

## 基于整体观念对中药治疗结直肠癌相关研究的多层次分析

王 峥<sup>1</sup>, 张春泽<sup>2,3\*</sup>

(1. 天津中医药大学中西医结合学院, 天津 301600; 2. 天津市人民医院, 南开大学第一附属医院结直肠外科, 天津 300121; 3. 天津市结直肠病研究所, 天津 300121)

**摘要:** 结直肠癌是威胁世界人民生命健康的主要癌种, 随着现代医学模式的转变, 以中药为代表的多靶点治疗策略已成为结直肠癌治疗的新研究方向。对于中药的研究, 除了本着还原论的思想解构中药成分靶点外, 更应注重中医药基础理论中的整体观念, 从整体上分析和理解中药治疗的作用机制。中药复方是单味药的集合, 单味药又由多种中药单体构成, 从不同层次去看待中药, 将不同单味药、不同单体看作整体, 有助于研究者更好地理解中药与中医。中药具有多靶点的特点, 除了直接作用于肿瘤细胞本身外, 还可以影响肠道菌群, 改善肿瘤微环境, 从整体上调节肿瘤患者的身体机能, 全方位多维度地治疗肿瘤, 全面改善患者的健康状况。本综述旨在从中药复方、单味药和中药单体3个层面出发, 基于临床试验和临床前研究成果, 系统地阐述中药在结直肠癌治疗中的疗效及多靶点作用机制。同时, 本文将结合系统生物学与中医整体观, 对中药治疗结直肠癌的相关研究进行深入分析。

**关键词:** 中药; 中医; 免疫细胞; 结直肠癌; 肠道菌群; 肿瘤细胞

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## Analysis of the research on the treatment of colorectal cancer with traditional Chinese medicine at different levels based on the holistic concept

WANG Zheng<sup>1</sup>, ZHANG Chun-ze<sup>2,3\*</sup>

(1. School of Integrative Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301600, China;  
2. Department of Colorectal Surgery, Tianjin Union Medical Center, the First Affiliated Hospital of Nankai University, Tianjin 300121, China; 3. Tianjin Institute of Coloproctology, Tianjin 300121, China)

**Abstract:** Colorectal cancer is a major cancer threatening the life and health of people worldwide. With the transformation of modern medical models, treatment strategies represented by traditional Chinese medicine (TCM) with multiple targets have become a new research direction in the treatment of colorectal cancer. In the study of TCM, in addition to deconstructing the components and targets of TCM based on reductionism, more attention should be paid to the holistic concept in the basic theories of TCM, analyzing and understanding the mechanism of action of TCM treatment from a holistic perspective. TCM compound prescriptions, as a collection of single herbs, are composed of various monomers. Viewing TCM from different levels and considering different herbs and monomers as a whole helps us better understand TCM. At the same time, TCM has the characteristic of multiple targets. In addition to directly acting on tumor cells themselves, it can also affect the intestinal flora to improve the tumor microenvironment, treating tumors in an all-round and multi-dimensional way, regulating the physical functions of tumor patients from a holistic perspective, and comprehensively improving the health status of the

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\*通讯作者 E-mail: chunze.zhang@nankai.edu.cn

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individual. This review aims to systematically elaborate on the efficacy and multi-target mechanism of TCM in the treatment of colorectal cancer from three levels: TCM compound prescriptions, single herbs, and TCM monomers, based on clinical trials and preclinical research results. Meanwhile, this article will combine systems biology with the holistic view of TCM to conduct an in-depth analysis of related research on TCM treatment of colorectal cancer.

