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电化学方法检测抗癌药物氟尿嘧啶的最新研究进展

——新材料修饰电极助力提升检测效果

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摘　要

5-氟尿嘧啶自合成以来，被广泛地应用于消化道癌和其他实体瘤的治疗。虽然获得了很好的疗效，然而，它的毒副作用也越来越引起科研人员的重视。为了进一步研究治疗过程中，该药在人群中产生的差异、以及环境污染与职业暴露对其的影响，我们总结了近年来5-氟尿嘧啶的检测方法，对比发现电化学检测凭借其检测限低，重现性好，预处理简单，实验操作简便等优势在众多方法中脱颖而出，特别是新型材料在修饰电极方面的应用，进一步提升了检测效果。

关键词

5-氟尿嘧啶，剂量管理，可检测浓度，电化学，电极材料

Recent Progress in Electrochemical Detection toward Anticancer Drug Fluorouracil

—Detection Performance Improved by Novel Electrode Material

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Abstract

5-fluorouracil has been widely used in the treatment of gastrointestinal cancer and other solid

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tumors since its synthesis. Although it has obtained good curative effect, its toxic and side effects have attracted more and more attention of researchers. In order to further study the difference of the drug in the population during the treatment process, as well as the impact of environmental pollution and occupational exposure, we summarized the detection methods of 5-fluorouracil in recent years, and found that electrochemical detection has stood out among many methods by virtue of its low detection limit, good reproducibility, simple pretreatment, simple experimental operation and other advantages, especially the application of new materials in modified electrodes, which further improved the detection effect.

Keywords

5-Fluorouracil, Dose Administration, Detectable Concentration, Electrochemistry, Electrode Materials

1. 引言

5-氟尿嘧啶(5-fluorouracil, 5-FU)于 1957 年被 C. Heidelberger 等人首次合成[1]。药物在细胞内转化为 5-氟-2'-脱氧尿苷，抑制胸苷酸合成酶，阻止脱氧尿苷酸甲基化为脱氧胸苷酸，进而抑制 DNA 合成[2]。另外，其转化为 5-氟尿嘧啶核苷后，可以被掺入 RNA 中，干扰核 RNA 的成熟(图 1) [3]。5-FU 被广泛应用于消化道癌如结直肠癌、食管癌、胃癌和转移性胰腺癌的治疗，在乳腺癌、卵巢癌的治疗中也有良好的效果[4]-[9]。因为具有抑制瘢痕形成的能力，5-FU 还被应用于防止瘢痕疙瘩的复发和青光眼滤除手术[10] [11]。此外，5-FU 还被制成乳膏，用于皮肤癌的局部治疗[12]。然而，5-FU 产生的毒性、狭窄的治疗窗、给药后患者之间的疗效差异、对环境的污染和造成的职业暴露限制了 5-FU 的发展。为此，学者们对其进行检测，不断地解决它所带来的问题。

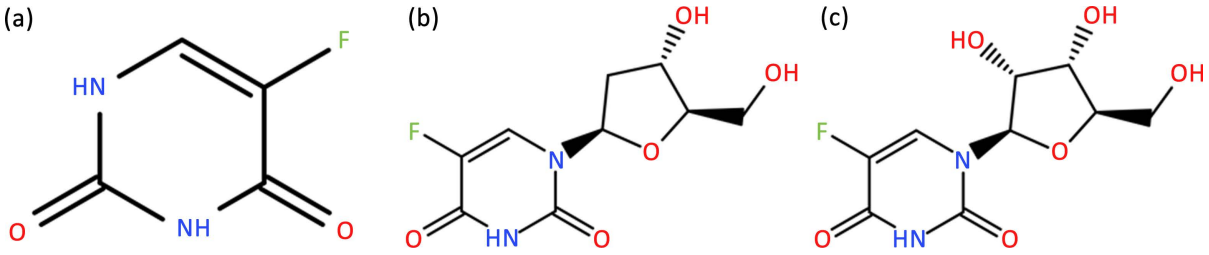

Figure 1. Chemically structural formula of 5-fluorouracil (a), Floxuridine (b), 5-Fluorouridine (c)
图 1. 5-氟尿嘧啶(a)、5-氟-2'-脱氧尿苷(b)、5-氟尿嘧啶核苷(c)的化学结构式

