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化疗药物诱导的胃肠黏膜损伤动物模型研究进展

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【摘要】 在全球癌症发病率逐年增加背景下,化疗药物诱导的胃肠黏膜损伤已成为影响患者治疗预后的重要因素,且缺乏有效治疗药物。因此,亟需建立更加理想的化疗药物诱导的胃肠黏膜损伤动物模型,以研究其发病机制,开发相关治疗药物。本文对 2019 — 2024 年期间发表的相关文献进行综述,从实验动物的选择、化疗药物及造模方式、模型评价指标及应用等方面进行总结分析,并提出当前模型存在的问题:缺乏统一标准的造模方法、缺少肿瘤背景的模型研究、新型细胞死亡机制的研究尚浅。此外整理文献后发现中医药治疗逐渐成为研究热点,在治疗胃肠黏膜损伤中展现出潜力,未来应继续挖掘有效药物,以丰富化疗后胃肠黏膜损伤的干预治疗手段。

【关键词】 化疗;胃肠黏膜损伤;动物模型;造模方法;发病机制
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Research progress in animal models of chemotherapy-induced gastrointestinal mucosal injury

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【Abstract】 The global incidence rate of cancer is increasing yearly, and chemotherapy-induced gastrointestinal mucosal injury has become a crucial factor affecting patients' therapeutic prognosis; however, there is currently a lack of effective therapeutic drugs to address this issue. There is thus an urgent need to establish more ideal animal models of chemotherapy-induced gastrointestinal mucosal injury, to support the exploration of its pathogenesis and the development of therapeutic drugs. This review considered relevant literature published during the period from 2019 to 2024, to provide a comprehensive summary and analysis from several perspectives, including the selection of experimental animals, chemotherapeutic drugs and modeling method, evaluation indicators, and practical applications. Furthermore, we highlight several existing issues with current models, including the lack of standardized modeling method, insufficient research on models with a tumor background, and inadequate exploration of novel cell death mechanisms. This collation of the literature also revealed the gradual emergence of traditional Chinese medicine

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as a research hotspot, with potential for the treatment of gastrointestinal mucosal injury. Further studies of effective medicines are warranted to identify interventional strategies for chemotherapy-induced gastrointestinal mucosal injury.

【Keywords】 Chemotherapy; gastrointestinal mucosal injury; animal model; modeling method; pathogenesis
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最新癌症统计数据显示,2022 — 2050 年期间,全球癌症新发病例数将从 2000 万上升至 3500 万[1],进一步加重人类疾病负担,并持续影响公共健康。化疗手段作为临床肿瘤治疗的主要方式之一,在抑制肿瘤细胞增殖、延长患者生存期等方面成效显著。但同时,化疗药物的非靶向性也常使代谢旺盛的胃肠黏膜细胞受到损伤[2],其程度与恶心呕吐[3]、腹痛腹胀[4]、腹泻[5]等多种胃肠症状的严重等级呈正相关,使患者继发营养不良[6],或出现抑郁等负面情绪[7],降低其治疗依从性,影响癌症治疗效果。据报道,80%的患者在接受化疗后会出现胃肠副反应症状[8],因此亟需通过深入研究来寻找有效解决方案。

目前,针对化疗药物诱导的胃肠黏膜损伤,临床上缺乏有效治疗药物,一般采用对症处理以减轻胃肠道不适症状。但这类药物在缓解症状的同时带来新的副作用,如便秘[9]、麻痹性肠梗阻[10]等。此外由于临床试验的局限性,研究通常依赖于动物模型,然而现有化疗药物诱导的胃肠黏膜损伤动物模型在造模方法、病理表现等方面仍存在一定不足,无法完全模拟临床肿瘤患者的实际病理变化。因此,本文对 2019 — 2024 年期间发表的相关文献进行整理,从实验动物的选择、化疗药物及造模方式、模型评价指标及应用等方面进行综述,旨在明确化疗药物诱导胃肠黏膜损伤动物模型的建立方法及优缺点,为该领域的基础研究及药物研发提供依据。

1 实验动物的选择

化疗药物诱导的胃肠黏膜损伤模型主要以啮齿类动物为主,包括小鼠和大鼠。小鼠模型常用品系有 C57BL/6, ICR, BALB/c 等。TAM 等[11]同时使用雌性与雄性 C57BL/6 小鼠建立伊立替康(irinotecan, CPT-11)诱导的胃肠道黏膜炎模型,WANG 等[12]利用雄性 ICR 小鼠建立 5-氟尿嘧啶(5-fluorouracil, 5-FU)诱导的结肠黏膜损伤模型,HUANG 等[13]用不同药物(5-FU、CPT-11、奥沙利铂)均成功诱导雄性 BALB/c 小鼠肠损伤模型。而大鼠模型一般应用 SD 和 Wistar 品系。如 LI 等[14]建立甲氨蝶呤(methotrexate, MTX)诱导的雄性 SD 大鼠小肠损伤模型,LU 等[15]选用雌性 Wistar 大鼠构建顺铂肠损伤模型。总体来说,小鼠和大鼠模型各有优势,小鼠饲养成本低、遗传背景明确;大鼠体型大,可采集的样本和检测指标相对丰富,研究者可根据具体研究进行选择。除了啮齿类动物,有研究开始使用大型动物如仔猪建立化疗药物诱导的胃肠黏膜损伤模型[16]。由于仔猪的肠道环境与人类相似,因此在模拟人类化疗相关胃肠损伤方面具有更高的相关性。但是该模型存在饲养成本高、管理难度大等问题,目前在基础研究中的应用仍较有限。

2 化疗药物及造模方式

化疗药物诱导的胃肠黏膜损伤动物模型属于诱发性疾病动物模型,主要选择临床一线类化疗药物为造模药物,如顺铂、5-FU、CPT-11 等。其中顺铂是使用最广泛的铂类化疗药,治疗卵巢癌、睾丸癌、肺癌等效果显著。然而,高发的恶心呕吐成为顺铂化疗受限的主要原因[17]。5-FU 通过影响 DNA 和 RNA 合成而具有抗肿瘤效果[18],在消化道系统肿瘤中较常用[19],但容易引发腹泻,增加死亡风险。CPT-11 属于天然抗肿瘤药物,可抑制 DNA 复制,被用于结直肠癌、胰腺癌、肺癌的治疗。其体内代谢产物 7-乙基-10-羟基喜树碱(7-ethyl-10-hydroxy-camptocampin, SN-38)在肠道蓄积可导致黏膜损伤,导致腹泻和便血[20],尤其以迟发性腹泻最为突出[21]。此外,也有文献报道采用紫杉醇、MTX 诱导胃肠黏膜损伤,紫杉醇通过与微管蛋白结合抑制微管解聚,使细胞在分裂期死亡,抑制肠上皮细胞的增殖,造成胃肠黏膜损伤[22]。MTX 则通过竞争性抑制二氢叶酸还原酶来治疗癌症(如乳腺癌、膀胱癌、骨肉瘤、白血病),但同时会抑制肠上皮和黏膜的生长与修复,引起较高的消化道黏膜炎发生率[23]。研究