**Key words:** Chinese herbal medicine; traditional Chinese medicine; immune cell; colorectal cancer; gut microbiota; tumor cell

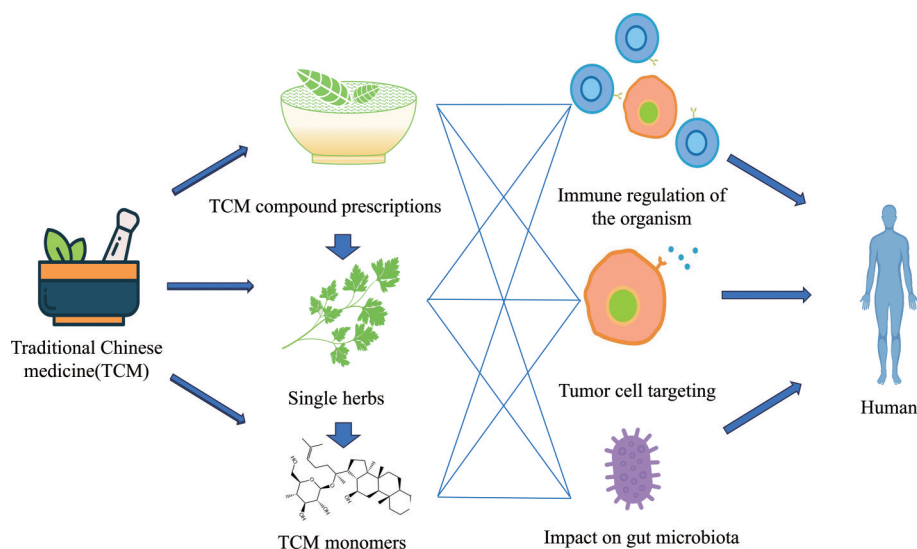
据统计,在世界范围内结直肠癌发病率在所有癌种中排名第三,死亡率位居第二,它是50岁以下美国男性最易发生的恶性肿瘤,预计到2030年将导致110万人死亡<sup>[1,2]</sup>。结直肠癌的病因涉及遗传和表观遗传,吸烟、肥胖、饮酒、食用红肉及加工肉类是其危险因素<sup>[3-5]</sup>。大多数结直肠肿瘤通过两种不同的途径(传统的腺瘤-癌途径和锯齿状肿瘤途径)产生,从异常隐窝到癌前病变再到结直肠癌需10~15年的时间,然而早期结直肠癌没有明显症状,随着病情的发展,患者常出现便血、贫血、排便习惯改变和体重减轻等不典型症状,大多数结直肠癌在发现时已达到III或IV期<sup>[6-9]</sup>。目前,临床上针对结直肠癌的治疗选择相对有限,多数治疗方法可能会损害患者的生活质量,手术、放化疗可能导致术后胃肠功能紊乱、周围神经病变等不良反应<sup>[10-14]</sup>。结直肠癌早期筛查诊断的普及,手术切除方案优化和靶向及免疫治疗的应用使结直肠癌的5年相对生存率从20世纪70年代中期的50%提高到了2011至2017年间的65%,但IV期结肠和直肠癌患者的5年生存率仅为11%和15%<sup>[15]</sup>。

中药被广泛应用于包括结直肠癌在内的多种疾病中,由于中药多组分多靶点的特点,很难系统、科学地

研究和解释其独特疗效<sup>[16]</sup>。整体观念是中医理论的一大特征之一,中医认为人体是一个有机的整体,各脏腑之间相互作用,调节机体的生命活动<sup>[17]</sup>。中医对于生命与疾病认知的整体观与系统生物学强调的从整体上研究生物体内分子、细胞、组织、器官间相互作用的理念不谋而合<sup>[18]</sup>。组分中药及系统药理学的提出也从药物层面强调了中药配伍、药物有效成分及药物作用靶点的整体性认识在研究中药疗效中的关键作用。不同于过去还原论的研究方法,中药研究需遵循整体论,以便更好地理解和阐述中医药理论,研究中药的治病机制<sup>[19,20]</sup>。因此,本综述试图从中药复方、单味药和中药单体3个层次探讨中药对结直肠癌的疗效,以此给科研工作者展现中药治疗结直肠癌研究的立体结构,以便更好地从整体把握中药治疗结直肠癌的研究现状(图1)。

## 1 中药复方

中药复方通过不同药味之间的组合以针对性调节人体五脏六腑,肢体经络间的平衡,抑制机能亢进的器官及组织,调补衰弱脏腑的机能,维持脏腑经络间的相互作用,保持机体稳态。中医强调辨证论治,即中药复方的配伍必须根据患者的症状和体征,结合舌脉,在把



