青蒿素及其衍生物纳米药物递送系统和抗肿瘤机制研究

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摘要:青蒿素是从菊科蒿属植物黄花蒿中分离得到的倍半萜内酯,具有显著的截疟、消炎、抗肿瘤等生物活性。但其具有溶解度低、生物利用度差、结构不稳定等缺点,因此青蒿素衍生物蒿甲醚、青蒿琥酯、双氢青蒿素等应运而生,得以改善以上缺点。目前,青蒿素及其衍生物的抗肿瘤活性受到了广泛关注,并针对其作用机制展开深入研究,科学地解释了其抗癌的特异性和高效性。此外,为了提高青蒿素及其衍生物的生物利用度,还设计了一系列纳米药物递送系统,将其精准地靶向到肿瘤部位,提高其药效。总结和展望了青蒿素及其衍生物的抗肿瘤机制以及新型纳米制剂,以期对青蒿素的研究和新药研发提供帮助。

关键词:青蒿素;青蒿素衍生物;恶性肿瘤;抗肿瘤机制;纳米药物递送系统
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Study on the Nano-drug Delivery System and Anti-tumor Mechanism of Artemisinin and Its Derivatives *HU Xiao-xian, ZHAO Yu, WANG Yun, XU Xiao, HAN Chao** (School of Traditional Chinese Pharmacy, China Pharmaceutical University, Nanjing 210000, China)

Abstract: Artemisinin is a sesquiterpene lactone isolated from *Artemisia annua* L., family Asteraceae, with remarkable biological activities such as malaria interception, anti-inflammatory and anti-tumor. However, it has the disadvantages such as low solubility, poor bioavailability, and unstable structure. Thus, artemisinin derivatives such as artemether, artesunate, and dihydroartemisinin have been developed to overcome the above shortcomings. At present, the anti-tumor activity of artemisinin and its derivatives has received widespread attention, and in-depth studies have been carried out on their mechanism of action, scientifically explaining their anticancer specificity and efficiency. In addition, to improve the bioavailability of artemisinin and its derivatives, a series of nano-drug delivery systems have been designed to precisely target the tumor sites and enhance their therapeutic efficacy. In this regard, the anti-tumor mechanisms of artemisinin and its derivatives as well as novel nanoformulations were summarized, aiming to provide support for further research and new drug development based on artemisinin.

Key words: artemisinin; artemisinin derivatives; malignant tumors; anti-tumor mechanism; nano-drug delivery system

癌症也称恶性肿瘤,是由于机体细胞失去正常调控,过度增殖而引起的疾病。国际癌症研究机构的统计数据显示,2020 年,全球约有 1 930 万癌症新发病例和近 1 000 万癌症死亡病例,证实癌症已经成为世界范围内死亡的主要原因,是阻碍人类预期寿命增加的主要障碍之一[1]。目前临床上常采用手术、放疗和化疗 3 种常规方法治疗癌症。但这些治疗方法往往会产生恶心、呕吐、脱发等强烈副作用,并且人体低耐受性和肿瘤选择性限制了包括美登素在内的许多强效抗癌药物的广泛临床应用[2]。因此,探索高效且安全的抗癌药物是当前临床治疗的重要任务。目前,美国食品和药物管理局批准的抗癌市售药物中,60%以上来源于天然化合物或以天然成分为骨架合成的衍生物[3],其中青蒿素(Artemisinin, ART)及衍生物的抗癌活性受到广泛关注并逐步应用于临床[4,5]。

二十世纪七十年代,屠呦呦教授受传统中医药古籍《肘后备急方》的启发,从黄花蒿中分离出 ART。ART 是一种倍半萜内酯类成分(图 1),分子式为 $C_{15}H_{22}O_5$,含有一个特殊的过氧桥结构,其生物活性也多与该结构有关[6,7]。ART 本身难溶于水,经结构改造后得到双氢青蒿素(Dihydroar-

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temisinin,DHA)、青蒿琥酯(Artesunate,ARS)和蒿甲醚(Artemether,ARM)等衍生物,有效改善了 ART 的溶解性和成药性[8]。ART 是典型的抗疟药物,其组合疗法属于世界范围内既定的疟疾标准治疗方法[9]。除抗疟生物活性外,ART 及其衍生物可抑制多种癌细胞的增殖和诱导凋亡[10,11]。但是在 ART 及其衍生物应用于抗癌的过程中暴露出一些致命的缺点,如溶解度低、生物利用度低、体内代谢快、血浆峰值浓度高以及在体内不稳定、易分解等问题[12,13]。