中采用何种化疗药物建立模型,应根据化疗药物本身特性及研究目的加以选择。需要注意的是,临床上化疗药物常联合使用,因此更加符合实际情况的动物模型应采用多种化疗药物联合造模,以模拟胃肠黏膜损伤的真实程度。

给药方式是建立动物模型的关键操作。临床上化疗药物以静脉注射用药为主,因此在动物实验中尾静脉注射是最佳的给药方式[24],能够更好地重现药物在体内的分布和作用机制。然而,由于静脉注射对操作技术有一定要求,且易引起血药浓度突然升高,使不良反应迅速发生而影响模型稳定性[25],因此多数研究选择腹腔注射[26]、灌胃[27]进行给药。尽管在一定程度上简化了实验流程,但从模拟临床实际的角度考虑,静脉给药仍是最理想的选择。

在给药频次方面,单次给药在顺铂诱导的模型中较为常见,ZENITANI 等[28]在实验第 3 天给予顺铂(7 mg/kg)、ZOU 等[29]在实验第 10 天给予顺铂(10 mg/kg),以诱导胃肠黏膜损伤;而且,单次给药亦可用于模拟首次化疗反应,以观察药物在短期内对机体造成的损伤。而 5-FU 和 CPT-11 等药物,研究更倾向于多次给药,以再现临床上的周期化疗过程及其累积毒性特征。有研究连续 4 d 给予小鼠 5-FU(50 mg/kg)[30],或连续 4 d 给予小鼠 CPT-11(36.8 mg/kg)[31],以建立胃肠损伤模型。SHIGA 等[32]同时进行了单次给药和连续给药的对比研究,结果发现连续给药大鼠的回肠绒毛明显萎缩,而单次给药大鼠则未观察到此现象。这一结果说明高给药频率可能具有累积毒性,在动物模型的建立过程中需要重点关注肠毒性的程度。

此外,当前的研究策略包括了两种模式:一类是在模型建立后进行干预[33],旨在评估干预措施对已形成损伤的治疗效果;另一类则是在建模前进行干预[34],主要关注干预措施的预防作用。这两种研究路径在研究目的和评价指标上各有侧重,前者强调损伤后的修复能力,后者则更关注保护作用及其潜在机制。

3　模型评价指标

目前化疗药物诱导的胃肠黏膜损伤动物模型,其评价指标多样,包括一般观察指标、组织大体观察指标、组织病理学观察指标、生化指标及肠屏障功能指标等。一般观察指标根据所用的化疗药物而有所区别,在顺铂诱导的模型中,高岭土摄入量常被用于评估动物恶心呕吐程度[35];而 5-FU 和 CPT-11 因易诱发腹泻,故常采用腹泻评分[36]与粪便含水量[37]作为主要观察指标。大体组织观察方面,可通过计算胃损伤指数[38]、测量小肠和结肠[39]长度来评估消化道的整体变化。由于化疗药物可引起从胃[40]、小肠[41]至大肠[42]的广泛黏膜损伤,组织病理学观察指标的选择通常依据研究者的研究方向进行区分。生化指标包含血清二胺氧化酶(diamine oxidase, DAO)[43]和血清 D-乳酸(D-lactate, D-LA)[44],其水平可反映肠黏膜通透性变化。肠屏障功能中常通过检测其紧密连接蛋白,如闭锁小带蛋白 1(zonula occludens 1, ZO-1)、闭合蛋白(occludin, OCLN)和紧密连接蛋白 1(claudin-1, CLDN-1)的表达水平[45],评估黏膜屏障结构的完整性;同时,有研究对大鼠肠系膜淋巴结进行细菌移位检测,从而间接推测肠屏障受损程度[46]。以上评价指标从整体表现、组织结构、生化变化及分子水平等多种维度,用于反映化疗药物导致胃肠黏膜损伤的程度。

综合以上分析,本文将报道较多的 3 种化疗药物(顺铂、5-FU、CPT-11)所建立的胃肠黏膜损伤模型进行整理,并按实验动物分类,便于从药物应用角度呈现造模方法(见表 1~表 3)。

4　模型的应用

4.1　机制探索

关于化疗药物诱导的胃肠黏膜损伤,其具体发病机制尚未完全阐明,但已有研究聚焦于细胞凋亡、细胞焦亡和铁死亡等[47]。本文以经典化疗药物——顺铂为例,从不同的细胞死亡形式进行综述,探讨其在化疗诱导胃肠损伤中的作用机制,以期为理解和干预化疗胃肠黏膜损伤提供新的视角。

4.1.1　细胞凋亡

夏娟[48]研究发现,顺铂给药后小鼠肠组织出现细胞核破碎、肠绒毛缩短、肠隐窝消失;TUNEL 染色结果显示肠组织中凋亡细胞现象明显;Western Blot 检测显示抗凋亡蛋白 B 淋巴细胞瘤-

2(B-cell lymphoma-2, Bcl-2)表达下调,促凋亡蛋白 Bcl-2 相关 X 蛋白(Bcl-2 associated X protein, Bax)表达上调,上述结果表明细胞凋亡是顺铂损伤胃肠黏膜的主要机制之一。顺铂诱导胃肠黏膜细胞凋亡的发生与 PI3K/AKT/mTOR 信号通路密切相关。XIA 等[49]建立 ICR 小鼠肠损伤模型,结果表明顺铂能够抑制磷酸化磷脂酰肌醇 3 激酶(phospho-phosphoinositide3-kinase, p-PI3K)和磷酸化蛋白激酶 B(phosphorylation protein kinase B, p-AKT)蛋白表达,PI3K/AKT/mTOR 信号通路的抗凋亡能力下降,进而影响 Bcl-2 表达下调和 Bax 表达上调,最终促进细胞凋亡[50]。基于现有研究基础,未来可以进一步探索顺铂与该通路中其他分子的调控机制,以期筛选出关键的靶分子。

4.1.2 细胞焦亡

顺铂导致胃肠黏膜损伤的另一种主要形式是细胞焦亡。研究表明,顺铂经核因子 kappa B

表 1 顺铂诱导的胃肠黏膜损伤动物模型造模方法

Table 1 Modeling method of cisplatin-induced gastrointestinal mucosal injury in animal models