**Figure 1** Analysis of the impact of traditional Chinese medicine (TCM) on the human body, cells, and gut microbiota at three levels: TCM compound prescriptions, single herbs, and TCM monomers. Some images in Figure 1 have been modified from Abstract Vectors by Vecteezy (<https://www.vecteezy.com/free-vector/abstract>)

握患者身体所处的不平衡状态的基础上,通过不同药物间的相互配合,个性化针对性地调节患者的身体机能,调平纠偏,从而治疗疾病。中药复方体现了中医对生命理解的整体观念与处方用药的整体思维,中药复方作为一个有机整体通过不同药物间的相互配合发挥治疗作用,不仅可以减毒增效,还可产生原有药物不存在的治疗效果。

### 1.1 临床疗效

中药复方灵活多变,医生根据患者的病情加减用药,以全面改善患者的身体状况,方剂治疗可以缓解结直肠癌患者的症状、延长生存期、改善手术预后、减少复发转移、降低西药毒性、增加患者放化疗的依从性。将中药复方治疗与传统的结直肠癌治疗(手术、放疗、靶向治疗和免疫治疗)联合使用可增强结直肠癌的治疗效果,个性化针对性地治疗疾病,并可贯穿结直肠癌治疗的全过程<sup>[21]</sup>(表1)。

扶正祛邪是中医治疗疾病的基本思路,抗癌Ⅱ方依据“健气抗癌”思路化裁,方中黄芪、党参、茯苓和薏苡仁可以增强细胞和体液免疫,抑制肿瘤生长。在一项多中心回顾性队列研究中,Wang等<sup>[22]</sup>根据是否长期合理服用抗癌Ⅱ方将529例结直肠癌患者分为中药组和空白组。经过倾向得分匹配后,数据显示长期服用抗癌Ⅱ方的患者1~6年的总生存期(OS)和无进展生存期(PFS)显著提高,Cox回归分析表明中药复方对结直肠癌的复发和转移具有预防作用。一项随机对照临床试验(RCT)评估了祛邪胶囊对晚期结直肠癌患者中位生存时间和生活质量的影响,在40名接受常规结直肠癌治疗的患者中,额外服用祛邪胶囊的患者显示出延长的生存时间、较低的死亡率、更晚的病情进展时间和更高的生活质量<sup>[23]</sup>。另一项研究表明,祛邪胶囊能减少根治性手术后Ⅱ期和Ⅲ期结直肠癌的复发和转移<sup>[24]</sup>。癌症相关性疲劳(CRF)是指因癌症或癌症治疗而产生的与近期活动不相称的疲惫或衰弱感,中医认为脾胃是气血生化之源,脾虚则气血不生,人体易感疲劳,同时脾虚也是结直肠癌患者的常见证候。补中益气汤是治疗脾虚的经典中药复方,可有效缓解CRF,预防手术引起的免疫抑制、白细胞减少和肠道损伤,提高患者的生活质量<sup>[25-28]</sup>。经络是联系脏腑与机体间相互作用的桥梁,脏腑通过经络运输经气濡养机体,是调节人体正常生理功能的关键网络<sup>[29]</sup>。观心饮可以疏通经络调节自主神经活动,改善自主神经功能紊乱<sup>[30]</sup>。非随机对照试验显示,观心饮可增强结直肠癌患者的体力,减轻癌症相关症状,提高生活质量<sup>[31]</sup>。痛则不通是中医对于疼痛机制的简单概括,经络不通常导致疼痛产生,温经止痛方热敷背部经络结合世界

卫生组织三阶梯镇痛药物疗法可以更好地缓解癌症相关疼痛<sup>[32-34]</sup>。单靶点化疗药物治疗常常伴有明显的不良反应,而中药作为多靶点药物在治疗疾病的同时可以充分调节身体机能,减轻药物带来的毒副作用。一项贝叶斯网络荟萃分析证明,中药注射液可显著降低化疗药物导致的恶心呕吐、血小板及白细胞减少症等不良反应的发生频率,提高CD3<sup>+</sup>、CD4<sup>+</sup>、CD8<sup>+</sup>淋巴细胞数量<sup>[35]</sup>。