2. 为什么要检测 5-FU

2.1. 5-FU 的检测与毒性

5-FU 产生的毒性一部分与剂量有关，对其进行剂量监测能够预防或减少毒性的发生。5-FU 常见的毒性有恶心呕吐、腹泻、黏膜炎[13]。N. E. Kemeny 等人输注 5-FU 辅助治疗结直肠癌肝转移，得出输注 5-FU 超过 2000 mg/m^2 时，会产生剂量限制性毒性(Dose-limiting toxicity, DLT)，为恶心和腹泻[14] [15]。

R. Whittington 等人长期静脉输注 5-FU 联合放疗治疗局限性胰胆癌，得出 5-FU 的最大耐受剂量(Maximum tolerated dose, MTD)为 250 mg/m^2/d，DLT 是口腔粘膜炎[16] [17]。5-FU 会产生骨髓毒性：轻度骨髓抑制可导致剂量减少和治疗延迟，而重度骨髓抑制可导致危及死亡的并发症，如致命感染和无法控制的出血[18]。O. Leon 等人在治疗局部晚期肛门癌患者的过程中，测定了 5-FU 的 MTD，为 800 mg/m^2，DLT 是中性粒细胞和血小板减少症以及放射性皮炎[19] [20]。5-FU 会引起心脏毒性，造成冠状动脉血管痉挛和对心肌的直接损伤[21]。M. de. Forni 等人对 367 名接受连续输注 5-FU 的患者进行了检查，在剂量超过 800 mg/m^2/d 时患者表现出更严重的心脏毒性[22]。5-FU 还会产生神经毒性，通常表现为脑病，如共济失调、眼球震颤、全身性癫痫发作等[23]。S. Cascinu 等人用 5-FU 和紫杉醇组合治疗晚期胃癌，测得 5-FU 的 MTD 为 500 mg/m^2，DLT 为神经毒性[24]。

2.2. 5-FU 的检测与治疗

5-FU 的治疗窗窄，曲线下面积(area under curve, AUC)范围为 20~30 mg*h/L，因此维持 5-FU 的最佳治疗浓度也非常需要重复、准确地测定生物液中的药物浓度[25]。R. Deng 等人用 My5-FuTM Kit 测定 5-FU 血药浓度，发现接受以 AUC 为基础的药物代谢动力学化疗的患者与接受体表面积(body surface area, BSA)引导化疗的患者相比，在治疗窗内的百分比从 24.52%增加到 89.71%，化疗疗效从 79.22%提高到 90.79%，毒副作用从 51.95%减少到 31.58% [26]。

2.3. 5-FU 的检测与个性化化疗方案

依据生物节律制定的低毒副作用、高疗效的时间疗法被广泛用于癌症治疗。5-FU 的节律反应和毒性一部分取决于负责 5-FU 消除的限速酶：二氢嘧啶脱氢酶(dihydropyrimidine dehydrogenase, DPD)活性的昼夜节律振荡[27]。DPD 活动在午夜附近达到峰值，DPD 活动在下午早些时候达到低谷。长期连续输注期间，全身 5-FU 水平从峰值到低谷的变化为 2.3 倍[28]。然而，时间疗法不能够应用于全部患者的治疗，5-FU 的药物代谢动力学(Pharmacokinetics, PK)的呈现非线性动力学特征导致患者之间出现明显个体差异，根据他们的 PK 参数值将患者分为不同的亚组并分别建立给药数学模型，对时间疗法进行改进，可能会实现给药的精准化和个性化[29]。但这不能够防止 5-FU 急性毒性的产生，DPD 的缺乏会导致过量的 5-FU 在体内蓄积，产生很高的毒性[30]。对于 DPD 缺乏导致的氟尿嘧啶血症，已建议部分缺乏患者的 5-FU 阈值为 16 ng/mL，而对于完全缺乏的患者，则建议阈值为 150 ng/mL [31]。C. Marin 开发了一种液相色谱－紫外(UPLC-UV)方法，它能够区分 DPD 非缺陷患者(即 5-FU 水平 < 16 ng/mL)与有严重毒性风险的缺陷患者(即 5-FU > 16 ng/mL)。DPD 缺乏患者需要减少 5-FU 剂量[32]。此外，5-FU 的剂量调整还与多参数方法有关：女性较男性低的 5-FU 清除率、肌肉质量的减少、肾功能的损害都会增加 5-FU 相关毒性的风险[25]。已有研究表明，肌肉质量是一种剂量限制毒性因素，基于瘦体重(Lean Body Mass, LBM)而不是 BSA 的化疗剂量是一种很有前途的预防毒性、提高化疗完成率、改善生存质量的新方法[33]。