模型 Models	实验结果 Experimental results	实验动物 Laboratory animals	给药方式 Route of administration	给药剂量 (mg/(kg·d)) Administered dose (mg/(kg·d))	给药频次 Frequency of administration	优缺点 Advantages and disadvantages
小鼠模型 Model of mice	小肠长度缩短;苏木素-伊红(HE)染色切片可见小肠黏膜溃疡、水肿、出血,肠绒毛顶端缺失,绒毛高度和数量减少[27] Length of intestinal segment was shortened. HE stained sections showed ulceration, edema and hemorrhage of the small intestinal mucosa, loss of the apical villi, and a decrease in the height and quantity of villi[27]	雄性 C57BL/6 小鼠接种 B16 细胞 Male C57BL/6 mice implanted with B16 cells	灌胃 Intragastric administration	15	连续 7 d 7 consecutive days	优点:造模方法相对简单,且能较好模拟顺铂致恶心呕吐这一病理反应,模型具有较高临床相关性 缺点:基于荷瘤小鼠的顺铂诱导胃肠黏膜损伤研究相对较少,限制了模型在模拟临床化疗过程中的准确性 Advantages: modeling methods are relatively simple and can simulate the clinicopathological reaction of cisplatin-induced nausea and vomiting. Models have high clinical relevance Disadvantages: there are relatively few studies on cisplatin-induced gastrointestinal mucosal injury based on tumor-bearing mice, limiting the accuracy of the model in the process of simulated clinical chemotherapy
	结肠出现溃疡,上皮细胞和隐窝受损,杯状细胞脱落[29] Ulceration appeared, epithelial cells and crypts were damaged, and goblet cell were lost in the colon[29]	雄性 C57BL/6 小鼠 Male C57BL/6 mice	腹腔注射 Intraperitoneal injection	10	第 10 天 Day 10	
	结肠隐窝萎缩,固有层炎症细胞浸润;高岭土摄入量增加[35] Crypt atrophy appeared and lamina propria exhibited an increased infiltration of inflammatory cells in the colon, kaolin consumption rose[35]	雄性 C57BL/6 小鼠 Male C57BL/6 mice	腹腔注射 Intraperitoneal injection	3	每周两次,共 4 周 Twice a week for 4 weeks	
	大体观察可见胃黏膜颜色鲜红,表面片状出血,胃组织损伤指数明显升高[38] Color of gastric mucosa was bright red, and bleeding flakes appeared on the surface, the gastric mucosal injury index was markedly elevated[38]	雄性 C57BL/6 小鼠 Male C57BL/6 mice	腹腔注射 Intraperitoneal injection	27	第 1、4 天 Day 1, 4	
	十二指肠绒毛凹凸不平,部分绒毛萎缩、脱落,腺体和隐窝消失;血清 DAO 活性显著升高[43] Villi of duodenum were uneven. Some villi atrophied and exfoliated, and glands and crypts disappeared, the activity of DAO in serum increased significantly[43]	雄性 ICR 小鼠 Male ICR mice	腹腔注射 Intraperitoneal injection	20	第 7 天 Day 7	

续表 1

模型 Models	实验结果 Experimental results	实验动物 Laboratory animals	给药方式 Route of administration	给药剂量 (mg/(kg·d)) Administered dose (mg/(kg·d))	给药频次 Frequency of administration	优缺点 Advantages and disadvantages
大鼠模型 Model of rats	回肠绒毛断裂,杯状细胞减少;血清 DAO 含量显著增加[24] Villi of ileum were broken, and goblet cells were decreased, the level of DAO in serum was increased dramatically[24]	雌性 Wistar 大鼠 Female Wistar rats	静脉注射 Intravenous injection	6	第 7 天 Day 7	优点:造模方法相对简单,且能较好模拟顺铂致恶心呕吐这一病理反应,模型具有较高临床相关性 缺点:基于荷瘤小鼠的顺铂诱导胃肠黏膜损伤研究相对较少,限制了模型在模拟临床化疗过程中的准确性 Advantages: modeling methods are relatively simple and can simulate the clinicopathological reaction of cisplatin-induced nausea and vomiting. Models have high clinical relevance Disadvantages: there are relatively few studies on cisplatin-induced gastrointestinal mucosal injury based on tumor-bearing mice, limiting the accuracy of the model in the process of simulated clinical chemotherapy
	空肠黏膜萎缩,隐窝受损[28] Jejunal mucosa atrophied, and crypt layer was injured[28]	雄性 SD 大鼠 Male SD rats	腹腔注射 Intraperitoneal injection	7	第 3 天 Day 3	
	回肠绒毛畸形、隐窝结构受损;高岭土摄入量增加[34] Villi of ileum were deformed, and crypt structure was damaged, the daily kaolin intake increased[34]	雄性 Wistar 大鼠 Male Wistar rats	腹腔注射 Intraperitoneal injection	6	第 3 天 Day 3	
	胃黏膜上皮细胞结构受损,固有层毛细血管中白细胞增多;高岭土摄入量增加[40] Epithelial cells of the gastric mucosa surface were damaged, and the number of leukocytes in the capillaries of the lamina propria increased, kaolin intake increased[40]	雄性 Wistar 大鼠 Male Wistar rats	腹腔注射 Intraperitoneal injection	6	第 0 天 Day 0	
	结肠杯状细胞大量裂解[42] Massive goblet cells in the colon were disintegrated[42]	雄性 Wistar 大鼠 Male Wistar rats	腹腔注射 Intraperitoneal injection	7.5	第 14 天 Day 14	

(nuclear factor kappa B, NF-κB)途径激活 NOD 样受体蛋白 3(NOD-like receptor protein3, NLRP3)炎症小体,最终通过消皮素 D(gasdermin D, GSDMD)介导引发细胞焦亡,被称为经典半胱氨酸天冬氨酸特异性蛋白酶(cysteinyl aspartate specific proteinase, Caspase)-1 途径。顺铂可诱导回肠组织 NF-κB mRNA 表达上调,NF-κB 磷酸化水平增加[51]。NLRP3 炎症小体是由 NLRP3、凋亡相关斑点样蛋白(apoptosis-associated speck-like protein, ASC)和 Caspase-1 组装而成,MENG 等[52]发现顺铂可增加胃窦和回肠中 NLRP3、ASC、Caspase-1 蛋白表达,从而促进 NLRP3 炎症小体生成,而小半夏汤具有抑制 NLRP3、ASC、Caspase-1 蛋白水平的作用。NLRP3 炎症小体可激活 Caspase-1, Caspase-1 切割 GSDMD 生成消皮素 D 成孔活性 N 端(gasdermin D N-terminal fragment, GSDMD-NT)片段[53],张瑞芳[54]发现顺铂作用 IEC-6 细胞后,GSDMD-NT/GSDMD 比值升高,表明细胞焦亡活跃,而连翘冻干粉及其主要有效成分能降低 GSDMD-NT/GSDMD 比值,抑制细胞焦亡。此外,细胞焦亡释放 IL-1β,顺铂可使 IL-1β 水平上升,两者协同加剧局部炎症反应,造成胃肠黏膜损伤[55]。上述实验证实顺铂可通过 NF-κB、Caspase-1、IL-1β 等关键分子,作用于经典 Caspase-1 通路中各环节,从而介导细胞焦亡的发生。

