化疗性恶心呕吐防治药物研究进展

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摘要: 化疗性恶心呕吐 (chemotherapy-induced nausea and vomiting, CINV) 是癌症治疗过程中最常见的不良反应。CINV的病理机制复杂, 涉及5-羟色胺、P物质和多巴胺等神经递质及其受体的多条途径参与。现有用于CINV防治的化学药物存在疗效单一、不良反应明显及价格昂贵等问题。中药因多成分、多靶点、高安全性、低不良反应及低成本等优势, 在防治CINV方面具有广阔应用前景。本文总结了现有CINV防治药物的结构类型、作用机制、构效关系及其应用, 同时介绍了近年来中药在防治CINV方面的研究现状, 以期为开发作用持久、高效且低成本的新型CINV治疗药物提供参考。

关键词: 化疗性恶心呕吐; 肿瘤; 化学合成药; 中药; 构效关系

中图分类号: R914　　**文献标识码**: A　　**文章编号**: 0513-4870(2026)02-0388-15

Research progress on drugs for prevention and treatment of chemotherapy-induced nausea and vomiting

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Abstract: Chemotherapy-induced nausea and vomiting (CINV) represents one of the most prevalent adverse reactions during cancer treatment. Its pathological mechanism is complex, involving multiple neurotransmitters and their biopathways, such as serotonin, substance P, and dopamine, along with their respective receptors. Existing chemical agents for CINV prophylaxis and management face challenges including limited efficacy, serious side effects, and high cost. In contrast, traditional Chinese medicine (TCM) holds considerable promise for CINV prevention and treatment, leveraging advantages such as multi-components, multi-targets, high safety, low side effects, and cost-effectiveness. The structural classes, mechanisms of action, structure-effect relationships, and clinical applications for currently available CINV drugs were systematically reviewed. Moreover, the recent research progress on TCM for preventing and treating CINV was also introduced It will provide significant references for the development of novel CINV therapeutics with sustained efficacy, high efficiency, and low cost.

Key words: chemotherapy-induced nausea and vomiting; tumour; chemical synthetic drug; traditional Chinese medicine; structure-activity relationship

化疗性恶心呕吐 (chemotherapy-induced nausea and vomiting, CINV) 是癌症患者在治疗中最常见的不良反应[1], 研究显示约70%～80%的肿瘤患者在化疗过程中会出现恶心呕吐, 进而导致生活质量下降并引发脱水、疲劳等一系列并发症[2]。呕吐由位于延髓的呕吐中枢所调控, 涉及中枢和外周通路, 外周通路通过刺激胃肠道,

收稿日期: 2025-06-13;　修回日期: 2025-08-19.

基金项目: 国家自然科学基金地区科学基金项目 (82460854); 江西省卫生健康委科技计划项目 (202510086); 中国中医科学院青年科技人才培养专项 (ZZ18-XRZ-091).

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DOI: 10.16438/j.0513-4870.2025-0662

经迷走神经向上传递信号至呕吐中枢; 中枢通路则是由大脑直接输入触发呕吐反应[3]。化疗药物可通过双重机制诱发呕吐反应: 一方面, 药物直接作用于中枢神经系统, 激活脑内神经递质系统, 如多巴胺、5-羟色胺(5-hydroxytryptamine, 5-HT, 又叫血清素) 等; 另一方面, 药物刺激胃肠道黏膜引发氧化应激反应, 促进炎症因子释放, 进而激活肠道嗜铬细胞分泌大量5-HT, 这些5-HT通过迷走神经传入纤维将信号传递至呕吐中枢, 最终导致呕吐反射的发生[4](图1)。临床上, 按发生时间将CINV分为急性、延迟性、预期性、爆发性及难治性5种类型[5]。临床上现用的止吐药物主要包括5-羟色胺3 (5-hydroxytryptamine 3, 5-HT3) 受体拮抗剂、神经激肽1 (neurokinin-1, NK1) 受体拮抗剂、多巴胺受体拮抗剂、糖皮质激素受体激动剂、大麻素受体激动剂等[6]。这些止吐药物具有明确的治疗效果和作用机制。尽管疗效确切, 其在临床应用中仍面临一些挑战, 例如对难治性恶心呕吐的控制效果有待提升、存在潜在的药物不良反应以及治疗成本相对较高。在此背景下, 中药凭借其多成分、多靶点的整体调节作用以及相对较低的毒副作用等优势, 在CINV防治领域逐渐受到关注, 其潜在的治疗价值正成为研究热点。本文系统地综述了目前临床上应用的抗CINV的化学合成药及其结构类型、作用机制、构效关系与应用, 并对近年来中药及复方防治CINV的研究现状进行了总结, 以期为未来开发作用持久、高效且廉价的止吐药物提供参考。

1 化学合成药

1.1 5-HT3受体拮抗剂 5-HT首次发现于肠嗜铬细胞, 是人体内最广泛的神经递质。5-HT3受体作为5-HT受体的一种亚型, 广泛分布于中枢和外周神经系统以及胃肠道神经元上[7]。5-HT通过外周途径与5-HT3受体结合

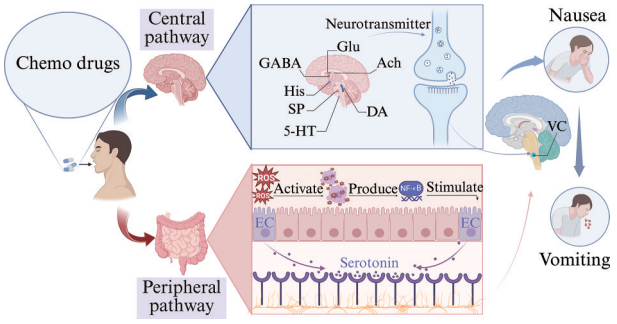
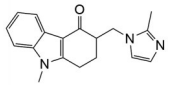
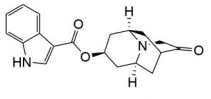
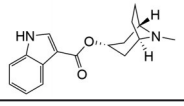


