中药活性成分纳米制剂抗肿瘤的研究进展

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摘要：恶性肿瘤是威胁我国居民健康的主要疾病之一，中医药在肿瘤防治中发挥着重要作用。然而中药活性成分的理化特性，如疏水性强、稳定性差、生物利用度低以及半衰期短等，限制了其临床使用。纳米制剂作为一种新型制剂，在靶向递送、控释和多药联用等方面具有独特的优势。纳米制剂与中药活性成分结合，可提高其生物利用度和生物活性。本文综述了近年来中药活性成分及其纳米制剂的作用特点和应用，以期为新型中药抗肿瘤药物的研发提供科学依据和参考。

关键词：中药活性成分；纳米制剂；抗肿瘤

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Research Progress on Anti-tumor Effects of Nanoformulations of Active Ingredients of Traditional Chinese Medicine

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ABSTRACT: Malignant tumors are among the primary diseases threatening public health in China, and traditional Chinese medicine has been proven to be an important means of cancer prevention and treatment. However, the strong hydrophobicity, poor stability, low bioavailability, and short half-life of active ingredients of traditional Chinese medicine limit their clinical use. Nanoformulations, as an innovative type of formulation, offer unique advantages in targeted delivery, controlled release, and combination therapy. The combination of nanoformulations with active ingredients of traditional Chinese medicine can improve their bioavailability and biological activity. This article reviews the characteristics and applications of active ingredients of TCM and their nanoformulations in recent years, aiming to provide scientific basis and reference for the development of novel anti-tumor drugs derived from traditional Chinese medicine.

KEYWORDS: active ingredients of traditional Chinese medicine; nanoformulations; anti-tumor

中国死因监测数据显示，恶性肿瘤死亡占居民总死因的近1/4[1]。随着人口老龄化加剧，以恶性肿瘤为代表的多种主要慢性疾病负担均呈现上升趋势。由于单纯手术切除无法彻底根除所有肿瘤组织，目前恶性肿瘤的主要治疗策略是手术切除肿瘤联合放化疗。传统的放化疗药物对正常组织也有不同的毒性，常出现严重的不良反应，开发高效低毒的抗肿瘤药物具有重大研究意义。

随着现代医学的发展，中医药治疗在抗肿瘤中的作用得到越来越多的证实和认可，成为除放化疗外的辅助治疗手段。许多抗肿瘤的天然药物来自中药[2]，在肿瘤治疗中起到协同抑瘤、优势互补、减毒增效的作用。然而，中药活性成分的疏水性强、稳定性差、生物利用度低和半衰期短等理化特性限制了其药用价值。

近年来，纳米技术领域取得了显著的进步，特别是纳米材料与药物的结合，给疾病的诊断和治疗带来了革命性的变化。纳米制剂具有粒径小、性质稳定的特点，已被证明能够有效地运输各种小分子，包括传统化疗药物、中药活性化合物、光敏剂和光热剂等[3,4]。本文对现有的中药活性成分纳米制剂抗肿瘤作用进行总结，以期为新型中药抗肿瘤药物的研发提供科学依据和参考。

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1 中药活性成分抗肿瘤作用

中药活性成分含有广泛的生物活性。大量研究表明，来源于中药的生物碱、多糖、皂苷、黄酮类化合物及其衍生物，不仅具有单独抗肿瘤的潜力，还可以与其他抗肿瘤药物或疗法联合应用。生物碱是一类含氮的碱性有机化合物，具有复杂的环状结构，是中药中最重要的生物活性成分之一。目前，已有多种中药生物碱及其衍生物用于肿瘤的临床治疗[5]。多糖是由10个以上单糖组成的天然大分子聚合物，单糖的组成、分子量和多糖的附着影响其结构，进而影响其性质和作用机制[6]。近年来，大量研究表明多糖具有广泛的生物学作用，包括抗病毒、抗衰老、抗凝血、抗肿瘤和抗炎等多种生物活性[7]。皂苷是由皂苷配基与糖、糖醛酸等缩合而成的一类中药常见的苷类活性成分，广泛分布于陆生植物中，少量存在于海星、珊瑚等海洋生物中[8]，根据其糖苷碳骨架结构可分为三萜类和甾体类皂苷类。皂苷在中药中广泛存在，具有抗肿瘤、抗病毒、抗炎、抗菌、解热、镇静等生物活性[9]。黄酮类化合物是由3个碳原子连接2个苯环（A环和B环）而形成的具有C_6-C_3-C_6结构的一类化合物，广泛存在于多种植物中，具有抗炎、抗肿抗氧化等作用[10]。这些中药活性成分已被证明抗肿瘤作用，见表1。