然而细胞焦亡的触发路径并非仅限于经典 Caspase-1 途径,还存在其他通路,如 Caspase-3-GSDME 途径。有研究证实顺铂在体外诱导 IEC-6 细胞发生损伤,可使细胞中消皮素 E 成孔活性 N 端(gasdermin E N-terminal fragment, GSDME-NT)和活性半胱氨酸天冬氨酸特异性蛋白酶 3(cleaved cysteinyl aspartate specific proteinase-3,

表 2 5-氟尿嘧啶诱导的胃肠黏膜损伤动物模型造模方法

Table 2 Modeling method of 5-fluorouracil-induced gastrointestinal mucosal injury in animal models

模型 Models	实验结果 Experimental results	实验动物 Laboratory animals	给药方式 Route of administration	给药剂量 (mg/(kg·d)) Administered dose (mg/(kg·d))	给药频次 Frequency of administration	优缺点 Advantages and disadvantages
小鼠模型 Model of mice	结肠绒毛缩短、隐窝受损、杯状细胞减少[12] Villi of colon were shortened, crypts were disrupted, and goblet cells were reduced[12]	雄性 ICR 小鼠 Male ICR mice	腹腔注射 Intraperitoneal injection	25	2 d 一次，连续 14 d Once every two days for 14 days	优点：适用于消化道肿瘤方向的化疗药物引起的胃肠副作用研究 缺点：静脉注射 5-FU 易导致血药浓度骤升，不良反应迅速发生，影响模型稳定性 Advantages: it's suitable for the study of gastrointestinal (GI) side effects induced by chemotherapy treating GI tumors Disadvantages: intravenous injection of 5-FU is prone to a sudden increase in blood concentration and adverse reactions occur rapidly, affecting the stability of the model
	腹泻指数和粪便潜血评分增高；结肠长度缩短；HE 染色可见空肠绒毛缩短、隐窝增生，结肠炎症细胞浸润、隐窝面积减少[13] Diarrhea index and fecal occult blood score rose, length of colon was shortened, HE stained sections showed shortening of villi and crypt hyperplasia in the jejunum, as well as infiltration of inflammatory cells and loss of crypt area in the colon[13]	雄性 BALB/c 小鼠接种 CT26 细胞 Male BALB/c mice implanted with CT26 cells		100	连续 5 d Consecutive 5 days	
	腹泻评分升高；肠道长度缩短；HE 染色可见肠绒毛断裂，隐窝消失，炎症细胞浸润；病理损伤评分显著增加；ZO-1 和 Occludin 的蛋白水平降低[19] Scores for diarrhea increased, the length of intestine was shortened, HE stained sections showed breakage of intestinal villi, loss of crypts, and infiltration of inflammatory cells, histopathological score increased, the expression of ZO-1 and Occludin declined[19]	雄性 C57BL/6 小鼠 Male C57BL/6 mice		50	连续 5 d Consecutive 5 days	
	十二指肠绒毛萎缩，黏膜水肿，隐窝细胞数量减少[30] Atrophy of villi, edema in the mucosa, and loss of crypt cells appeared in the duodenum[30]	雄性白化小鼠 Male Albino mice		50	连续 4 d Consecutive 4 days	
	腹泻评分显著升高；回肠绒毛结构受损，肠上皮细胞衰老[36] Scores for diarrhea increased, the structure of ileal villi was damaged, and intestinal epithelial cells were senescent[36]	雄性 BALB/c 小鼠 Male BALB/c mice		40	第 2、4、6、8、10 天 Day 2, 4, 6, 8, 10	
	腹泻评分显著升高；HE 染色可见小肠绒毛萎缩；血清 D-LA 水平显著升高，小肠组织 DAO 降低[44] Scores for diarrhea increased, HE stained sections showed atrophy of villi in small intestine, level of D-LA in serum significantly augmented, while level of DAO in small intestine was decreased[44]	雄性 ICR 小鼠 Male ICR mice		30	连续 7 d Consecutive 7 days	
	空肠和回肠的绒毛长度和隐窝深度明显减少；紧密连接蛋白 ZO-1、Claudin-1 和 Occludin 的 mRNA 表达下调[45] Villi length and crypt depth in jejunum and ileum were markedly decreased, the mRNA expression of tight junction-associated proteins, ZO-1, Claudin-1 and Occludin, was down-regulated[45]	雄性 C57BL/6 小鼠 Male C57BL/6 mice		30	第 0 ~ 4 天 Day 0 ~ 4	

续表 2

模型 Models	实验结果 Experimental results	实验动物 Laboratory animals	给药方式 Route of administration	给药剂量 (mg/(kg·d)) Administered dose (mg/(kg·d))	给药频次 Frequency of administration	优缺点 Advantages and disadvantages
大鼠模型 Model of rats	回肠黏膜绒毛萎缩、脱落；紧密连接蛋白 Occludin、ZO-1 和 Claudin-1 表达量降低[26] Atrophy and shedding of ileal mucosal villi appeared, and expression of tight junction-associated proteins, Occludin, ZO-1 and Claudin-1, was down-regulated[26]	雄性 SD 大鼠 Male SD rats	腹腔注射 Intraperitoneal injection	150	第 7 天 Day 7	同上 Same as above
	空肠绒毛萎缩，上皮细胞坏死，隐窝受损；肠系膜淋巴结的细菌移位显著增加[46] Villi of jejunum atrophied, epithelial cells were necrosed, and crypts were damaged, bacterial translocation in mesenteric lymph node significantly increased[46]	雌性 Wistar 大鼠 Female Wistar rats		300	第 3 天 Day 3	

cleaved Caspase-3)水平上升，细胞发生焦亡；沉默 GSDME-NT 或 Caspase-3 的表达，IEC-6 细胞中 IL-1β、白细胞介素-18（interleukin-18，IL-18）等含量减少，细胞焦亡程度降低[56]。但该结论的广泛适用性及在生物体内的实际效应仍需进一步验证，未来的研究可致力于深入探索 Caspase-3-GSDME 通路在顺铂诱导胃肠黏膜细胞焦亡过程中的具体作用机制，同时在现有 Caspase-1 通路研究基础上，积极寻找靶向细胞焦亡的关键分子，以减轻顺铂引起的胃肠黏膜损伤。