2.4. 5-FU 的检测与环境污染和职业暴露

此外，5-FU 往往通过患者体液的代谢和药物的注射以完整的形式释放到环境中，即使在低浓度下也会对环境造成破坏和职业暴露。医院废水和癌症患者家庭排放到环境中的 5-FU 在水生植物类、鱼虾类、甲壳类中有残留并显示出遗传毒性，对环境造成长期不利影响(图 2) [34]。残留在废水中的药物会被可食用植物吸收，最终通过食物链对人类免疫系统的细胞造成了显著的遗传毒性损伤，其程度高于直接接触单一抗肿瘤药物的淋巴细胞[35]。D. Hilliquin 等人采用液－质联用和气相色谱－串联－质谱法对 5-FU 进行定量，发现药瓶的外部、运输手提箱的内部和接受的区域受到了污染。因此应在收到瓶子时清洁瓶子、对

待防护包装采取同样的预防措施并在注射的所有步骤中佩戴防护装备来减少污染[36]。职业接触人员、患者及家属可以通过吸入和皮肤接触不必要的 5-FU 而对身体造成损害。M. Karedal 等人建立了一种快速液相色谱串联质谱法，该方法的定量限为 0.04 至 2.4 ng，可以同时定量检测包括 5-Fu 在内的常用抗肿瘤药物的表面污染，还可以评估不同清洁溶液的去污效果[37]。

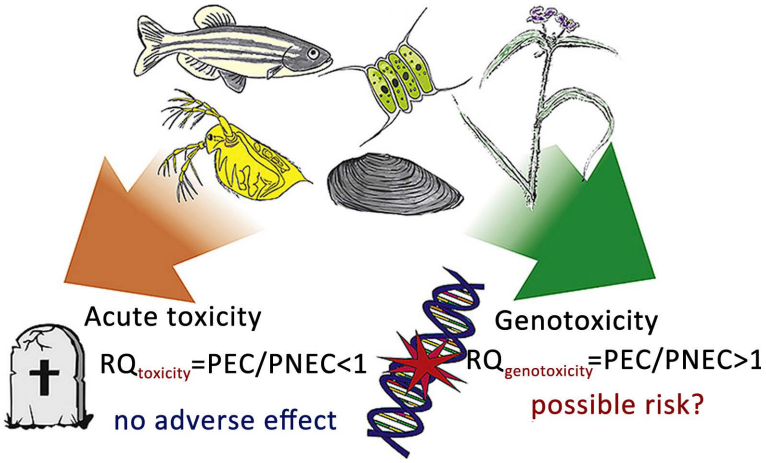

Figure 2. Genotoxicity toxicity of 5-fluorouracil in aquatic life [34]
图 2. 5-氟尿嘧啶在水生生物中的遗传毒性[34]

3. 5-FU 的检测方法

因此，建立可靠的检测技术、监测给药后生物体液中抗癌药物的浓度，是提高抗癌药物治疗指数、降低其毒副作用、发现与修正机制、实现个性化化疗方案和减少环境污染与职业暴露的有效途径。表 1 列出了 2018 年以来对人体体液中 5-FU 检测方法的研究。

Table 1. Detection method of 5-FU in human body fluids since 2018
表 1. 2018 年以来人体体液中 5-FU 的检测方法

序号	检测方法	线性范围 (ng/mL)	检出限 (ng/mL)	优势	局限	参考文献
1	高效液相色谱法	900~60,000	100	精确、准确、应用范围广	前处理复杂、灵敏度低	[38] [39]
2	液相色谱－质谱法	4~1000	4	选择性好、预处理简单	样品稳定性差	[40]
3	反相高效液相色谱－紫外检测法	100~10,000	2	操作简单、适用多样品	色谱柱不通用	[41] [42]
4	毛细管电泳法	1~1000	0.11~0.14	灵敏、高载量	预富集	[43]
5	增强拉曼散射测流免疫层析法	0.0001~100	0.0044	灵敏、荧光稳定、不易受杂质干扰	材料昂贵	[44]
6	荧光检测法	10^2~10^6	64.5	灵敏	需特殊荧光材料	[45]

注：1~5 检测人体血液中的 5-FU，6 检测人体尿液中的 5-FU。6 线性范围和检出限的单位为 nM。

为了更早发现药物的作用效果并减少毒性的发生，使用的检测方法应具有低的检出限和广泛的线性范围。5-FU 和其它药物联合应用治疗癌症的方法的广泛应用，要求检测方法应能够同时定量测出几种药物并且排除体内药物、代谢干扰物的影响。此外，还应考虑到检测的时间的长短、是否环保和成本的高低。近年来广泛应用的色谱法虽然具有良好的准确度、精密度，但它需要较长的分析时间、复杂的前处