### 1.2 对细胞的影响

复方同时针对多个药物靶点,通过不同的细胞信号通路,促进细胞凋亡、抑制肿瘤生长、增强免疫细胞浸润、减少瘤内血管生成、减低肿瘤迁移和侵袭能力、逆转肿瘤细胞耐药、增强抗肿瘤药物对肿瘤细胞的细胞毒性,可以对肿瘤不同标志特征进行综合治疗。

**1.2.1 对肿瘤细胞的影响** 在裸鼠模型中,高剂量的柴苓膏通过抑制HIF-1 $\alpha$ /SDF-1 $\alpha$ -CXCR4/PI3K-Akt信号通路,减少VEGF的合成和释放,降低MMP-2对胶原IV的降解,抑制肿瘤生长及肝脏转移<sup>[36]</sup>。化疗耐药被认为是导致90%以上转移性癌症患者治疗失败的原因,肿瘤耐药涉及多种细胞和分子机制,如增强药物外排、提高外源物质代谢和DNA修复等。在许多实体瘤中,存在一小部分癌症干细胞(CSCs),这些CSCs具有持续自我更新、多系分化的能力并对传统治疗耐药,CSCs可诱发癌症复发和转移,最终导致临床抗癌治疗的失败。CSCs可通过表达ATP结合盒(ABC)家族的转运蛋白,如ABCB1和ABCG2,将各种外源性物质从细胞中泵出,减少化疗药物在细胞内的积累,从而产生化疗耐药<sup>[37,38]</sup>。片仔癀可降低ABCB1和ABCG2的转录水平,改善HT-29结直肠癌细胞系干细胞群耐药<sup>[39]</sup>。同时,它还能通过抑制Notch1和STAT3通路、降低血管生成因子iNOS、eNOS、VEGF-A、bFGF及其特异性受体VEGFR-2、bFGFR的表达抑制结直肠癌干细胞生长、细胞增殖和肿瘤血管生成,促进癌细胞凋亡<sup>[40-42]</sup>。

随着中药成分和靶点的挖掘,中药的物质基础慢慢浮现在人们面前。然而,其复杂的成分和药物靶点,使人们难以从整体上认识其治疗机制,探索其背后的规律。网络药理学将靶点、疾病和药物信息整合,建立互作网络,分析多组分、多靶点药物对人体的影响<sup>[43]</sup>。由于网络药理学的整体性和系统性与中医学的整体观念相契合,因此被广泛应用于中医药研究中,通过系统分析中药对人体的影响,寻找有效成分和主要治疗靶点,整体全面地认知药物与靶点间的相互作用<sup>[44]</sup>。

Shang等<sup>[43]</sup>使用蛋白-蛋白相互作用网络、GO分析、KEGG通路富集分析、分子对接(通过模拟药物与靶点的相互作用,预测药物与靶蛋白结合构象并计算