目前,普遍有两种方法解决这一问题,其一为设计具有增强治疗效果以及稳定性的新型 ART 衍生物,其二是构建多功能纳米药物递送系统荷载 ART 及其衍生物,然后将其精准地递送到癌症病灶并释放[14]。纳米药物载体是一种新型载体,通常由天然或合成高分子材料制成。目前已上市或处于临床研究阶段的纳米制剂主要包括脂质体、纳米晶体、胶束和纳米粒等[15]。与常规药物制剂相比,纳米制剂具有许多难以比拟的优势,例如改善药物递送、改善药物稳定性、延长体内循环时间、增加药物安全性等,因而常被用于递送难溶性药物、抗肿瘤药物、基因药物以及需要突破血脑屏障的药物等[16,17]。目前已经有许多关于 ART 纳米递送系统的研究,取得了比较理想的成果[18]。

1 青蒿素及其衍生物抗肿瘤活性机制

自 2015 年诺贝尔生理学或医学奖授予中国科学家屠呦呦教授以来,ART 引起了全世界的关注[19]。除了具有公认的抗疟疾作用之外,ART 及其衍生物还具有潜在的抗癌作用(图 1),其抗癌活性在肺癌[20]、肝癌[21]、结肠直肠癌[22]、乳腺癌[23]、宫颈癌[24]和前列腺癌[25]等多种癌细胞中得到证实。

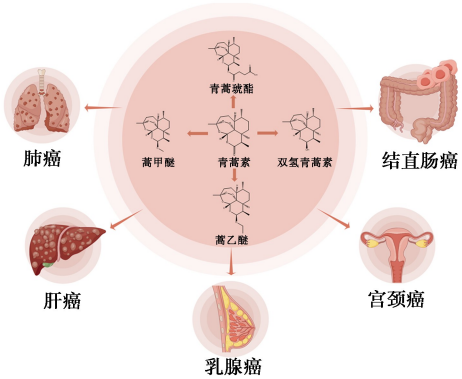


图 1 青蒿素及其衍生物结构与抗肿瘤活性

Fig.1 Structure and anti-tumor activity of artemisinin and its derivatives

1.1 肺癌

随着医疗水平的提高,目前可手术治疗的肺癌患者比例明显增加,但肺癌仍是全球致死率最高的癌症[26,27]。其中约 85%的肺癌属于非小细胞肺癌,因此对于 ART 及其衍生物抗肺癌活性的研究也多集中于非小细胞肺癌[28]。

Zhang 等[29]实验研究证明,ARS 和 DHA 可以下调 A549 肺癌细胞中铁死亡的核心负调节器胱氨酸/谷氨酸转运体,并上调转铁蛋白受体 mRNA 水平,从而使细胞表面过表达转铁蛋白受体,转铁蛋白与受体结合后,通过受体介导的摄取作用提高细胞内铁含量[30,31]。ART 衍生物的过氧化桥结构与亚铁离子反应后断裂,产生以碳为核心的自由基或活性氧(Reactive oxygen species,ROS)[32,33]。过量的 ROS 触发线粒体膜通透性转换孔的开放导致细胞凋亡,并推动脂质过氧化诱导铁死亡[34,35]。ART 及其衍生物抑制肺癌发展的另一重要机制是影响肺癌细胞的信号通路,如 MAPK 通路[36],ERK/c-Myc 通路[37],Wnt/β-catenin 通路[38]以及 STAT3 通路[39]等。并且,ART 及其衍生物可以通过阻滞细胞周期[40]和抑制肿瘤血管生成[20]发挥抗肺癌作用。此外,ART 及其衍生物还可以与其他抗癌药物联合使用,促进 ROS 的产生和累积,诱导 A549 肺癌细胞 caspase-3 程序性细胞凋亡或损伤其 DNA[41,42]。

1.2 肝癌

肝癌是最常见的原发性恶性肿瘤,约占据原发性恶性肿瘤总比例的 80%,是全球恶性肿瘤致死的主要类型之一。当代社会肥胖症的流行使非酒精性脂肪肝成为肝癌发展的主要危险因素[43]。由于肝癌患者诊断时多处于晚期,所以临床治疗非常具有挑战性,目前常采用化疗和免疫疗法[44]。