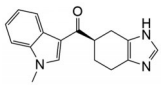
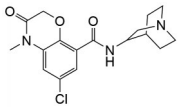
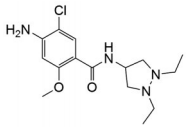
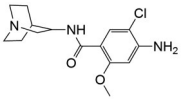
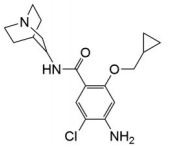
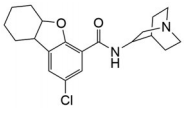
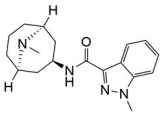
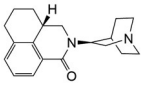
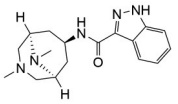
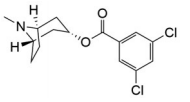
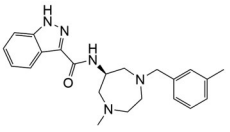
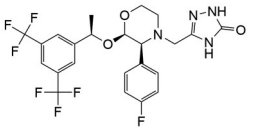
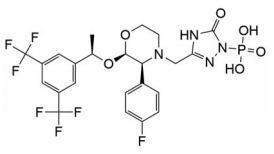
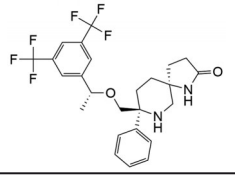
Figure 1 Pathological mechanisms of chemotherapy-induced nausea and vomiting. Glu: Glutamate; Ach: Acetylcholine; GABA: γ-Aminobutyric acid; His: Histamine; SP: Substance P; DA: Dopamine; 5-HT: 5-Hydroxytryptamine; EC: Enterochromaffin cells; VC: Vomiting center

参与CINV的病理生理过程。当化疗药物损伤胃肠道中的肠嗜铬细胞时, 使5-HT释放与其受体相结合, 进而激活迷走神经, 将其信号传递至呕吐中枢, 最终引起呕吐反应。5-HT3受体拮抗剂可通过竞争性拮抗5-HT3受体, 阻断神经信号传导, 发挥止吐作用[8]。常见的5-HT3受体拮抗剂如表1[9-49]所示, 这类药物是临床上治疗CINV的主要药物, 包括昂丹司琼、格拉司琼、帕洛诺司琼等, 虽然这类药物耐受性高, 但存在头疼、便秘等不良反应[50]。该类药物的分子结构由芳环、连接基团、碱性中心三部分组成, 其中苯环是活性所必需的部分, 主要与受体疏水区相结合; 羰基及连接基团具有特定的空间定位和优势构象, 药物分子能够以特定的三维构象接近靶点, 还通过氢键、范德华力及疏水作用等分子间作用力, 使其与受体的结合更加稳定; 碱性中心位于环内的氮原子, 多为叔胺可质子化形成阳离子与受体结合。同时在芳环旁边连接吡咯、咪唑或吡唑等基团以提高活性; 此外结构中的含氮杂环可以为药物提供结构的多样性[51]。

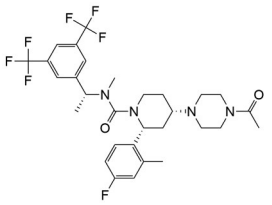
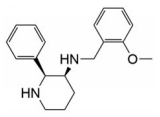
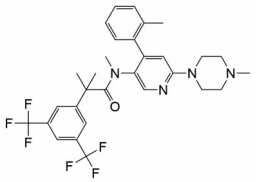
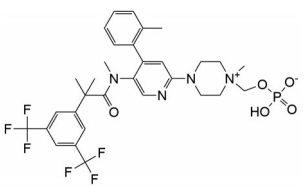
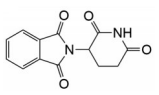
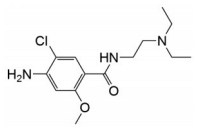
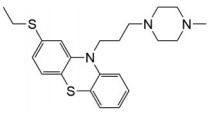
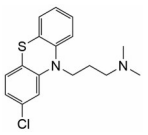
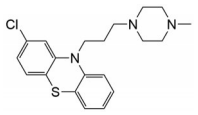
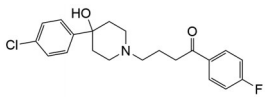
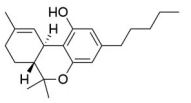
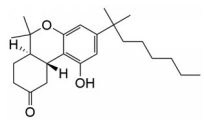
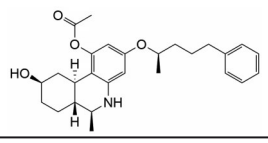
Table 1 Chemical structure of chemically synthesized antiemetic drugs and their application in prevention and treatment of CINV. 5-HT3: 5-Hydroxytryptamine 3; CINV: Chemotherapy-induced nausea and vomiting; HEC: Highly emetogenic chemotherapy; MEC: Moderately emetogenic chemotherapy; NK1: Neurokinin-1; CMF: Cyclophosphamide methotrexate flourouracil; [a]Clinical-stage drugs; [b]Research and development-stage drugs; [*]Refers to the National Medical Products Administration (NMPA), China; [#]Refers to the US Food and Drug Administration (USFDA); [▲]Refers to the Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Drug class	Drug name	Structural class	Chemical structure	Application	Ref.
5-HT3 receptor antagonists	Ondansetron[a*#]	Indoles		Alleviates chemotherapy-induced nausea and vomiting in both pediatric hematologic malignancy patients and glioma patients	[9,10]
	Dolasetron[a*#]	Indoles		Alleviates CINV with antiemetic efficacy comparable to that of ondansetron	[11]
	Tropisetron[a*#]	Indoles		Alleviate acute nausea and vomiting induced by moderately to highly emetogenic drugs	[12]