理程序、用于分离的有毒的有机溶剂和昂贵的设备。相比之下，电化学分析技术具有成本低、灵敏度高、响应快、分析时间短、小型便携、无需复杂的前处理方式以及通过修饰电极表面来提高其选择性和专属性等优点。

4. 5-FU 的电化学检测方法

研究员们通过改变衬底电极和修饰电极的材料来改良对 5-FU 检测的性能，表 2 总结了 2017 年以来 5-FU 的电化学检测。

Table 2. Electrochemical detection of 5-FU since 2017
表 2. 2017 年以来 5-FU 的电化学检测

序号	衬底电极	修饰	线性范围(μM)	检出限(nM)	pH	参考文献
1	PGE	AgNPs@PANINTS	1.0~300.0	60	8.0	[46]
2	GCE	α-Sm_2S_3/MoS_2	0.10~1166	15	7.0	[47]
3	GCE	AuNPs@CS-PMAA	0.1~497	30	7.0	[48]
4	GCE	PNIPAM-PEDOT	0.03~182 0.6~185	15 370	7.0	[49]
5	GCE	N-CQD@Fe_2O_3/MWCNT	0.5~120	19	7.0	[50]
6	GCE	CuNPs/MWCNT/IL/Chit	1~550	150	9.0	[51]
7	GCE	Pd-Au/MWCNT-rGO	0.05~75	9.4	9.0	[52]
8	GCE	GQDs-PANI/ZnO-NCs	0.10~50.0	23	10.0	[53]
9	CPE	(Pr:Er)NPs	0.01~50	0.98	7.0	[54]
10	CPE	GQD/BPBr	0.001~400	0.5	7.0	[55]
11	SPC	GOs/MWCNTs	0.05~5 5~1200	16	7.0	[56]

注：1~8 为差分脉冲伏安法(Differential Pulse Voltammetry, DPV)，9~11 为方波伏安法(Square wave voltammetry, SWV)。4 线性范围和检出限中有温度区别 0.03~182 (40℃) 0.6~185 (25℃)，15 (40℃) 370 (25℃)。11 尽管在 pH 值约为 6.0 时获得了最大的峰值电流，但由于更高的选择性和分辨率，生理上更重要的 pH 值 7 被选为最佳值。

2017 年以来，检测 5-FU 常用的电化学研究方法为 DPV 和 SWV，检测的线性范围大多数在 μM 级别，检出限大多数在 nM 级别，衬底电极大多数为玻碳电极(Glassy carbon electrode, GCE)和碳糊电极(Carbon paste electrode, CPE)，检测 pH 在 7.0~10.0 之间。检测方法应具有良好的重复性、稳定性、回收率和抵抗生物体液中多种杂质干扰的性能，并能够在生物样品中完成进一步的检测。

电化学检测的优势在于能够通过修饰材料来改变检测性能。金、银等金属纳米粒子(AuNPs, AgNPs)具有高导电性和大表面积，但容易聚集，需要聚合物对其进行修饰如：聚苯胺(PANINTS)和聚甲基丙烯酸(PMAA)增强其分散稳定性，从而加快电子转移速率，增加电极有效表面积[46] [48]。氧化铁纳米颗粒(Fe_2O_3 NPs)与氮掺杂碳量子点(N-CQD)杂化，增强了对 5-FU 及其结构相似的尿酸(UA)和黄嘌呤(XA)的电催化性能，使它们能够同时定量分析(图 3) [50]。多壁碳纳米管(MWCNT)修饰其它材料时，可以增加材料的化学稳定性、导电性和比表面积并加快电子转移速率[50] [51] [52] [56]。尺寸小、低毒性的 GQD 修饰其它材料时，可以增加材料的生物相容性、稳定性和导电性并加快电子转移速率[53] [55]。此外，修饰电极的材料应该绿色环保，如壳聚糖(Chitosan, CS)、离子液体(Ionic liquid, IL)；应该有较低的成本，如 CuNPs (相较于 AuNPs、AgNPs)；还应该有较低的毒性，如氧化锌(ZnO) [51] [53]。