众所周知,血管内皮生长因子受体 2(Vascular endothelial growth factor receptor 2,VEGFR2)是血管生成和癌症进展的关键效应因子,新型 ART 衍生物 FO8643 可抑制 HUH-7 肝癌细胞中 VEGFR2 激酶活性并调控其下游的 MAPK 和 PI3K/Akt 信号通路,抑制肝癌进一步发展[45]。除干扰此信号通路之外,ARS 还可通过结合 STAT3 的 SH2 结构域来干扰 STAT3 二聚化的能力,促进肿瘤细胞凋亡[21,46]。ART 则通过调节 N-cadherin/Snail/E-cadherin 轴抑制肝癌细胞迁移和侵袭,在给予抗

逆转录病毒治疗后,肝癌细胞中的 Hippo-YAP 信号转导也明显失活,其作用机制如图 2 所示[47]。铁稳态异常是肝癌的典型特征,干扰铁代谢是治疗肝癌的有效策略。Jiang 等[48]证实 ARS 通过酸化溶酶体促进储存铁蛋白的溶酶体降解,从而增加癌细胞内的不稳定铁,不稳定铁在内质网中累积导致内质网被严重破坏并产生过量 ROS,进而促进癌细胞死亡。此外,全转铁蛋白也可以显著增强 ART 的抗癌活性[49]。

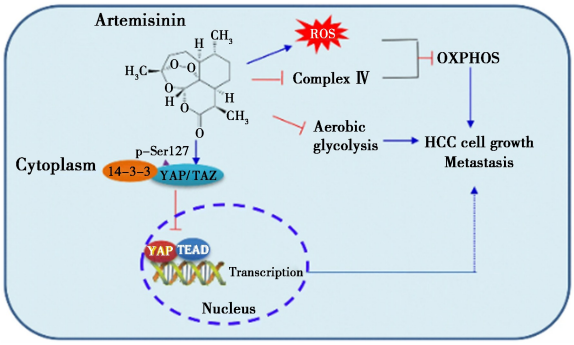


图 2　青蒿素抑制肝癌细胞迁移和侵袭作用机制[47]

Fig.2　Mechanism of artemisinin inhibiting the migration and invasion of liver cancer cells[47]

1.3　结直肠癌

结直肠癌每年导致近七十万人死亡,使其成为世界第四大致命癌症[50]。虽然新药的研发使晚期结直肠癌患者的平均生存时间延长一倍,但患者仍多数在 3 年内死亡[51]。

Lu 等[52]研究表明,DHA 可以通过抑制肌浆/内质网钙 ATP 酶活性释放细胞内质网 Ca^{2+},引起内质网应激,并通过上调 CHOP 表达激活线粒体凋亡通路,诱导结直肠癌细胞凋亡。随着合成技术的日渐成熟,多种新型 ART 衍生物应运而生。其中含有哌嗪和氟基团的新型 ART 衍生物被证实主要通过线粒体介导的途径诱导细胞凋亡[53]。另一种新型衍生物 10-苯基三唑基 ART 则主要通过降低癌细胞通透性糖蛋白(permeabilityglycoprotein,P-gp)的表达量,抑制 P-gp 转运紫杉醇。通过控制获得性耐药途径恢复紫杉醇的抗癌作用,这有助于开发针对多药耐药性癌症的抗癌药物[22]。

1.4　乳腺癌

乳腺癌是女性中发病率最高的恶性肿瘤,是一种由于乳腺上皮细胞发生癌变而形成的肿瘤。大量证据表明生活方式(高脂肪饮食、饮酒、缺乏体育锻炼)和环境因素影响乳腺癌的发生发展,消除这些因素可能有助于降低发病率和死亡率[54,55]。

药理研究表明,ART 及其衍生物主要作用于乳腺癌细胞的线粒体。ART 可以通过影响 VEGF 的旁分泌作用来抑制线粒体生成、血管生成以及癌细胞在内皮细胞之间的迁移[23]。DHA 和多柔比星联合使用,显著降低线粒体膜电位,激活了 caspase 级联反应,促进癌细胞凋亡[56]。此外,ART、ARS 和 DHA 还能阻滞癌细胞周期或 TGF-β 信号通路,从而抑制乳腺癌的进程[57,58]。