2 纳米制剂在肿瘤治疗中的优势

纳米制剂是应用纳米载体技术，将药物结合在载体表面或包裹于载体内部的一类新型药物制剂。其剂型包括脂质体、纳米胶束、聚合物囊泡、纳米粒等多种形式[64]。纳米制剂可提高游离药物的溶解度和生物相容性，克服递送障碍，并通过靶向递送、控释和多药联用，进一步增强抗肿瘤效果。

2.1 靶向递送

纳米制剂的靶向递送可以通过多种机制实现，其中一种机制是利用纳米制剂粒径小以及肿瘤组织的强渗透性和滞留性特点[65]。肿瘤细胞的快速生长可导致新生血管不规则形成，诱导血管壁结构异常和血管通透性增加。而粒径小的纳米制剂能更轻松地穿过血管壁并深入肿瘤组织[66]，进而促进其在肿瘤部位的积累，选择性地识别并附着在癌细胞表面的特定受体上[66]。Lian等[68]利用叶酸对白藜芦醇纳米粒表面进行修饰，使其在肿瘤化疗中实现靶向给药，提高肿瘤部位的药物浓度，从而增强抗肿瘤作用。

2.2 控释

纳米制剂的另一个优点在于它们能够实现药物的精准控制释放，这种控释机制保证了药物的及时和靶向递送，从而提高其在特定病变部位的浓度[69]，增强抗肿瘤效果并降低毒性。纳米制剂控制释放的方法主要分为肿瘤微环境响应型释药和外源刺激响应型释药。

肿瘤微环境响应型释药方法是利用肿瘤发生发展过程中缺氧、低pH值、氧化应激增加以及高浓度谷胱甘肽等肿瘤微环境特征，将聚合物或可生物降解材料与特定的化学基团结合，例如硫酮键（Tk

表1 中药活性成分抗肿瘤

种类	活性成分	肿瘤类型	参考文献
生物碱	长春新碱	急性淋巴细胞性白血病、乳腺癌、胃癌、弥漫大B细胞淋巴瘤	[11-13]
	胡椒碱	黑色素瘤、前列腺癌、肝癌	[14-17]
	苦参碱	卵巢癌、乳腺癌、甲状腺乳头状癌	[18-20]
	小檗碱	子宫内膜癌、卵巢癌、皮肤癌、胃癌、结直肠癌	[21-25]
	粉防己碱	卵巢癌、肝癌、黑色素瘤	[26-28]
黄酮	半枝莲黄酮	卵巢癌、肝癌	[29]
	槲皮素	乳腺癌、肺癌、宫颈癌、肝癌	[30-33]
	白花蛇舌草总黄酮	肝癌、肺癌、乳腺癌、胃癌	[34-37]
皂苷	黄芪皂苷	肝癌、肺癌	[38-40]
	人参皂苷	卵巢癌、肝癌、白血病、乳腺癌	[41-44]
	柴胡皂苷	宫颈癌、胰腺癌、肝癌	[45-47]
	三七皂苷	乳腺癌、咽鳞状细胞癌、肝癌、结直肠癌	[48-50]
多糖	灵芝多糖	肺癌、肝癌、结肠癌、宫颈癌	[51-54]
	枸杞多糖	胆囊癌、肝癌、膀胱癌	[55-57]
	黄芪多糖	结肠癌、宫颈癌、肺癌、黑色素瘤	[58-61]
	甘草多糖	肝癌、结肠癌	[62,63]

键）和二硫键（s-s键）等化学基团被设计为对pH、GSH、活性氧（ROS）等刺激作出反应，促进基于肿瘤微环境的精准药物释放[70-72]。外源性刺激响应型释药方法为利用光照、热、磁性和超声等外源性刺激，使抗肿瘤药物在特定条件下触发靶向药物释放[73]。这些方法通常被用于纳米药物制剂联合开发，实现药物精准控制释放，提高药物作用的选择性，提高安全性，降低毒不良反应。

