive	[97]
	Solid lipid nanoparticles	Improving stability, enhancing targeting and toxicity to cancer cells	Active	[98]
	Nano emulsion	Enhancing the inhibitory effect of cancer and promoting cell apoptosis	Passive	[99]
	MOFs	Improving pharmacokinetics, stability, and solubility	Passive	[100]

臣佐使、增效减毒。而目前大多研究尚未通过超分子纳米技术将中药复杂多元组分纳米化, 当前单体成分纳米化和作者中药临床使用多成分、多靶点、协同起效的理念有偏差。有最新研究表明, 药对、复方中的成分在配伍过程中会发生相互作用。在对中药汤剂所进行的超分子结构研究中, 众多汤剂中均发现了超分子现象, 研究表明中药成分可以通过成分间协同作用和增溶作用等使其生物活性得到显著的提升[103]。超分子纳米药物展现出独特的药理效应, 根据中药组方配伍制备多元组分的无载体超分子药物, 将是今后研究的热点和亟待突破的瓶颈。与此同时, 中药组分的纳米化离不开新型材料的发现和制备, 尤其是当前生物源纳米材料已在部分单体成分的体内递药开展探索应用, 例如细胞膜[104,105]、病毒外壳[106]、血小板[107]等, 这为多元中药组分的超分子纳米递药提供了新的选择。总之, 未来中药抗肿瘤成分纳米化研究, 应立足临床抗肿瘤有效的中药复方, 结合临床应用经验, 借助超分子技术开展无载体和有载体纳米化研究, 开发中药抗癌多组分纳米体系, 传承精华、守正创新, 让传统中医药焕发青春活力, 服务国家大健康战略。

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