1.5　宫颈癌

宫颈癌是全球女性癌症相关的主要死亡原因之一。早期患者积极配合治疗可使 5 年生存率达到 90%,但癌细胞发生转移后患者的预后会非常差[59,60]。

Zhang 等[61]证明,ARS 通过抑制 HOTAIR 的表达,调控 COX-2 的表达量以及催化活性,发挥抗宫颈癌转移作用。Zhang 等[24]利用荧光探针标记 ARS,确定 ARS 可以与线粒体蛋白结合并引起线粒体裂变,进而通过 PINK1 途径诱导细胞保护性线粒体自噬。因此可以通过抑制线粒体自噬增强 ARS 的抗癌活性,为开发 ARS 成为治疗宫颈癌新药提供新思路。

1.6　前列腺癌

前列腺癌是男性患者最常被确诊的非皮肤恶性肿瘤,是一种雄激素敏感的癌症[62]。前列腺癌患者通常病史悠久,个体临床进展多样且不确定,为治疗带来重重困难[63]。

雄激素受体(Androgen receptor,AR)是一种类固醇受体转录因子,控制前列腺发育和生理功能所需基因的表达,因此被认为是治疗前列腺癌的潜在靶点[64]。DNA 甲基转移酶(DNA methyltransferase,DNMT)介导的基因甲基化修饰在癌症病理过程中普遍存在[65]。Wang 等[25]则通过实验证明,ARS 可以通过抑制 AR 和 DNMT3b 的表达来抑制前列腺癌细胞的生长。DHA 及 ART 衍生的碳二聚体同样具有抗前列腺癌活性,其中 DHA 主要通过 caspase 依赖的内在信号级联反应诱导癌细胞凋亡[25],而 ART 衍生的碳二聚体则能刺激癌细胞产生大量 ROS 促进其凋亡[66]。

2　青蒿素及衍生物纳米药物递送系统

尖端的纳米技术为发明新疗法和提高当前医学治疗的有效性提供了前所未有的机会。纳米药物递送系统可以将生物活性分子靶向到病灶部位,维持药物释放并能显著提高药物的治疗效

果[67]。目前 ART 及其衍生物也被设计成多种纳米制剂(表 1),主要包括脂质体、金属有机框架纳米粒、碳基纳米粒、纳米囊、胶束等。

表 1 青蒿素及其衍生物纳米制剂与抗肿瘤类型

Tab.1 Artemisinin and its derivatives nano preparations and anti-tumor types

名称	纳米制剂类型	抗肿瘤类型
青蒿素	脂质体[68,69],金属有机框架纳米粒[70],纳米囊[71],胶束[72,73]	乳腺癌[68,72,74,75],肠腺癌[69],宫颈癌[70],黑色素瘤[71]
双氢青蒿素	脂质体[76-78],金属有机框架纳米粒[79],碳基纳米粒子[80],胶束[81]	乳腺癌[76,79,80],肝癌[77],结直肠癌[78],人口腔表皮癌[81]
青蒿琥酯	脂质体[82],碳基纳米粒子[83],纳米囊[84,85]	肝癌[82],乳腺癌[83-85]
蒿甲醚	脂质体[86]	脑癌[86]

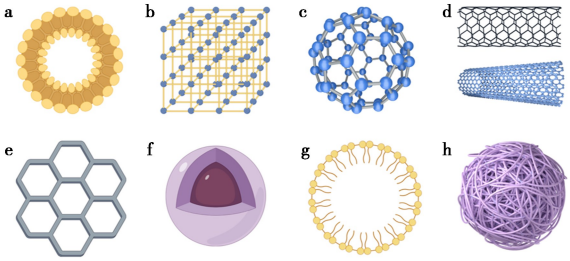
2.1 脂质体

脂质体是由磷脂双分子层组成的球形囊泡(图 3a)。脂质体既无毒又可被生物降解,是多种药物首选的递送材料。它们通过稳定化合物结构、克服细胞和组织摄取的障碍、增加药物在体内靶点的生物分布以及最大限度减少全身毒性,来提高药物的治疗效果[87]。