4.1.3　铁死亡

铁死亡是一种由铁依赖的脂质过氧化驱动的细胞死亡方式，近年来，学者们逐渐关注其在顺铂诱导胃肠黏膜损伤中的作用。谷胱甘肽过氧化物酶 4（glutathione peroxidase 4，GPX4）能还原脂质过氧化物，进而抵抗脂质过氧化；而谷胱甘肽（glutathione，GSH）减少可导致 GPX4 失活[57]。二氢乳清酸脱氢酶（dihydroorotate dehydrogenase，DHODH）在体内具有平衡脂质过氧化和铁死亡的作用。LIU 等[58]的实验表明，顺铂可降低小肠组织中 GSH 含量，并下调 GPX4 与 DHODH mRNA 及蛋白表达，减弱了对脂质过氧化的抑制作用；同时，脂质过氧化代谢的终产物丙二醛（malondialdehyde，MDA）显著累积，证实了脂质过氧化的发生，表明顺铂加速铁死亡进程。

目前，顺铂诱导肾损伤中铁死亡机制的研究较为深入，但针对胃肠损伤的铁死亡发病机制的研究尚处初级阶段。在顺铂诱导的急性肾炎模型中，铁和羟基自由基增多、肾总铁含量上升，提示铁死亡可能是关键病理机制，而铁死亡抑制剂能缓解这些损伤[59]。ZHOU 等[60]建立的顺铂诱导急性肾损伤模型显示顺铂可使小鼠肾组织 MDA 含量上升，GSH 水平减少、GPX4 活力下降，表明肾组织发生铁死亡。基于此，未来研究可借鉴顺铂诱导肾损伤研究成果，聚焦其胃肠黏膜铁死亡机制，同时深入探索干预策略（如铁死亡抑制剂）的作用效果，为减轻顺铂治疗相关的胃肠黏膜损伤提供新的思路。

4.2　药物开发

化疗药物诱导的胃肠黏膜损伤动物模型是开发有效治疗药物的重要工具。SHEN 等[61]的实验结果显示，桔梗可以逆转化疗药物导致的小鼠小肠组织中 Caspase-9、Caspase-3 和细胞色素 C（cytochrome C，Cyt C）的表达增加，缓解细胞凋亡程度，显示其在胃肠道保护方面的潜力。另有研究显示小半夏汤具有下调胃窦和回肠中 NLRP3 炎症小体组成蛋白表达的能力，从而抑制顺铂引起的大鼠胃肠黏膜细胞焦亡[52]。越来越多的研究证实多种中药单体及复方在缓解黏膜损伤中的潜在作用，值得进一步挖掘。

表 3 伊立替康诱导的胃肠黏膜损伤动物模型造模方法

Table 3 Modeling method of irinotecan-induced gastrointestinal mucosal injury in animal models

模型 Models	实验结果 Experimental results	实验动物 Laboratory animals	给药方式 Route of administration	给药剂量 (mg/(kg·d)) Administered dose (mg/(kg·d))	给药频次 Frequency of administration	优缺点 Advantages and disadvantages
小鼠模型 Model of mice	发生腹泻;结肠上皮受损、炎症浸润;结肠病理损伤评分上升[11] Diarrhea occurred, epithelial disruption and inflammatory infiltrate happened in colon, histopathological score of colons was higher[11]	C57BL/6 小鼠 C57BL/6 mice		270.0	一次 Once	
	腹泻指数和粪便潜血评分增高;结肠长度缩短;HE 染色可见空肠绒毛缩短、隐窝增生,结肠炎症细胞浸润、隐窝面积减少;空肠中紧密连接蛋白 Occludin 和 ZO-1 蛋白水平降低[13] Diarrhea index and fecal occult blood score rose, length of colon was shortened. HE stained sections showed shortening of villi and crypt hyperplasia in the jejunum, as well as infiltration of inflammatory cells and loss of crypt area in the colon, the expressions of Occludin and ZO-1 in jejunum were down-regulated[13]	雄性 BALB/c 小鼠接种 CT26 细胞 Male BALB/c mice implanted with CT26 cells		85.0	连续 5 d Consecutive 5 d	优点:良好地模拟临床中使用 CPT-11 后出现腹泻的病理过程 缺点:不适用存在可能干扰肝肠循环并影响 CPT-11 代谢的生理或病理状况的实验动物 Advantages: it can well simulate the pathological process of diarrhea that occurs after the use of CPT-11 in clinical practice Disadvantages: it's not applicable to experimental animals with physiological or pathological conditions that may interfere with the enterohepatic circulation and affect the metabolism of CPT-11
	稀便率、腹泻指数升高;小肠绒毛数量减少,绒毛脱落,隐窝结构消失[31] Rate of loose stools and diarrhea index increased, number of small intestinal villi reduced, shedding of villi and loss of crypt structures were visible[31]	BALB/c 小鼠 BALB/c mice	腹腔注射 Intraperitoneal injection	36.8	连续 4 d Consecutive 4 d	
	腹泻评分升高;结肠黏膜上皮细胞脱落,炎症细胞浸润[33] Scores for diarrhea increased, mucosal epithelial cells in colon shed and inflammatory cell infiltration was visible[33]	雌性 BALB/c 小鼠接种 CT26 细胞 Female BALB/c mice implanted with CT26 cells		350.0	一次 Once	
	发生不同程度腹泻,小肠和结肠的长度缩短,上皮细胞受损、杯状细胞减少;紧密连接蛋白 Claudin-1 表达下降[39] Various degrees of diarrhea occurred, lengths of the small intestine and colon were shortened, epithelial cells were damaged, and goblet cells reduced, expression of tight junction-associated proteins, Claudin-1, was down-regulated[39]	雌性 BALB/c 小鼠 Female BALB/c mice		75.0	连续 4 d Consecutive 4 d	
大鼠模型 Model of rats	粪便含水量增加,出现腹泻;结肠 IL-6、IL-1β mRNA 水平上升[37] Fecal water content increased, and diarrhea developed, the mRNA levels of IL-6 and IL-1β increased in the colon[37]	雄性 Wistar 大鼠 Male Wistar rats	静脉注射 Intravenous injection	100.0	连续 4 d Consecutive 4 d	
仔猪模型 Model of piglets	腹泻发病率上升,结肠 IL-6 和 IL-1β mRNA 表达增加,空肠和回肠的绒毛高度下降[16] Diarrhea incidence increased, mRNA expressions of IL-6 and IL-1β were up-regulated, villi height in jejunum and ileum decreased[16]	Yorkshire × Landrace × Duroc 断奶仔猪 Yorkshire × Landrace × Duroc weaned piglets	腹腔注射 Intraperitoneal injection	15.0	连续 4 d Consecutive 4 d	

5　总结和展望

化疗后胃肠黏膜损伤引起的不良反应,包括食欲不振、呕吐不止、腹痛腹泻,极大削弱了患者的身体机能与耐受能力,迫使化疗中断,严重影响癌症的综合预后。构建理想的化疗药物诱导胃肠黏膜损伤动物模型,对于深入研究化疗药物损伤胃肠系统的机制,以及开发有效药物不可或缺。然而,现有化疗药物诱导胃肠黏膜损伤动物模型仍有欠缺,可采用以下策略加以改善。