**Table 1** Clinical studies on the treatment of colorectal cancer with traditional Chinese medicine (TCM)

Herbal formula	Study title	Study design	Phase	Status	NCT No.
Teng-Long-Bu-Zhong-Tang	A pilot study of Teng-Long-Bu-Zhong-Tang based herbal therapy in combination with chemotherapy in patients with metastatic colorectal cancer	Multicentric, randomized, controlled clinical trial	I/II	Completed	NCT01975454
Brucea Javanica Oil Emulsion Injection	Clinical study on the effect of Brucea Javanica Oil Emulsion Injection on the survival of patients with advanced colorectal cancer who failed to receive multi-line treatment	Prospective, multicenter, randomized controlled clinical trial	IV	Recruiting	NCT05897749
ChangTai Keli	Synergistic anti-tumor effect of ChangTai Keli based on chemotherapy for colon cancer patients: a randomized, parallel-group, double-blind, multicenter clinical study	Randomized, parallel-group, double-blind, multicenter clinical study	II/III	Unknown status	NCT02510118
Jianpi Huatan Decoction	Efficacy evaluation of Jianpi Huatan Decoction in the treatment of advanced colorectal cancer and analysis of dominant population characteristics and methylation characteristics	Randomized controlled clinical trial	III	Unknown status	NCT05187481
Compound Kushen injection	Survival benefit of Compound Kushen Injection in the treatment of advanced colorectal cancer	Multi-center, randomized, parallel controlled clinical trial	IV	Recruiting	NCT05894694
Jianpi Huatan dispensing granule	Evaluation and mechanism of strengthening the spleen and reducing phlegm method in improving radical resection rate of colorectal cancer	Large sample, multicenter, randomized, double-blind study	III	Unknown status	NCT03716063
Bushen-Jianpi Dedoction and cinobufotalin injection	Study of "same TCM syndrome for different diseases" and "same treatment for different diseases" of primary hepatocellular carcinoma and colorectal cancer under the perspective of system science	Single group assignment	I	Unknown status	NCT03189992
Traditional Chinese medicine formula LC09	A phase III randomized, placebo-controlled, double-blind trial to determine the effectiveness of traditional Chinese medicine formula LC09 for treatment of capecitabine-induced hand and foot syndrome	Multicenter, randomized, double-blind, placebo-controlled study	III	Completed	NCT02794493
Traditional Chinese medicine formula KD018	A phase II multicenter, randomized, placebo controlled, double blinded clinical study of KD018 as a modulator of irinotecan chemotherapy in patients with metastatic colorectal cancer	Multicenter, randomized, placebo controlled, double blinded clinical study	II	Completed	NCT00730158
Chia Tai Tianqing Pharmaceutical	Phase I clinical study of single-center, randomized, double-blind, single-dose, parallel comparison of the pharmacokinetics and safety of ramucirumab injection and Cyramza® in healthy male volunteers	Single-center, randomized, double-blind, single-dose, parallel phase I study	I	Completed	NCT05800418
Xian-Lian-Jie-Du Optimization Decoction	Efficacy of Xian-Lian-Jie-Du Optimization Decoction as an adjuvant treatment for prevention of recurrence of stage IIIB/IIIC colon cancer: a study protocol for a randomized controlled trial	Multi-center, randomized, double-blind, placebo-controlled trial	III	Recruiting	NCT05709249
Yiqi Wenjing Prescription	A randomized, double-blind, placebo-controlled, multicenter, phase III clinical trial of Yiqi Wenjing Prescriptions for preventing oxaliplatin-induced peripheral neuropathy	Randomized, placebo-controlled, double-blind, and multicenter clinical trial	III	Unknown status	NCT04690283
Fuzheng Yiliu Formulation	Based on the real world prospective cohort study, two-way analysis of the dominant population and corresponding phenotypic characteristics of patients with colorectal cancer treated by Fuzheng Yiliu therapy combined with adjuvant chemotherapy	Real world prospective cohort study	II	Recruiting	NCT04459754
Shenbai Granules	Clinical evidence-based evaluation of the efficacy of Shenbai Granules in preventing recurrent colorectal adenomas after polypectomy and its therapeutic mechanism	Randomized controlled clinical trial	II/III	Completed	NCT03616444

参数, 推测其与靶蛋白之间相互作用的可能性<sup>[45]</sup>) 等方法, 分析了四君子汤 (SJZD) 的 143 个化合物和 897 个潜在靶点, 寻找出 SJZD 治疗结直肠癌的潜在机制, 并通过细胞和小鼠模型证明了 SJZD 可通过 PI3K/Akt/