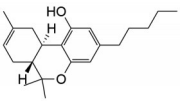
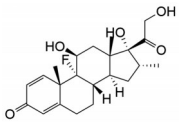
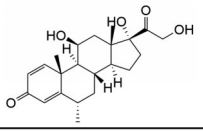
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Drug class	Drug name	Structural class	Chemical structure	Application	Ref.
	Ramosetron[a*#]	Indoles		Inhibition of nausea and vomiting caused by chemotherapy in patients with breast cancer and esophageal cancer	[13,14]
	Azasetron[a*#]	Benzamides		Treats acute and delayed nausea and vomiting induced by cisplatin	[15]
	Dazopride[b]	Benzamides		Improves vomiting response induced by cisplatin in dogs	[16]
	Zacopride[b]	Benzamides		Improves vomiting behavior induced by cisplatin in cats	[17]
	Pancopride[b]	Benzamides		Improving nausea and vomiting caused by highly emetogenic chemotherapy drugs	[18,19]
	RG-12915[b]	Benzamides		Improves cisplatin-induced vomiting in ferrets and dogs	[20]
	Granisetron[a*#]	Organic heterocycles		Improves the nausea, vomiting and anorexia caused by chemotherapy in bladder cancer patients	[21]
	Palonosetron[a*#]	Organic heterocycles		Improvement of acute and delayed nausea and vomiting due to HEC and MEC drugs	[22,23]
	Indisetron[a▲]	Organic heterocycles		Improves nausea and vomiting in gynecologic and lung cancer patients after chemotherapy	[24,25]
	Bemesetron[b]	Organic heterocycles		Controls nausea and vomiting caused by cisplatin chemotherapy	[26]
	DAT-582[b]	Organic heterocycles		Reduces the frequency of vomiting episodes in dogs and ferrets and prolongs the vomiting latency period	[27]
NK-1 receptor antagonists	Aprepitant[a*#]	Triazoles		Treats acute and delayed nausea and vomiting in patients with various cancers after chemotherapy, including gastric, lung, and colorectal cancers	[28-31]
	Fosaprepitant[a*#]	Triazoles		Treatment of nausea and vomiting caused by cisplatin chemotherapy in patients with head and neck squamous cell carcinoma	[32]
	Rolapitant[a#]	Piperidines		Treatment of nausea and vomiting caused by drug chemotherapy for HEC	[33]

Continued

Drug class	Drug name	Structural class	Chemical structure	Application	Ref.
	Casopitant[b]	Piperidines		Reduces nausea and vomiting caused by HEC drug chemotherapy in cancer patients	[34]
	CP-99, 994[b]	Piperidines		Improves acute and delayed cisplatin-induced nausea and vomiting in ferrets	[35]
	Netupitant[b]	Piperazines		Inhibition of vomiting behavior in ferrets and shrews caused by various emetogenic drugs	[36]
	Fosnetupitant[a▲]	Piperazines		Suppression of nausea and vomiting caused by HEC drug chemotherapy	[37]
	Thalidomide[b]	Organic heterocyclic compounds		Improvement of delayed nausea and vomiting	[38]
Dopamine receptor antagonists	Metoclopramide[a*#]	Benzamides		Improving cisplatin-induced CINV	[39]
	Thiethylperazine[a#]	Phenothiazines		Treatment of nausea and vomiting caused by chemotherapy in breast cancer patients	[40]
	Chlorpromazine[a*#]	Phenothiazines		Treatment of nausea and vomiting caused by HEC drugs	[41]
	Prochlorperazine[a#]	Phenothiazines		Improvement of delayed nausea and vomiting caused by adriamycin	[42]
	Haloperidol[a*#]	Butyrophenones		Equivalent efficacy to olanzapine in controlling CINV	[43]
Cannabinoid receptor agonists	Δ9-THC[b]	Cannabinoid compounds		Reduces the frequency of vomiting induced by cisplatin in shrews	[44]
	Nabilone[a#]	Cannabinoid compounds		Treatment of nausea and vomiting caused by chemotherapy in lung cancer patients	[45]
	Levonantradol[b]	Cannabinoid compounds		Treatment of refractory nausea and vomiting	[46]

Continued

Drug class	Drug name	Structural class	Chemical structure	Application	Ref.
	Δ8-THC[b]	Cannabinoid compounds		Inhibition of vomiting caused by chemotherapy in patients with malignant tumors of the hematopoietic system	[47]
Glucocorticoid receptor agonists	Dexamethasone[a*#]	Steroids		Improving nausea and vomiting caused by cisplatin chemotherapy in cancer patients	[48]
	Methylprednisolone[a*#]	Steroids		Alleviating nausea and vomiting caused by CMF chemotherapy in breast cancer patients	[49]