脂质体最常采用的是具有亲水性和生物相容性的聚乙二醇(Polyethylene glycol,PEG)修饰,该修饰可以防止脂质体被血清蛋白吸收,显著延长其血液循环时间[88]。ART PEG 脂质体药物包封率高达 92%,可以明显增强 ART 的细胞毒性[68]。长循环 DHA PEG 脂质体稳定性好,有望在减少给药剂量和给药频率的同时保持良好的抗肿瘤活性[76]。pH 响应脂质体是近年来研究的热点。转铁蛋白修饰的脂质体纳米颗粒能荷载 DHA、1-丁硫氨酸-亚砜胺和荧光探针,RGD 肽修饰的 pH/ROS 双敏感纳米脂质体能荷载 DHA 和磷酸氯喹,均能将药物靶向递送到肿瘤部位并将药物靶向释放,进而上调癌细胞内 ROS 水平,发挥抗肿瘤功效[78,79]。此外,ART 还可以改善现有抗癌药物的疗效。如将 ARM 与紫杉醇联用,加以甘露糖-维生素 E 偶联物和脱氧喹啉-脂质衍生物偶联物两种新型功能材料修饰,帮助药物透过血脑屏障[89]。这为治疗侵袭性脑胶质瘤提供新的策略。

2.2 金属有机框架纳米粒

金属有机框架(Metal organic framework,MOFs)纳米粒是一种多功能多孔结构纳米晶体材料,具有金属离子与多齿有机基团配位的结构(图 3b)[90]。一方面,MOFs 的高比表面积和大孔径能提高药物的载药量[91]。另一方面,MOFs 表面可被化学基团修饰,进而能控制药物释放及靶向病灶[92]。



a.脂质体;b.金属有机框架纳米粒;c.富勒烯;d.碳纳米管;e.石墨烯;f.纳米囊;g.胶束;h.纳米纤维

图 3 青蒿素及其衍生物纳米制剂类型

Fig.3 Types of artemisinin and its derivatives nanoformulations

Wang 等[70]制备了新型核壳 PB@MIL-100(Fe)双金属有机框架纳米颗粒,并研究其体内联合治疗效果。该纳米粒子在靶向到肿瘤部位后,MIL-100(Fe)发生低 pH 响应性降解,释放出荷载的 ART。纳米粒子的内核 PB MOF 在近红外区具有强吸收,可以用于光热治疗。采用该纳米药物的光热治疗和化疗,在动物肿瘤模型中实现有效的肿瘤消融。Wan 等[79]设计了一种能实现 DHA 程序性释放的纳米粒 Fe-TCPP。采用 $CaCO_3$ 涂层包被该纳米粒,可有效防止 DHA 在血液运输过程中泄漏。当纳米粒到达肿瘤部位时,弱酸性肿瘤微环境和高浓度谷胱甘肽触发 DHA 的释放和 TCPP 的激活,从而实现 Fe^{2+}-DHA 介导的化学动力学治疗、Ca^{2+}-DHA 介导的肿瘤治疗和 TCPP 介导的光动力治疗的协同抗肿瘤作用。该纳米药物的制备及释放流程示意图如图 4 所示。

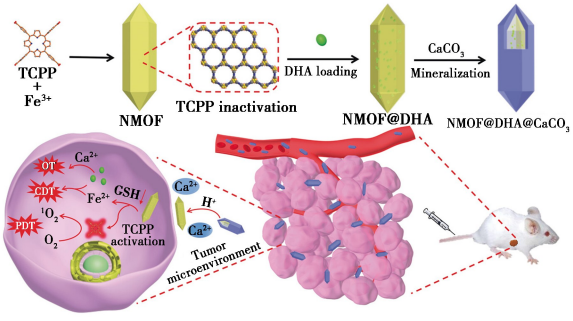


图 4 NMOF@DHA@$CaCO_3$ 制备和程序化药物释放示意图[79]

Fig.4 Schematic diagram of NMOF@DHA@$CaCO_3$ preparation and programmed drug release[79]

2.3　碳基纳米粒

石墨烯、碳纳米管和富勒烯等碳基材料已被用于制备纳米药物递送系统(图 3c~3e)。该材料具有比表面积大、可修饰等优点,选择合适的修饰方法可以显著提高其生物相容性和生物降解性[93]。

ART 及其衍生物内的过氧桥结构容易与 Fe^{2+} 反应生成 ROS,诱导癌细胞凋亡,因此 ART 碳基纳米制剂常加以转铁蛋白修饰。Zhang 等[83]将透明质酸枝接到富勒烯上,得到具有良好生物相容性的水溶性材料,负载 ARS,再与转铁蛋白结合,得到具有显著肿瘤靶向作用和光动力治疗能力的多功能纳米药物递送系统。此外,靶向线粒体介导的凋亡也是一种非常有前途的治疗策略。Han 等[80]设计了一种基于氧化石墨烯的纳米传感器,该纳米传感器携带线粒体靶向香豆素衍生物 Cou-DHA 以产生抗肿瘤疗效,携带 Cy5 标记的 DNA 适配体用于细胞凋亡实时成像,成功实现可视化抗肿瘤药物的高选择性靶向递送。