mTOR 途径, 诱导结直肠癌细胞自噬和凋亡, 抑制结直肠癌肿瘤的生长。

**1.2.2 对肿瘤免疫的影响** Foxo1 是人叉头转录因子家族的成员, 在多种癌症中调控细胞周期停滞、凋亡和

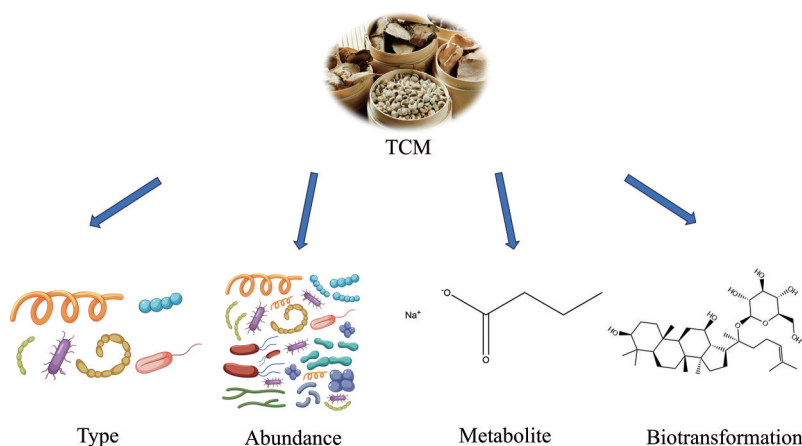
免疫反应<sup>[46]</sup>。细胞和动物实验证明,祛邪胶囊可通过减低 Foxo1 蛋白磷酸化,激活 Foxo1 介导的信号通路,上调 Fas、Bim 等凋亡蛋白和 caspase-3 的裂解促进细胞凋亡,同时提高 Th1/Th2 和 Th17/Treg 细胞的比例以及 T-bet 蛋白表达 (Th1 和 Th2 细胞的关键调节因子),下调 Foxp3 (Treg 细胞的关键调节因子) 激活抗肿瘤免疫反应,从而发挥抗癌作用<sup>[47]</sup>。由枸杞、覆盆子、淫羊藿、补骨脂、蛇莓、菟丝子、半夏、葛根、黄芩、桑椹、夏枯草、藤梨根和地黄组成的中药复方可以有效抑制荷瘤鼠的肿瘤生长,显著提高肿瘤组织和外周血中活化的 CD8<sup>+</sup> T 细胞、自然杀伤细胞和 Th17 细胞的比例,通过高效液相液质联用分析发现该中药复方中存在如桃叶珊瑚苷 (aucubin) 等多种调节免疫、抑制肿瘤生长的中药单体<sup>[48]</sup>。大黄附子败酱汤可以增加 PD-1<sup>int</sup>TCF1<sup>+</sup> T 细胞亚群,抑制前体耗竭 T 细胞向终末分化 T 细胞的转变,在肥胖微环境中抑制 CCL2 的表达,保留了前体耗竭 T 细胞,并增强 PD-1 检查点阻断的效果,改善 T 细胞低反应性的适应状态,减轻低度炎症,从而抑制与肥胖相关的结直肠癌的发生率<sup>[49]</sup>。

### 1.3 对肠道菌群的影响

人体肠道中约有 1 000 种细菌,受到遗传、饮食、经济状况在内的多种因素影响,因此每个人的肠道菌群都有其自身的特点,这与中医体质学说的观点不谋而合<sup>[50-52]</sup>。细菌与宿主相互作用,影响代谢、营养吸收、免疫和炎症反应等与多种疾病的发生发展相关的生理过程,肠道菌群的结构变化对结直肠癌的发生和发展起着重要的调节作用<sup>[53-55]</sup>。中药通过口服到达肠道后直接与肠道菌群相互作用,调节肠道菌群的组成,增加菌群相关的有益代谢物,并被菌群代谢为更具活性的物质 (图 2)。方剂对肠道菌群的调控在维持肠道平衡和防止结直肠癌发生方面发挥着重要作用,肠道微生

物群作为人体内的一个复杂的生态系统,是人体生物互作网络的一个部分,研究中药化学成分网与肠道微生物群这个有机整体间的相互作用,分析肠道菌群中不同微生物的丰度和种属的变化及中药组分含量与种类的改变,可以动态反映出中医对机体产生的影响,更好地从整体上理解中医整体观念的物质基础。