1.2 NK1受体拮抗剂 神经肽P物质 (substance P, SP) 和NK1受体作为速激肽系统的核心组成部分, 广泛分布于胃肠道迷走神经及脑干呕吐中枢, 如孤束核、极后区[52,53]。SP是NK1受体的内源性配体, 与NK1受体结合参与呕吐、疼痛等多种病理生理过程[54,55]。NK1受体拮抗剂的止吐机制是通过竞争性阻断SP与NK1受体结合, 从而抑制SP介导的呕吐反应[56]。目前临床应用的NK1受体拮抗剂如表1所示, 代表药物有阿瑞匹坦、福沙匹坦、罗拉匹坦、奈妥匹坦、福思奈妥匹坦等, 这类药物安全性高, 不良反应发生率较低, 在治疗延迟性恶心呕吐方面, 止吐效果优于5-HT3受体拮抗剂。该类拮抗剂按结构类型可分为三唑类、哌啶类、哌嗪类, 其共同特征是具有两个芳香环和一个烷基取代基构成的核心药效团。当两个芳香环垂直排列时, 药物与NK1受体可产生高亲和力结合。此外, 其结构中的甲氧基可通过静电相互作用增强结合效能, 而三氟甲基则通过疏水效应进一步提升药物与受体的亲和力[57]。

1.3 多巴胺受体拮抗剂 多巴胺 (dopamine, DA) 为儿茶酚胺类神经递质, 是神经系统中最常见的神经递质, 参与多种生理功能[58]。多巴胺受体广泛存在于中枢和外周神经系统[59], 可分为D1和D2两种类型, D1家族主要包括D1和D5亚型, D2家族包括D2、D3、D4亚型[60]。研究表明, 多巴胺D2和D3受体在催吐反应中起着关键作用[61,62], 当内源性多巴胺或外源性受体激动剂与胃肠道及中枢神经系统中的D2、D3受体结合后, 可通过激活中枢和外周两条通路来介导催吐反应[63,64]。多巴胺受体拮抗剂通过阻断多巴胺与D2和D3受体结合, 发挥止吐作用[65]。常见的多巴胺受体拮抗剂如表1所示, 包括甲氧氯普胺、氯丙嗪、氟哌啶醇等, 这类药物止吐疗效显著, 但过多服用易引起锥体外系症状、胃肠不适等不良反应[66,67]。该类拮抗剂的主要结构类型有苯甲酰胺类、酚噻嗪类和丁酰苯类。苯甲酰胺类药物的苯甲酰胺基团, 通过极性或带电区域与D2受体表面的互补电荷残基发生静电相互作用; 芳环取代基通过疏水作用, 稳定配体−受体复合物[68]。酚噻嗪类药物以吩噻嗪三环为核心药效基团, 在苯环2位上引入吸电子基团可增强药理活性; 侧链末端取代基的碱性强度会影响药物与多巴胺受体的亲和力[69]。丁酰苯类药物的核心基团为丁酰苯基, 对位氟取代可增强疏水性, 促进血脑屏障穿透; 侧链的哌啶或四氢吡啶环通过叔胺结构与D2受体结合, 阻断多巴胺信号, 从而发挥止吐作用[70]。

1.4 大麻素受体激动剂 大麻 (*Cannabis sativa* L.) 及其有效成分具有镇痛、抗呕吐等药理作用[71]。内源性大麻素系统通过内源性大麻素、大麻素受体及代谢酶参与生理调节, 其中大麻素1型受体 (cannabinoid receptor type 1, CB1) 是该系统最经典的受体[72], CB1受体主要分布于中枢神经系统, 通过调控神经递质释放、抑制呕吐中枢活动, 成为抗CINV的重要治疗靶点[73,74]。常见的大麻素受体激动剂如表1所示, 代表药物有Δ9-四氢大麻酚、Δ8-四氢大麻酚、nabilone等。大麻素受体激动剂对以往止吐药物无效的癌症患者表现出更好的治疗效果[75], 然而, 长期使用可能引发一系列毒性反应, 包括心率加快、眼压降低、嗜睡、癫痫发作等, 此外大麻素的医疗应用还受到法律和伦理的挑战[76]。Nabilone已被美国食品药品监督管理局 (Food and Drug Administration, FDA) 批准用于治疗CINV, 其止吐机制是激活CB1受体, 调控神经递质的释放, 降低恶心呕吐的频率, 并通过中枢神经系统发挥神经作用从而阻断呕吐信号的传递[77]。大麻素受体激动剂可分为植物大麻素和合成大麻素, 植物大麻素Δ9-THC和Δ8-THC具有相似的结构, 其核心结构为二苯并吡喃, 通过结合CB1受体正构口袋来调节活性[78]。关键修饰位点C3侧链的C1′位上连接不同的取代基, 可改变药物与受体的结合能力[79]。此外, 甲基通过电子效

应或改变空间构型来影响活性; 羟基与受体极性区域形成氢键增强亲和力; 长链烷基则通过疏水作用稳定受体复合物[80]。基于植物大麻素的结构特征, Walsh等[81]合成了一系列大麻素结构类似物, 这些化合物在保留母核结构的基础上进行了定向修饰, 使其与CB1受体表现出显著的高亲和力。进一步的临床研究证实, 该类大麻素类似物可通过选择性激活 CB1 受体通路, 有效发挥止呕作用。这类激动剂的核心药效基团由芳香环系统、脂肪族侧链、疏水基团共同组成。