5.1　建立统一标准的造模方法

目前,化疗药物诱导胃肠黏膜损伤动物模型,借助顺铂、5-FU、CPT-11 等的作用特点,成功模拟胃肠黏膜损伤的病理表现,包括黏膜炎症、恶心呕吐、腹泻及相应生化指标改变等。但在造模方法上缺乏统一的标准,如造模药物的种类、剂量、给药方式等参数,以及模型的评价指标,导致不同实验室之间的模型差异较大,影响研究结果的可比性。未来应进行更多化疗胃肠损伤动物模型的比较医学研究,确定最佳造模方法,统一标准以便于缩短实验周期,加速药物研发的进程。

5.2　拓展荷瘤动物为基础的建模方法

现有的模型多以正常动物为实验对象,研究单一药物的损伤效应,实验结果明确但又无法完全模拟临床患者的实际情况。为加强基础实验与临床的相关性,应拓展以肿瘤为背景的动物模型,研究化疗药物在荷瘤动物体内的胃肠黏膜损伤效应,同时以此为工具探索预防性或治疗性药物干预对肿瘤与胃肠黏膜的作用,从而开发既不影响肿瘤治疗又能缓解胃肠损伤的有效药物。

5.3　探索病理机制研究

对于化疗药物诱导胃肠黏膜损伤的发病机制,现有成果主要集中于细胞凋亡和细胞焦亡,其他新型细胞死亡机制,如铁死亡仍处于起步阶段。未来深入探究该机制的作用路径与调控因素,可以准确评估其在化疗药物诱导胃肠黏膜损伤中的作用效果,为改善化疗胃肠损伤及提高肿瘤综合治疗效果提供坚实的理论依据。

值得注意的是,在探索化疗胃肠损伤机制的过程中,越来越多的研究发现中药单体或复方能改善这一病理变化,中医药的多靶点调节作用逐渐显现。基于此,采用化疗胃肠损伤动物模型筛选有效中药成为当下研究热点,但未来研究仍需继续深入揭示其作用机理,促进中医药在化疗相关副反应治疗中的应用,为改善肿瘤患者化疗后的不良反应提供有效的治疗策略,提高肿瘤治疗的整体效果。

参　考　文　献(References)

[1] BRAY F, LAVERSANNE M, SUNG H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA Cancer J Clin, 2024, 74(3): 229-263.

[2] GAO R, YUE B, LV C, et al. Targeted inhibition of Gus-expressing *Enterococcus faecalis* to promote intestinal stem cell and epithelial renovation contributes to the relief of irinotecan chemotoxicity by dehydrodiisoeugenol [J]. Acta Pharm Sin B, 2024, 14(12): 5286-5304.

[3] LIANG W, REN Y, WANG Y, et al. Xiao-Ban-Xia decoction alleviates chemotherapy-induced nausea and vomiting by inhibiting ferroptosis via activation of the Nrf2/SLC7A11/GPX4 pathway [J]. Adv Biol (Weinh), 2024, 8(12): e2400323.

[4] 张西洁. 半夏泻心汤治疗化疗性肠黏膜炎的治疗效果分析 [J]. 生命科学仪器, 2024, 22(1): 205-207.
ZHANG X J. Analysis of therapeutic effect of Banxia Xiexin Decoction on chemotherapeutic intestinal mucositis [J]. Life Sci Instrum, 2024, 22(1): 205-207.

[5] OTA K, TAKEUCHI T, KOJIMA Y, et al. Fluoropyrimidine-induced intestinal mucosal injury is associated with the severity of chemotherapy-related diarrhea [J]. Scand J Gastroenterol, 2019, 54(2): 227-232.

[6] GEBREMEDHIN T K, CHERIE A, TOLERA B D, et al. Prevalence and risk factors of malnutrition among adult cancer patients receiving chemotherapy treatment in cancer center, ethiopia: cross-sectional study [J]. Heliyon, 2021, 7(6): e07362.

[7] LIN Y, JIANG X, HUANG X, et al. The influence of olfactory dysfunction on risk of malnutrition is mediated by depressive symptoms in cancer patients undergoing chemotherapy [J]. Ann Palliat Med, 2021, 10(10): 10600-10606.

[8] ALCORTA A, LÓPEZ-GÓMEZ L, CAPASSO R, et al. Vitamins and fatty acids against chemotherapy-induced intestinal mucositis [J]. Pharmacol Ther, 2024, 261: 108689.

[9] ROBERTS A, GRAFTON G, POWELL A D, et al. CSTI-300 (SMP-100): a novel 5-HT_3 receptor partial agonist with potential to treat patients with irritable bowel syndrome or carcinoid syndrome [J]. J Pharmacol Exp Ther, 2020, 373

(1): 122-134.

[10] 王宁军, 薛鹏, 芦殿荣, 等. 半夏泻心颗粒剂预防盐酸伊立替康所致腹泻的临床观察 [J]. 西部中医药, 2023, 36(6): 98-102.
WANG N J, XUE P, LU D R, et al. Clinical observation on Banxia Xiexin Granules in the prevention of diarrhea induced by irinotecan hydrochloride [J]. West J Tradit Chin Med, 2023, 36(6): 98-102.

[11] TAM J S Y, CRAME E E, ELZ A S, et al. Effects of a novel toll-like receptor 4 antagonist IAXO-102 in a murine model of chemotherapy-induced gastrointestinal toxicity [J]. Cancer Chemother Pharmacol, 2022, 90(3): 267-278.

[12] WANG C, WANG S, PENG D, et al. Agarwood extract mitigates intestinal injury in fluorouracil-induced mice [J]. Biol Pharm Bull, 2019, 42(7):1112-1119.

[13] HUANG B, GUI M, NI Z, et al. Chemotherapeutic drugs induce different gut microbiota disorder pattern and NOD/RIP2/NF-κB signaling pathway activation that lead to different degrees of intestinal injury [J]. Microbiol Spectr, 2022, 10(6): e0167722.

[14] LI P, INOUE Y, MIYAMOTO D, et al. Therapeutic effect and mechanism of Daikenchuto in a model of methotrexate-induced acute small intestinal mucositis [J]. PLoS One, 2023, 18(3): e0283626.

[15] LU M, XIE L, YIN S, et al. The gut microbial lipid metabolite 14(15)-EpETE inhibits substance P release by targeting GCG/PKA signaling to relieve cisplatin-induced nausea and vomiting in rats [J]. J Microbiol Biotechnol, 2024, 34(9): 1769-1777.

[16] LI M, HUANG Y, JIN H, et al. Vitamin A ameliorated irinotecan-induced diarrhea in a piglet model involving enteric glia modulation and immune cells infiltration [J]. Nutrients, 2022, 14(23): 5120.

[17] MO Z, XIAN Y, ZHANG R, et al. 6-Gingerol, a major ingredient of ginger, attenuated cisplatin-induced pica in rats via regulating 5-HT3R/Ca^{2+}/CaMKII/ERK1/2 signaling pathway [J]. J Funct Foods, 2023, 100: 105389.