湿热是结直肠癌常见证候,中医认为过食肥甘厚腻可导致痰湿内生,日久化热变为湿热,这与饮食习惯导致肠道菌群的失衡的过程大致相似<sup>[56]</sup>。蚕梅方可降低与肥胖呈正相关的脱硫弧菌 (*Desulfovibrionaceae*) 的相对丰度,延缓偶氮甲烷 (AOM)/葡聚糖硫酸钠 (DSS) 和高脂饮食处理的小鼠的结直肠癌的发生发展<sup>[57]</sup>。Sui 等<sup>[58]</sup>发现,薏苡附子败酱散能够延缓携带腺瘤性息肉病基因 (APC) 突变的 APC<sup>Min/+</sup> 小鼠肠道肿瘤的发展,显著增加几种益生菌属 [双歧杆菌属 (*Bifidobacterium*) 和普氏菌属 (*Prevotellaceae*)] 的丰度,并降低了厚壁菌门 (Firmicutes) 中乳酸杆菌 (*Lactobacillus*) 和杜博伊氏菌 (*Duboisella*) 等细菌的数量,通过粪菌移植证明服用薏苡附子败酱散患者的肠道微生物群可预防肿瘤进展。另一项研究表明,薏苡附子败酱散可有效限制由肠毒性脆弱拟杆菌 (*Bacteroides fragilis*) 菌落失调诱发的 p-STAT3 介导的 M2 巨噬细胞促结肠癌作用<sup>[59]</sup>。结肠炎相关性结直肠癌 (CAC) 是结直肠癌的一种亚型,由胃肠道慢性炎症引起,常发生于炎症性肠病 (IBD) 如克罗恩病或溃疡性结肠炎的患者中<sup>[60]</sup>。补充益生菌和减少致病菌被认为是 CAC 的有效治疗方法<sup>[61,62]</sup>。乌梅丸能平衡拟杆菌门 (Bacteroidetes) 和厚壁菌门的数量,维持肠道微生物稳态,调节 NF- $\kappa$ B/IL-6/STAT3 通路,改善结肠炎症,预防 CAC<sup>[63]</sup>。葛根芩连汤 (GQD) 是治疗湿热证的经典方剂,研究表明,葛根芩连汤可通过减少巨单胞菌



**Figure 2** Interactions between bacteria and TCM. Some images in Figure 2 have been modified from Abstract Vectors by Vecteezy (<https://www.vecteezy.com/free-vector/abstract>)

属 (*Megamonas*) 和韦荣氏菌属 (*Veillonella*), 增加拟杆菌属 (*Bacteroides*)、阿克曼菌属 (*Akkermansia*) 和普雷沃菌属 (*Prevotella*) 产生更多短链脂肪酸, 降低五羟色胺 (5-HT) 水平, 减轻消化道症状, 抑制 NF- $\kappa$ B 和 TNF- $\alpha$  表达, 缓解全身炎症反应, 促进 ZO-1 和闭合蛋白的表达改善结直肠癌患者的肠道屏障功能, 并增加 CD4<sup>+</sup>CD8<sup>+</sup> 和 NKT 细胞增强机体免疫<sup>[64]</sup>。此外, GQD 联合 PD-1 阻断剂可改变肠道菌群结构, 增加产酸拟杆菌 (*Bacteroides acidifaciens*) 和拟杆菌目 S24-7 群 (*Bacteroidales\_S24-7\_group*), 减轻炎症并增强免疫, 抑制 CT26 肿瘤小鼠模型的肿瘤生长<sup>[65]</sup>。

中医根据阴阳五行学说, 将不同的事物依据特征进行归类, 以便更好地从整体认知事物及事物间的相互关系, 基于这种分类方法, 中医将疾病与药物相联系, 根据患者的机体所处的病理生理状态即证候, 确定治法治则, 并根据中药的特性及其在治疗中的作用确定不同药物间君、臣、佐、使的治疗地位, 构成一个完整的中药结构即中药复方。这种组合构成的药物网络, 使中药复方成为一个结构完整、功效明确的整体, 通过同时作用于多个靶点增效减毒, 协同治疗疾病。研究中药复方及其组方思路是全面系统理解中医理论、不同中药间协同效益以及药物成分与治疗效果间关系的关键。