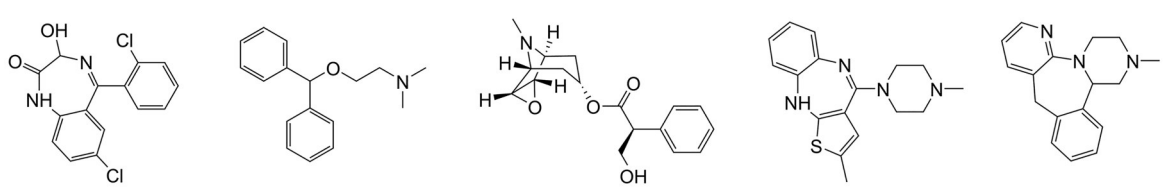
1.5 糖皮质激素受体激动剂 糖皮质激素是通过肾上腺皮质分泌的一类甾体激素。糖皮质激素受体 (glucocorticoid receptor, GR) 是一种配体依赖性转录因子, 以特异性方式激活或抑制成百上千个基因的表达[82]。糖皮质激素是GR的内源性配体, 通过激活GR参与调控新陈代谢、免疫应答及应激反应等生理过程。根据 Chu 等[83]研究表明, 糖皮质激素受体激动剂抗CINV的药效机制主要包括: 调控孤束核产生中枢止吐作用, 抑制外周神经系统中 5-HT、NK1 等神经递质的释放, 抑制肠道炎症因子的释放发挥抗炎作用, 调节下丘脑−垂体−肾上腺轴的活动等。常见的糖皮质激素受体激动剂如表1所示, 代表药物有地塞米松和甲泼尼龙。它们在结构上属于甾体类化合物, 甾体母核是其发挥生物活性最关键的结构, 通过增强C11位羟基化提高与GR的结合能力[84]。

1.6 GABA 受体激动剂 谷氨酸和 γ-氨基丁酸 (γ-aminobutyric acid, GABA) 是中枢神经系统中最主要的兴奋性和抑制性神经递质[85]。其中 γ-氨基丁酸A型受体 (GABA-A) 作为中枢神经系统中至关重要的抑制性神经递质受体, 具有重要的生理和治疗意义[86]。苯二氮卓类药物通过与该受体结合增强GABA效应, 使氯离子通道开放频率增加, 从而增强抑制性神经传递[87]。劳拉西泮 (图2, **1**) 是典型的苯二氮卓类药物, 可治疗高剂量顺铂诱导的预期性恶心呕吐[88]。其机制是通过增强GABA-A受体功能, 缓解患者焦虑, 间接改善预期性恶心呕吐, 这一机制已被 James 等[89]研究证实。苯二氮卓类药物从结构上看七元亚胺内酰胺环是活性所必需的结构, 引入吸电子取代基可显著增强药物活性, 然而引入五元含氮杂环可增加结构的稳定性[90]。

1.7 组胺受体拮抗剂 组胺 (histamine, His) 是一种重要的神经递质, 广泛存在于中枢神经系统和外周神经系统中, 参与多种生理过程[91]。研究表明, 组胺在中枢神经系统中是通过激活 H1 和 H2 受体诱发呕吐反应。这一机制在临床前研究中得到了验证, Bhargava 等[92]通过静脉注射阿扑吗啡或口服硫酸铜诱导狗产生催吐反应, 发现 H1 和 H2 受体均与呕吐反应相关。在临床应用方面, Song[93]采用托烷司琼联合苯海拉明 (图2, **2**) 和地塞米松治疗CINV, 结果显示该方案在预防恶心呕吐方面优于单独使用托烷司琼的对照组。其药理机制是通过阻断组胺与H1受体结合, 从而抑制呕吐信号的传递。

1.8 M 胆碱受体拮抗剂 乙酰胆碱 (acetylcholine) 是一种重要的神经递质, 通过激活毒蕈碱型乙酰胆碱受体 (muscarinic acetylcholine receptors, mAChRs) 发挥作用, 参与多种生理过程[94]。毒蕈碱乙酰胆碱受体由M1～M5共5种受体亚型组成, 每个亚型具有不同的组织分布和功能特性, 这些受体广泛分布于中枢神经系统、外周神经系统等组织中[95]。东莨菪碱 (图2, **3**) 是一种胆碱能受体拮抗剂, 它被用于治疗术后恶心呕吐[96]及CINV[97], 其作用机制是通过拮抗 mAChRs, 从而减少乙酰胆碱的神经信号传递, 阻断前庭冲动的传入, 缓解恶心和呕吐症状。

1.9 葡萄糖依赖性促胰岛素多肽受体激动剂 葡萄糖依赖性促胰岛素多肽 (glucose-dependent insulinotropic polypeptide, GIP) 是一种肠促胰素, 在食物等营养物质刺激下由肠道内分泌细胞合成的肠道激素[98], 大部分位于十二指肠和近端空肠, 少数发生在小肠中[99]。其受体属于G蛋白偶联受体, 广泛分布于外周组织和大脑中[100]。GIP及其受体通过调控血糖、糖脂代谢及体重、抑制摄食、减轻心血管功能并保护骨骼等, 成为代谢疾病治疗的核心靶点[101]。最新的研究发现, 背侧迷走复合体 (dorsal vagal complex, DVC) 的孤束核和极后区神经元中, 存在新型葡萄糖依赖性促胰岛素多肽止吐系统。该系统的止吐机制源于GIP受体激动剂对DVC特定 γ氨基丁酸 (GABA) 能神经元亚群的激活作用: 逆转化疗药物诱导的神经功能失调, 恢复



Lorazepam, **1** Diphenhydramine, **2** Hyoscine, **3** Olanzapine, **4** Mirtazapine, **5**

Figure 2 Chemical structures of lorazepam, diphenhydramine, hyoscine, olanzapine and mirtazapine