修饰材料的多样性也为电化学检测的发展提供了可能。二硫化钼(MoS_2)相邻单层之间可以插入或捕获其他 2D 层状材料，如金属氧化物、金属硫化物和基于石墨烯的材料来实现层间膨胀。这种大的层间膨胀的异质结构显示出独特的电子和物理化学性质[47]。镧系元素化合物的纳米结构具有有趣的电催化特性，将镨钨酸铒(Pr:Er)掺入 CPE 成分中，能提高电极的导电性[54]。聚(N-异丙基丙烯酰胺) PNIPAM 的热敏行为可以减少背景干扰，提高检测的选择性，聚(3,4-乙二氧基噻吩基) (PEDOT)用于增强 PNIPAM 电传感性能。PNIPAM-PEDOT 导电微凝胶膜首次用于实现 5-FU 的热开关控制，对温度高度敏感且完全可逆。这种新颖的类开关电化学传感器为热响应聚合物的应用提供了一个创新的概念[49]。用 Pd-Au/MWCNT-rGO 修饰电极，二茂铁(Fc)作为参比电极，双信号电化学比率法可以消除传感环境的干扰，同时定量测定氟尿嘧啶和伊利替康，这种比值计量法为 5-FU 的电化学检测提供了新的方向[52]。

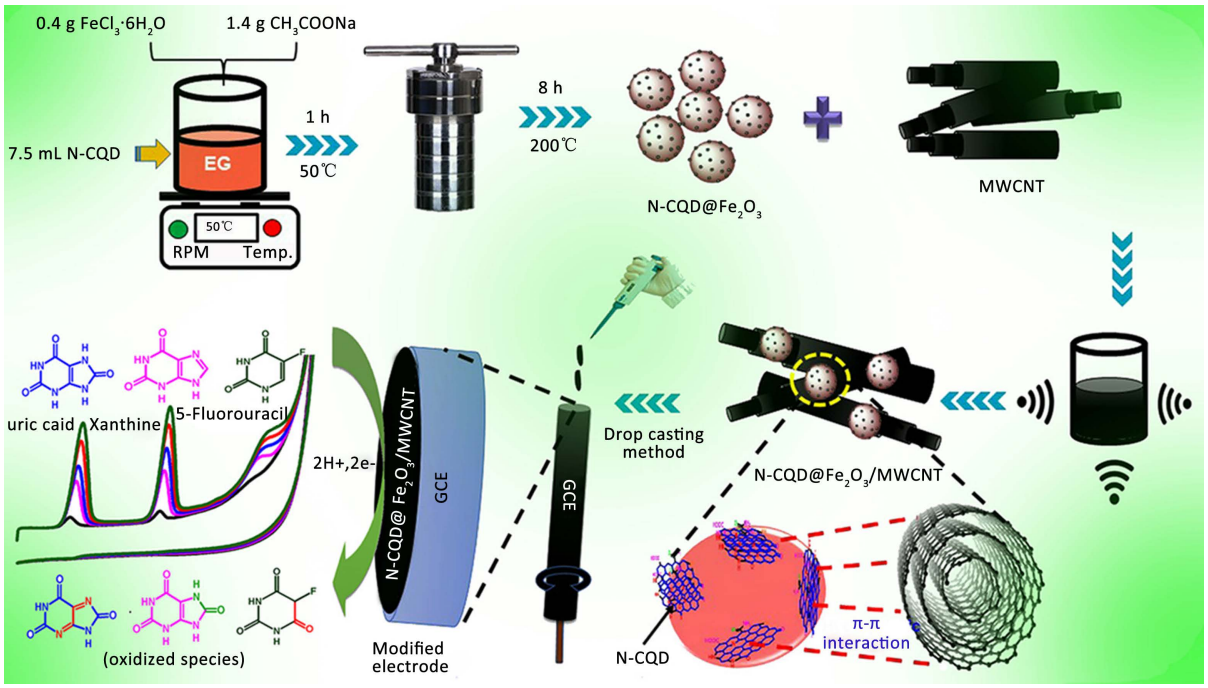

Figure 3. Schematic representation for the synthesis of ternary nanocomposite material, electrode fabrication process, and the simultaneous electrochemical detection of 5-FU, uric acid, and xanthine [50]
图 3. 三元纳米复合材料的合成、电极制造工艺和同时电化学检测 5-FU、尿酸和黄嘌呤的示意图[50]

5. 展望

5-氟尿嘧啶是一种重要的抗癌药物，但是近期它已经被归类于三类致癌物。针对该药物的药理学研究和痕量检测，对化疗应用和环境保护具有重要的理论和实际意义。电化学研究的方法众多，且其检测效果可以随着电极材料的不断涌现而不断更新。近年来，纳米粒子、量子点、多壁碳纳米管和石墨烯为电化学检测提供了更多可供选择的热门材料。采用这些新颖材料去修饰电极，可以预期达到更好的检测效果。

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