[18] KIWELER N, SCHWARZ H, NGUYEN A, et al. The epigenetic modifier HDAC2 and the checkpoint kinase ATM determine the responses of microsatellite instable colorectal cancer cells to 5-fluorouracil [J]. Cell Biol Toxicol, 2023, 39(5): 2401-2419.

[19] DENG S, WU D, LI L, et al. TBHQ attenuates ferroptosis against 5-fluorouracil-induced intestinal epithelial cell injury and intestinal mucositis via activation of Nrf2 [J]. Cell Mol Biol Lett, 2021, 26(1): 48.

[20] COSTA D V S, COSTA D V S, SOUSA C N S, et al. The alpha-lipoic acid improves survival and prevents irinotecan-induced inflammation and intestinal dysmotility in mice [J]. Pharmaceuticals (Basel), 2020, 13(11): 361.

[21] DENG C, LOU Y, GAO Y, et al. Efficacy and safety of Shengjiang Xiexin decoction in prophylaxis of chemotherapy-related diarrhea in small cell lung cancer patients: study protocol for a multicenter randomized controlled trial [J]. Trials, 2020, 21(1): 370.

[22] LI D, GAO L, LI M, et al. Polysaccharide from spore of *Ganoderma lucidum* ameliorates paclitaxel-induced intestinal barrier injury: apoptosis inhibition by reversing microtubule polymerization [J]. Biomed Pharmacother, 2020, 130: 110539.

[23] YAMAMOTO T, MACHIDA T, TANNO C, et al. Low-dose nafamostat mesilate ameliorates tissue injury and inhibits 5-hydroxytryptamine synthesis in the rat intestine after methotrexate administration [J]. J Pharmacol Sci, 2023, 152(2): 90-102.

[24] JIN S, ZHU T, DENG S, et al. Dioscin ameliorates cisplatin-induced intestinal toxicity by mitigating oxidative stress and inflammation [J]. Int Immunopharmacol, 2022, 111: 109111.

[25] 周晓明, 邵荣世, 刘钧, 等. 基于三七、莪术提取物联合氟尿嘧啶对胃癌 SGC-7901 细胞的干预作用及机制研究 [J]. 四川中医, 2024, 42(3): 74-78.
ZHOU X M, SHAO R S, LIU J, et al. Intervention effect and mechanism of *Panax notoginseng* and *Curcuma* zedoary extracts combined with fluorouracil on gastric cancer SGC-7901 cells [J]. J Sichuan Tradit Chin Med, 2024, 42(3): 74-78.

[26] 翁美华, 邓丽金, 胡静温, 等. 基于“脾主运化”理论探讨芪药鸡金粥通过 PI3K/Akt/NF-κB 通路防治化疗致胃肠黏膜损伤的机制 [J]. 现代中西医结合杂志, 2023, 32(18): 2519-2524, 2594.
WENG M H, DENG L J, HU J W, et al. Mechanism of prevention and treatment of chemotherapy-induced gastrointestinal mucosal injury with Qi-Yao-Ji porridge via PI3K/Akt/NF-κB pathway based on the theory of “the spleen governs the transport and transformation” [J]. Mod J Integr Tradit Chin West Med, 2023, 32(18): 2519-2524, 2594.

[27] LI Y, WANG X, LIN J, et al. Natural flavonoid sinensetin inhibits cisplatin-induced pyroptosis and attenuates intestinal injury [J]. Biochim Biophys Acta Mol Basis Dis, 2023, 1869(3): 166637.

[28] ZENITANI M, SASAKI T, OUE T. Kampo medicines Rikkunshito and Hangeshashinto prevent cisplatin-induced intestinal mucosal injury in rats [J]. J Pediatr Surg, 2021, 56(7): 1211-1218.

[29] ZOU Y T, ZHOU J, WU C Y, et al. Protective effects of *Poria cocos* and its components against cisplatin-induced

intestinal injury [J]. J Ethnopharmacol, 2021, 269: 113722.

[30] AL-HOSHARY D M, ZALZALA M H. Mucoprotective effect of ellagic acid in 5 fluorouracil-induced intestinal mucositis model [J]. J Med Life, 2023, 16(5): 712-718.

[31] 岳晓华, 张小平, 孙少伯, 等. 大补脾汤对伊立替康所致小鼠迟发性腹泻的影响 [J]. 中成药, 2023, 45(2): 569-572.
YUE X H, ZHANG X P, SUN S B, et al. Effect of Dabupi decoction on delayed diarrhea induced by irinotecan in mice [J]. Chin Tradit Pat Med, 2023, 45(2): 569-572.

[32] SHIGA S, MACHIDA T, YANADA T, et al. The role of nitric oxide in small intestine differs between a single and a consecutive administration of methotrexate to rats [J]. J Pharmacol Sci, 2020, 143(1): 30-38.

[33] ZHANG Q, JIANG F, TAO J, et al. Effects of Shu Bu Wenshen Guchang recipe on intestinal injury and the TLR4/NF-κB signaling pathways in mice with irinotecan-induced delayed-type diarrhea [J]. Transl Cancer Res, 2022, 11(9): 3250-3259.

[34] MENG Q, BI P, ZHANG G, et al. Forsythiae Fructus aqueous extract attenuates cisplatin-induced kaolin consumption (pica) by inhibiting NLRP3 inflammasome activation in rats [J]. Biosci Biotechnol Biochem, 2021, 85(9): 2054-2064.

[35] BIAGIONI C, TRAINI C, FAUSSONE-PELLEGRINI M S, et al. Prebiotics counteract the morphological and functional changes secondary to chronic cisplatin exposition in the proximal colon of mice [J]. J Cell Mol Med, 2024, 28(6): e18161.

[36] HE S, WANG Z, XIA J, et al. Dasabuvir alleviates 5-fluorouracil-induced intestinal injury through anti-senescence and anti-inflammatory [J]. Sci Rep, 2024, 14(1): 15730.

[37] KON R, IKARASHI N, YAMAGUCHI A, et al. Green tea extract prevents CPT-11-induced diarrhea by regulating the gut microbiota [J]. Sci Rep, 2023, 13(1): 6537.

[38] 李腾飞. 姜黄素对顺铂致小鼠胃肠粘膜损伤的保护机制研究 [D]. 沈阳: 辽宁中医药大学; 2020.
LI T F. Study on protective mechanism of curcumin against cisplatin-induced gastrointestinal mucosal injury in mice [D]. Shenyang: Liaoning University of Traditional Chinese Medicine; 2020.

[39] LI J P, CHU C L, CHAO W R, et al. Ling Zhi-8, a fungal immunomodulatory protein in *Ganoderma lucidum*, alleviates CPT-11-induced intestinal injury via restoring claudin-1 expression [J]. Aging (Albany NY), 2023, 15(9): 3621-3634.