DVC兴奋, 抑制动态平衡, 阻断呕吐信号。药理研究表明, 替尔泊肽可显著缓解其呕吐及厌食症状, 提示GIP受体有望成为防治CINV的新策略[102]。

1.10 多靶点药物 当前防治CINV的药物, 大多数针对特定的神经递质发挥拮抗或激动的作用, 而奥氮平(图2, **4**) 凭借着多靶点的作用机制显现出优势。临床研究表明, 奥氮平作为二苯并二氮卓类非典型抗精神病药, 可显著改善患者服用高度致吐性化疗药物(highly emetogenic chemotherapy drugs, HEC) 所致恶心呕吐的症状并联合其他止吐药物显著提高止吐疗效[103-106]。其作用机制是通过阻断5-HT、多巴胺、组胺及肾上腺素等多种神经递质与其受体结合以达到止吐的目的[107]。此外, 米氮平(图2, **5**) 是一种具有去甲肾上腺素能和特异性5-HT能作用的抗抑郁药[108], 除了抗抑郁外, 米氮平在肺癌患者化疗后引起的延迟性恶心呕吐也显现出良好的治疗效果。临床上, 米氮平已作为辅助药物添加在标准止吐药物方案中, 研究表明该止吐方案可显著缓解肺癌患者接受HEC治疗后所致的延迟性恶心呕吐, 其作用机制是米氮平可阻断5-HT和组胺与其受体相结合, 抑制神经递质的释放, 从而发挥止吐作用[109]。

2 中药及中药复方

2.1 单味中药 中药在防治CINV方面展现出独特优势, 其多成分、多靶点、多途径的协同作用特点是化学合成药物难以替代的[110]。近年来, 现代药理学研究及临床实践已证实多种中药及其活性成分具有显著的抗CINV作用。表2[111-131]系统总结了代表性止呕单味中药的提取物与药效成分在防治CINV方面的研究进展, 包括研究方法、药效评价及作用机制等, 这些研究成果不仅为阐明中药防治CINV的科学内涵提供了重要依据, 也为后续新药研发和临床应用奠定了理论基础。

2.2 中药复方 现代药理及临床研究表明, 中药复方在CINV方面具有显著疗效。表3[132-147]中总结了临床常用止呕中药复方的研究应用, 包括六君子汤、吴茱萸汤、橘皮竹茹汤、小半夏汤、丁香柿蒂汤、附桂理中汤、旋覆代赭汤、半夏泻心汤及中成药和中颗粒。这些复方均基于中医“辨证施治”原则, 通过不同药物组合治疗脾胃虚弱、肝胃不和、胃气上逆、痰阻气滞、中焦虚寒等不同证候, 其核心功效涵盖健脾益气、和胃降逆、温中散寒、化痰止呕等方面的作用。这些复方通过多成分、多靶点、多途径的协同作用机制发挥疗效, 显著改善肿瘤患者的食欲、营养状况和生活质量并降低了恶心呕吐的发生率。

3 总结与展望

随着肿瘤患者数量的持续攀升, 越来越多接受化学治疗的患者面临CINV的困扰, 这一现状不仅严重影响患者的生活质量和治疗依从性, 更对临床肿瘤治疗方案的制定与实施提出了严峻挑战。本文系统地综述了当前可用于CINV预防和治疗的药物及具有潜力的新型止吐候选物, 重点分析了各类止吐药物的结构类型、作用机制、临床应用及其构效关系, 旨在为新型止吐药的研发提供理论依据。目前临床应用的止吐药物主要包括5-HT3受体拮抗剂、NK1受体拮抗剂、多巴胺受体拮抗剂、组胺受体拮抗剂、M胆碱受体拮抗剂、糖皮质激素受体激动剂、大麻素受体激动剂以及中药及其复方制剂。

基础止吐药阶段 (1970～1990年) 的核心止吐药物为多巴胺受体拮抗剂如甲氧氯普胺、氯丙嗪, 糖皮质激素受体激动剂地塞米松, 组胺H1受体拮抗剂苯海拉明和M胆碱受体拮抗剂东莨菪碱。多巴胺受体拮抗剂主要通过阻断多巴胺与中枢神经系统中D2、D3受体结合, 对急性CINV有效, 但易诱发锥体外系反应。糖皮质激素受体激动剂通过抑制炎症因子和神经递质释放发挥作用, 但长期应用可能导致代谢紊乱。组胺H1受体拮抗剂主要适用于预期性CINV, 但中枢镇静不良反应明显, 且单用对化疗所致呕吐效果微弱。M胆碱受体拮抗剂通过阻断胃肠毒蕈碱受体, 可减轻前庭功能障碍相关症状。然而, 由于这些药物靶点单一, 对延迟性CINV疗效甚微, 且不良反应显著, 在《2024上海防治化疗性恶心呕吐指南》中已被列为二线治疗药物。

5-HT3受体拮抗剂阶段 (1990～2000年) 标志着CINV急性期控制的重大突破。研究发现, 化疗刺激胃肠道肠嗜铬细胞释放5-HT, 从而确立了5-HT3受体作为止吐新靶点。第一代5-HT3受体拮抗剂昂丹司琼、格拉司琼通过竞争性阻断肠道5-HT3受体, 将急性CINV控制率提升至70%～90%, 但对延迟性CINV效果仍不理想。为此, 研究人员开发了具有高亲和力、长半衰期特性的第二代5-HT3受体拮抗剂帕洛诺司琼在有效控制急性CINV的同时, 也提高了延迟性CINV的缓解率。显著的疗效使此类药物成为中高度致吐性化疗的一线用药, 但仍普遍存在作用机制单一及不良反应如头痛、便秘等问题。

NK1受体拮抗剂阶段 (2000～2010年) 通过靶向SP介导的延迟性呕吐通路, 显著提升了延迟期CINV的完全缓解率。自2003年阿瑞匹坦获FDA批准上市后, 仅有福沙匹坦和罗拉匹坦相继获批。尽管NK1受体拮抗剂有效改善了延迟性CINV症状, 但其临床应