2.4　纳米囊

纳米胶囊是由内部液核(水性/油性)组成的囊泡系统,周围环绕着聚合物壁,具有作为药物载体的巨大潜力(图 3f)[94]。

Tran 等[85]采用热均质法制备带负电荷的脂质纳米乳,然后通过静电相互作用包被带正电荷的壳聚糖,最终得到壳聚糖脂质纳米胶囊,ARS 位于纳米囊的内部液核中。Meng 等[84]以聚乙二醇单甲醚和 ARS 为原料,通过酯化反应合成了聚乙二醇化 ARS 前药。该产物具有两亲性,在水介质中形成纳米胶囊。通过 MTT 等药理实验证明,以上两种纳米制剂的肿瘤抑制作用均强于游离药物,有望应用于临床化疗。

2.5　胶束

胶束是一种聚合药物递送系统,由两亲性嵌段共聚物组成,形成用于包封亲脂性药物的疏水核(图 3g)。聚合物胶束的大小在 10~200 nm 之间,其结构可以延长药物血液循环时间,有助于药物持续释放[95]。

Lu 等[81]采用溶剂蒸发法制备了负载 DHA 的甲氧基聚乙二醇/聚乳酸两亲嵌段共聚胶束,其平均粒径小于 130 nm,具有低 pH 响应药物释放效应,并且细胞毒性明显高于游离 DHA。Manjili 等[72]首先合成了聚己内酯-聚乙二醇-聚己内酯三嵌段共聚物,然后采用纳米沉淀法将 ART 包埋在胶束内。该制剂可以显著增加 ART 在肿瘤部位的蓄积。与相同剂量的游离 ART 相比,静脉给药负载 ART 的胶束显著增加 ART 在体内的药物暴露时间。以上研究结果均证实了胶束是辅助 ART 及其衍生物达到最佳抗癌效果的理想材料。

3　总结与展望

ART 及其衍生物的过氧桥断裂是其产生抗肿瘤疗效的主要触发因素,其主要是通过 Fe^{2+} 催化的 Fenton 反应生成烷基自由基和 ROS,后者在诱导癌细胞周期停滞、抑制癌细胞增殖、抗肿瘤血管生成、诱导癌细胞铁死亡、凋亡以及自噬中起着核心作用。此外,ART 及其衍生物还可以与多柔比星、吉西他滨、紫杉醇和顺铂等著名化疗药物联合使用,通过化学增敏的机制发挥协同抗肿瘤的作用,是解决肿瘤化耐药性这一难题的潜在方案。但是,目前在文献中只能找到少数 ART 及其衍生物抗肿瘤的病例报告和临床试验,大部分抗肿瘤实验是在细胞水平以及动物肿瘤模型中验证。目前相关的病例报告和临床试验中大多数使用水溶性的 ARS,病人均表现出良好的耐受性,且没有严重的副作用,这证实了 ARS 的临床抗肿瘤潜力。总之,目前还需要开展广泛的临床研究,来探究 ART 及其衍生物的抗肿瘤功效。

虽然排除了 ART 及其衍生物对非癌细胞的毒性及人体副作用,但目前的研究表明,长期服用是预防肿瘤复发所必须的,而药物体内滞留时间是发挥疗效的重要参数。针对提高生物利用度和延长体内循环时间的问题,目前开发了纳米疗法。将 ART 及其衍生物包载于各种纳米药物递送系统中,加以修饰,实现靶向递送以及增强疗效等目的。除了常见的纳米药物递送系统外,近年来新兴的纳米载体如牛血清白蛋白纳米颗粒以及可注射水凝胶也同样具有开发潜力,有望进一步提高 ART 及其衍生物的疗效。此外,合成新型 ART 衍生物对解决以上问题也具有一定帮助。多年来,青蒿素一直被用作治疗癌症的先导化合物,许多衍生物保留了过氧桥的主干结构,在 10 位碳上对 ART 进行修饰,合成更高效的衍生物。目前,合成 ART 二聚体已被证实具有良好的抗癌生物活性,开发更多 ART 衍生物指日可待。

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