[40] LI Y Q, YANG Y H, ZHANG G L, et al. RNA-Seq reveals inflammatory mechanisms of Xiao-Ban-Xia-Tang decoction to ameliorate cisplatin-induced emesis in a rat pica model [J]. Biomed Pharmacother, 2020, 131: 110699.

[41] LANG W, WEN X, ZHANG S, et al. Cynaroside ameliorates methotrexate-induced enteritis in rats through inhibiting NLRP3 inflammasome activation [J]. Front Immunol, 2024, 15: 1405084.

[42] REHMAN M U, RATHER I A. Myricetin abrogates cisplatin-induced oxidative stress, inflammatory response, and goblet cell disintegration in colon of wistar rats [J]. Plants (Basel), 2019, 9(1): 28.

[43] HU J N, YANG J Y, JIANG S, et al. Panax quinquefolium saponins protect against cisplatin evoked intestinal injury via ROS-mediated multiple mechanisms [J]. Phytomedicine, 2021, 82: 153446.

[44] 秦美洁, 叶倩倩, 丁芮, 等. 小陷胸汤对5-氟尿嘧啶介导的小鼠肠黏膜损伤的保护作用研究 [J]. 海南医学院学报, 2024, 30(19): 1441-1450.
QIN M J, YE Q Q, DING R, et al. Study on the protective effect of Xiaoxianxiong decoction on 5-fluorouracil-induced intestinal damage in mice [J]. J Hainan Med Univ, 2024, 30(19): 1441-1450.

[45] HUANG T Y, YANG S S, LIAO C L, et al. SPAK deficiency attenuates chemotherapy-induced intestinal mucositis [J]. Front Oncol, 2021, 11: 733555.

[46] TEFAS C, CIOBANU L, BERCE C, et al. Beneficial effect of oral administration of zinc sulfate on 5-fluorouracil-induced gastrointestinal mucositis in rats [J]. Eur Rev Med Pharmacol Sci, 2020, 24(21): 11365-11373.

[47] 张学君, 林久茂, 林晨捷, 等. 电针“足三里”减轻大肠癌小鼠化疗后肠黏膜损伤及其对氧化应激和细胞凋亡的影响 [J]. 针刺研究, 2023, 48(12): 1249-1257.
ZHANG X J, LIN J M, LIN C J, et al. Protective effect of electroacupuncture at ST36 against damage of intestinal mucosa, oxidative stress and apoptosis induced by 5-FU chemotherapy in mice with colon cancer [J]. Acupunct Res, 2023, 48(12): 1249-1257.

[48] 夏娟. 淫羊藿有效成分的质量差异及其对顺铂致心肌和肠道损伤的保护作用研究 [D]. 北京: 中国农业科学院; 2021.
XIA J. Study on the quality difference of effective components of *Epimedium* and its protective effect on myocardial and intestinal injury induced by cisplatin [D]. Beijing: Chinese Academy of Agricultural Sciences; 2021.

[49] XIA J, HU J N, WANG Z, et al. Based on network pharmacology and molecular docking to explore the protective effect of Epimedii Folium extract on cisplatin-induced intestinal injury in mice [J]. Front Pharmacol, 2022, 13: 1040504.

[50] GAO J, LIU Y, CHEN J, et al. Curcumin treatment

attenuates cisplatin-induced gastric mucosal inflammation and apoptosis through the NF-κB and MAPKs signaling pathway [J]. Hum Exp Toxicol, 2022, 41: 9603271221128738.

[51] JIN S, GUAN T, WANG S, et al. Dioscin alleviates cisplatin-induced mucositis in rats by modulating gut microbiota, enhancing intestinal barrier function and attenuating TLR4/NF-κB signaling cascade [J]. Int J Mol Sci, 2022, 23(8): 4431.

[52] MENG Q, CHENG Q, FENG X, et al. The antiemetic effect of Xiao-Ban-Xia-Tang formula against cisplatin-induced Emesis is mediated through inhibition of NLRP3 inflammasome activation in a rat pica model [J]. Evid Based Complement Alternat Med, 2020, 2020: 5497078.

[53] YE B, ZHANG R, XIAN Y, et al. Forsythiae Fructus attenuates cisplatin-induced cytotoxicity in IEC-6 cells and J774A. 1 macrophages by inhibiting NLRP3/caspase-1/GSDMD mediated pyroptosis [J]. J Holist Integr Pharm, 2023, 4(2): 166-177.

[54] 张瑞芳. 基于NLRP3炎症通路和细胞焦亡探究连翘对化疗性小肠上皮细胞和巨噬细胞损伤的保护作用机制[D]. 广州: 广东药科大学; 2022.
ZHANG R F. Study on the mechanism of Forsythia Fructus in protecting the injury of small intestinal epithelial cells and macrophages induced by chemotherapy based on NLRP3 inflammatory pathway and pyroptosis [D]. Guangzhou: Guangdong Pharmaceutical University; 2022.

[55] ALSHOLI D M, YACOUB G S, REHMAN A U, et al. *Lactobacillus rhamnosus* attenuates cisplatin-induced intestinal mucositis in mice via modulating the gut microbiota and improving intestinal inflammation [J]. Pathogens, 2023, 12(11): 1340.

[56] LIAO X, YE B, HU W, et al. Xiaobanxia decoction alleviates chemotherapy-induced nausea and vomiting by inhibiting GSDME-mediated pyroptosis [J]. J Ethnopharmacol, 2024, 318: 116970.

[57] WEI Z, HANG S, WIREDU OCANSEY D K, et al. Human umbilical cord mesenchymal stem cells derived exosome shuttling mir-129-5p attenuates inflammatory bowel disease by inhibiting ferroptosis [J]. J Nanobiotechnology, 2023, 21(1): 188.

[58] LIU X, WANG S, JIN S, et al. Vitamin D_3 attenuates cisplatin-induced intestinal injury by inhibiting ferroptosis, oxidative stress, and ROS-mediated excessive mitochondrial fission [J]. Food Funct, 2022, 13(19): 10210-10224.

[59] IKEDA Y, HAMANO H, HORINOUCHI Y, et al. Role of ferroptosis in cisplatin-induced acute nephrotoxicity in mice [J]. J Trace Elem Med Biol, 2021, 67: 126798.

[60] ZHOU L, YU P, WANG T T, et al. Polydatin attenuates cisplatin-induced acute kidney injury by inhibiting ferroptosis [J]. Oxid Med Cell Longev, 2022, 2022: 9947191.

[61] SHEN Q, WEI X M, HU J N, et al. Saponins from *Platycodon grandiflorum* reduces cisplatin-induced intestinal toxicity in mice through endoplasmic reticulum stress-activated apoptosis [J]. Am J Chin Med, 2022, 50(7): 1927-1944.

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