Table 2 Research and applications of representative traditional Chinese medicine (TCM) herbs in prevention and treatment of CINV. ROS: Reactive oxygen species; FOLFOX: Folinic acid, fluorouracil, and oxaliplatin; [a]Clinical-stage drugs; [b]Research and development-stage drugs; ■Refers to the Pharmacopoeia of the People's Republic of China (2020 Edition)

Herb name	Extract/ pharmacodynamic component	Research method	Research result	Ref.
Zingiberis Rhizoma Recens (*Zingiber officinale Rosc.*)[a]■	Extracts	Double-blind, multi-center clinical trials	Ginger as an adjunct improves the severity of acute nausea and vomiting in cancer patients	[111]
	6-Gingerol	Phase II clinical trial for solid tumor patients receiving highly emetogenic chemotherapy	Improves nausea, vomiting, appetite, and quality of life in solid tumor patient post-chemotherapy	[112]
		Cisplatin-induced ferret vomiting model	Exhibits good antiemetic activity by inhibiting 5-HT, DA and SP levels	[113]
	6-Shogaol	Rat cisplatin-induced pica model	Reduces kaolin intake by ameliorating inflammatory damage in the gastric antrum and ileum through downregulation of inflammatory cytokine levels	[114]
Forsythiae Fructus (*Forsythia suspensa* (Thunb.) Vahl)[a]■	Forsythiae fructus extracts (decoction)	Mink vomiting model induced by various emetogenic agents including cisplatin	Prolongs the latency to vomiting induced by cisplatin, apomorphine, and copper sulfate, and reduces retching episodes	[115, 116]
	Forsythiae fructus extracts (decoction)	Chemotherapy-induced rat pica model	Suppresses chemotherapy-induced pica behavior by lowering serum and brain levels of 5-HT and downregulating expression of 5-HT3 receptors	[117]
	Forsythiae fructus extracts (decoction)	Chemotherapy-induced rat pica model	Reduces serum ROS levels, downregulates expression of inflammatory factors, indirectly inhibits 5-HT release	[118, 119]
Portulaca oleracea (*Portulaca oleracea* L)[a]	*n*-Butanol and methanol extracts	Pigeon vomiting model	Alleviates cisplatin-induced vomiting by reducing levels of 5-HT and DA in the brain and intestine	[120]
Ganoderma (*Ganoderma lucidum* (Leyss.ex Fr.) Karst) or (*Ganoderma sinense* Zhao, Xu et Zhang)[a]■	Ganoderma lucidum extract	Rat cisplatin-induced pica model	Reduces kaolin intake	[121]
	Ganoderma lucidum polysaccharides	Rat cisplatin-induced pica model	Reducing the intake of kaolin in mice	[122]
Panacis quinquefolia Radix (*Panax quinquefolium* L)[a]■	American ginseng berry extract and ginsenoside Re	Chemotherapy-induced rat pica model	Improves chemotherapy-induced pica behavior in rats	[123]
Ginseng Radix et Rhizoma (*Panax ginseng* C. A. Meyer)[a]■	Ginseng extracts	Cisplatin-induced rat pica model	Markedly reduces kaolin intake and improves food consumption and body weight in rats	[124]
	Non-saponin and saponin components	Chemotherapy rat pica model	Effectively alleviates cisplatin-induced pica behavior in rats	[125]
Ginseng Radix et Rhizoma (*Panax ginseng* C. A. Mey)[a]■	Ginseng raw powder	Cisplatin-induced pica model of rat	Inhibits cisplatin-induced vomiting, reduces kaolin intake in chemotherapy rats	[126]
	Water extract of ginseng and its different polar fractions	Chemotherapy-induced rat pica model	Saponins are the main components of ginseng for the prevention and treatment of CINV	[127]
Astragli Radix (*Astragalus membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) *Hsiao)* or *(Astragalus membranaceus* (Fisch.) *Bge*)[a]■	Astragali Radix Wall-Broken herbal pieces	Nausea and vomiting caused by FOLFOX chemotherapy drugs in patients with colorectal cancer	Reduces appetite fluctuations and the incidence of nausea and vomiting	[128]
	Astragalus polysaccharide injection	Nausea and vomiting post-chemotherapy in cervical cancer patients	Improves nausea and vomiting post-chemotherapy in cervical cancer patients	[129]
Scutellariae Radix (*Scutellaria baicalensis Georgi*)[a]■	Scutellaria baicalensis extracts	Rat cisplatin-induced pica model	Reduces the intake of kaolin in chemotherapy rats	[130]
Pinelliae Rhizoma (*Pinellia ternata* (Thunb.) Breit.)[a]■	Pinellia ternata alkaloids	Guinea pig isolated ileum experiment	Blockade of 5-HT3 receptors and NK1 receptors in the ileum	[131]

Table 3 Research and applications of representative TCM prescriptions in prevention and treatment of CINV. [a]Clinical-stage drugs; [b]Research and development-stage drugs