2.3 多药联用

由于肿瘤病理机制复杂，无论是传统化药或新型生物药，仅依靠单一抗肿瘤机制的单药治疗很难在临床上取得令人满意的疗效[74]。临床及临床前研究发现，与单药疗法相比，多药联用具有显著优势，多药联用总体治疗益处大于单独药物作用的总和：（1）多药联用通过作用于相同或不同的信号通路，能在较低剂量下获得相等或更优的治疗效果[75]；（2）利用药物组合缓解或中和单药治疗引起的不良反应[76]；（3）降低药物耐受性和耐药性的发生[77]。多药联用纳米制剂可以通过将各种治疗药物靶向递送到特定组织或细胞，同时发挥协同效应，达到多种治疗增效目的。

3 抗肿瘤中药纳米制剂

中药活性成分在肿瘤治疗中具有多靶点、低毒性的显著优势。然而，其疏水性强、稳定性差、生物利用度低和半衰期短等特性限制了其在肿瘤治疗中的应用[78]。纳米制剂技术可通过改善中药活性成分的亲水性、稳定性和靶向性等，显著提高其生物利用度，从而增强其抗肿瘤作用[79]。已有研究[80,81]证明，含有中药活性成分的纳米制剂对周围组织的伤害最小，在血液中保持稳定，且不易引发溶血反应。抗肿瘤中药纳米制剂的相关总结，见表2。

4 展望

根据世界卫生组织国际癌症研究机构发布的2020年全球最新癌症负担数据，中国面临的癌症挑战尤为突出。近年来，中医药在肿瘤治疗中的作用逐步被证实，越来越多的抗肿瘤中药活性成分被发现，中药已成为肿瘤防治的重要手段。然而，中药活性成分在实际应用中仍存在限制，如溶解性差、生物利用度低等。将纳米制剂与中药活性成分结合，可显著提高中药活性成分的生物利用度和生物

表2 抗肿瘤中药纳米制剂

活性成分	纳米制剂类型	肿瘤类型	参考文献
黄芪甲苷	介孔二氧化硅纳米粒	结肠癌	[82]
当归多糖	纳米粒	乳腺癌	[83]
黄芪多糖	纳米粒	乳腺癌	[84]
南蛇藤醇	聚合物纳米粒、纳米乳剂	黑色素瘤	[85,86]
姜黄素	纳米纤维、脂质体	肺癌、结肠癌	[87,88]
喜树碱	纳米纤维	脑癌	[89]
二氢丹参酮	仿生纳米粒	肝癌	[90]
表没食子儿茶素没食子酸酯	聚合物纳米粒、纳米粒	乳腺癌、胶质母细胞瘤、黑色素瘤	[91-93]
人参皂苷	脂质体、环糊精纳米粒	神经胶质瘤、结直肠癌	[94,95]
灵芝多糖	金纳米颗粒	乳腺癌	[96]
淫羊藿素	聚合物纳米粒	肝癌、黑色素瘤	[97]
去甲斑蝥素	脂质体	肝癌	[98]
葛根素	纳米乳剂	乳腺癌	[99]
鬼臼毒素	脂质纳米粒	肺癌	[100]
槲皮素、木香内酯	聚合物胶束	结直肠癌	[101]
水飞蓟宾	脂质体、聚合纳米粒	乳腺癌	[102,103]
紫草醌	乳铁蛋白纳米颗粒、脂质体、聚合物胶束	结直肠癌、黑色素瘤	[103-106]
丹酚酸B	脂质体	乳腺癌	[107]
熊果酸	脂质体	乳腺癌、肺癌、宫颈癌、结肠癌	[108-110]
吴茱萸碱	纳米胶束、纳米粒	宫颈癌、乳腺癌、结肠癌	[111-115]
淫羊藿苷	纳米颗粒、脂质体	肝癌	[116,97]
木犀草素	纳米颗粒、纳米粒	神经胶质瘤、黑色素瘤、乳腺癌	[117-119]
α-倒捻子素	纳米胶束、聚合纳米颗粒、纳米粒	黑色素瘤、胰腺癌、乳腺癌	[120-122]

活性，是中药抗肿瘤研究的重要突破方向。本文重点总结了中药活性成分和纳米制剂在抗肿瘤中的应用与优势，为新型抗肿瘤药物的研发提高新思路。

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