TCM prescription	Composition	Research method	Research result	Ref.
Liu Junzi Decoction[a]	Ginseng Radix et Rhizoma, Atractylodis macrocephalae Rhizoma, Poria, Glycyrrhizae Radix et Rhizoma, Citri Reticulatae Pericarpium, Pinelliae Rhizoma	Clinical trial for nausea and vomiting induced by chemotherapy in cervical cancer patients	Improves nausea, vomiting, and anorexia in cervical cancer patients	[132]
Wuzhuyu Decoction[a]	Euodiae Fructus, Ginseng Radix et Rhizoma, Zingiberis Rhizoma Recens, Jujubae Fructus	Clinical trial for nausea and vomiting induced by chemotherapy in cancer patients	Reduces the incidence of chemotherapy-induced nausea and vomiting	[133]
		Chemotherapy-induced rat pica model	Improves cisplatin-induced nausea and vomiting, reduces gastrointestinal inflammation by lowering serum 5-HT levels and inhibiting intestinal γ-H2AX and CD45 expression	[134]
Jupi Zhuru Decoction/ Granules[a]	Citri Reticulatae Pericarpium, Bambusae caulis in taenias, Jujubae Fructus, Zingiberis Rhizoma Recens, Glycyrrhizae Radix et Rhizoma, Ginseng Radix et Rhizoma	Clinical trial for nausea and vomiting post-chemotherapy in cancer patients	Improves appetite, health status, and quality of life by inhibiting 5-HT release and repairing gastrointestinal mucosal inflammation	[135, 136]
Xiao Banxia Decoction[a]	Pinelliae Rhizoma, Zingiberis Rhizoma Recens	Clinical trial for nausea and vomiting post-chemotherapy in gastric cancer patients	Improves quality of life in patients	[137]
		Clinical trial for nausea and vomiting post-chemotherapy in gynecological tumor patients	Reduces the frequency and severity of delayed nausea and vomiting	[138]
		Chemotherapy-induced rat pica model	Improves rat weight, food intake, kaolin intake, regulates neurotransmitters, inhibits release of inflammatory factors, and improves gastrointestinal dysfunction	[139-141]
Dingxiang Shidi Decoction[a]	Caryophylli flos, Kaki calyx, Ginseng Radix et Rhizoma, Zingiberis Rhizoma Recens	Chemotherapy-induced rat pica model	Improves rat weight, food intake, kaolin intake by significantly reducing serum and ileal 5-HT levels	[142]
Fu Gui Li Zhong Decoction[a]	Ginseng Radix et Rhizoma, Zingiberis Rhizoma, Atractylodis Macrocephalae Rhizoma, Glycyrrhizae Radix et Rhizoma, Aconiti lateralis radix Praepapata, Cinnamomi cortex	Clinical trial of nausea and vomiting caused by chemotherapy in breast cancer patients	Reduces the incidence of delayed nausea and vomiting	[143]
Xuanfu Daizhe Decoction[a]	Inulae flos, Pinelliae Rhizoma, Codonopsis radix, Zingiberis Rhizoma Recens, Haematitum, Glycyrrhizae Radix et Rhizoma, Jujubae Fructus	Clinical trial for nausea and vomiting post-chemotherapy in lung cancer patients	Combination of Chinese herbal formula shows better efficacy in treating delayed nausea and vomiting compared to control group	[144]
Banxia Xiexin Decoction[a]	Pinelliae Rhizoma, Coptidis Rhizoma, Scutellariae Radix, Ginseng Radix et Rhizoma, Zingiberis Rhizoma, Jujubae Fructus, Glycyrrhizae Radix et Rhizoma	Clinical trial for nausea and vomiting post-chemotherapy in breast cancer patients	Reduces the incidence of delayed nausea and vomiting and alleviates symptoms	[145]
		Clinical trial for nausea and vomiting post-chemotherapy in lung cancer patients	Alleviates gastrointestinal reactions such as nausea and vomiting	[146]
Hezhong Granules[a]	Pinelliae Rhizoma, Zingiberis Rhizoma Recens, Euodiae Fructus, Ginseng Radix et Rhizoma, Poria, Coptidis Rhizoma, Scutellariae Radix, Cinnamomi cortex	Phase II clinical trial for nausea and vomiting post-chemotherapy in colorectal cancer patients	Improvement of delayed nausea and vomiting	[147]

用通常需联合其他药物使用, 且安全性仍需长期关注。

综合发展阶段 (2010 年至今), 为更有效控制 CINV, 研究策略呈现出多元化趋势。联合用药标准化: 由 5-HT3 受体拮抗剂、NK1 受体拮抗剂和糖皮质激素受体激动剂组成的三联方案已成为当前标准止吐方案; 多靶点药物开发: 以奥氮平、米氮平为代表的多靶点药物, 通过同时阻断多种神经递质受体展现出更优的止吐效果; 老药新用与新靶点探索: 2017 年在中国进行的一项 III 期临床试验评估了沙利度胺预防高致吐性化疗患者延迟性 CINV 的有效性与安全性。2023 年一项临床前研究提出, 以激动葡萄糖依赖性促胰岛素受体为新型靶点, 如降糖药替尔泊肽可显著改善 CINV,

为挖掘新靶点提供了方向。此外, 中医药现代化研究显示, 中药凭借其来源安全、疗效确切、配伍灵活及多成分、多靶点、多途径调控的优势, 在止吐领域展现巨大潜力。然而, 目前的研究仍存在明显不足: 止吐机制尚未完全阐明; 部分研究局限于动物实验或小规模临床试验; 缺乏标准化的剂量和给药方案; 对具体分子靶点的深入探讨不足。

基于当前局限性, 未来研究应聚焦以下方向: 优化现有化合物结构以减少不良反应; 开发多靶点药物通过协同作用以提升疗效; 推动中药及天然药物的机制研究与标准化应用; 开展大规模、多中心的临床研究以验证这些中药的疗效和安全性; 开发长效低成本制剂以提高依从性; 探索新靶点以实现现代医疗保健中有效、长期控制恶心和呕吐的最终目标。

作者贡献: 肖月湘进行了文献调研、手稿设计与撰写; 鄢星进行了手稿修改; 李慧与王志鑫获取经费资助并指导整个研究。

利益冲突: 本文所有作者声明不存在利益冲突关系。

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