## 2 单味药

中医认为, 不同的单味药具有不同的特性, 能够对机体产生不同的影响, 适当地对机体施加这些影响可以有效治疗各种疾病。通过大量的临床实践, 中医将这些特性归纳为性味归经。根据药性和中医原理选择合适的单味药是治疗结直肠癌的关键, 因此从整体上把握单味药的特性和对机体的影响是理解复方的组方思路的关键。

### 2.1 临床疗效

一些单味药的特性适用于结直肠癌的治疗, 可以有效减少结直肠癌治疗过程中的不良反应和各种并发症, 提高患者的依从性, 增强化疗效果, 延长患者的生存期<sup>[27]</sup>。

结直肠癌患者常因服用化疗药物而出现恶心、呕吐、口腔疼痛、骨髓抑制和免疫抑制等症状。人参、黄芪是中医常用的健脾补气药, 大量研究表明人参可缓解结直肠癌患者的 CRF、改善睡眠、增强食欲、提高生活质量<sup>[66-68]</sup>。一项基于 RCT 的荟萃分析研究了黄芪对结直肠癌患者的化疗不良反应的治疗效果。结果表明, 含有黄芪的药物能降低恶心呕吐的发生概率, 并对免疫功能正常的淋巴细胞及其特定亚群产生有益的影响, 激活免疫功能正常的淋巴细胞<sup>[69]</sup>。一项临床研究

表明, 黄芪配伍皂角在维持肠黏膜通透性、促进肠蠕动功能恢复、缩短肠鸣音恢复时间、降低结直肠癌手术患者血液中内毒素和 TNF- $\alpha$  水平等方面的作用与丙-谷二肽 (*L-alanyl-L-glutamine*) 相似<sup>[70]</sup>。一项荟萃分析研究了 13 项临床试验中云芝对癌症患者生存期的疗效, 结果显示, 与单独使用标准抗癌方案相比, 接受云芝治疗的患者的 5 年死亡率降低了 9%, 并且在接受化疗的乳腺癌、胃癌或结直肠癌患者中的治疗效果更为显著<sup>[71]</sup>。中药治疗可以调控基因表达对结直肠癌的发生发展起到预防作用, 一项关于覆盆子对结直肠癌患者影响的 I 期临床试验显示口服覆盆子粉对结直肠癌患者组织中的遗传和表观遗传生物标志物具有保护作用。20 名结直肠癌患者被给予每天 60 g 的覆盆子口服治疗, 持续 1~9 周。在治疗前后, 对相邻正常和结肠肿瘤组织进行活检, 发现覆盆子能够保护性地调节肿瘤和相邻正常样本中的细胞增殖、凋亡、血管生成和 Wnt 信号通路的生物标志物, 引发相关肿瘤抑制基因启动子区域的去甲基化, 并呈剂量依赖性<sup>[72]</sup>。中药复方配伍成分多变, 很难把握其基本规律, 除了临床针对性研究外, 研究人员还通过数据挖掘和统计分析, 从临床试验和临床病历中寻找有效的抗结直肠癌单味药。白花蛇舌草是中医治疗结直肠癌的常用药<sup>[73,74]</sup>, 一项关于以奥沙利铂为基础的化疗联合中药治疗结直肠癌的荟萃分析, 从 42 个 RCT 的数据中发现白花蛇舌草、黄芪和半枝莲 3 种单味药单用或联合使用可提高化疗方案的肿瘤反应率, 三药联合在治疗结直肠癌中可能具有潜在的协同效益<sup>[75]</sup>。在另一项以 5-氟尿嘧啶 (5-FU) 为基础的化疗联合中药治疗结直肠癌的荟萃分析中, 对特定单味药的敏感性分析发现, 白花蛇舌草、茯苓、半枝莲、莪术、白术、黄芪、薏苡仁和党参可以显著增加结直肠癌患者的肿瘤应答率, 提高以 5-FU 为基础的化疗方案治疗结直肠癌的疗效<sup>[76]</sup>。此外, 以卡培他滨为基础的化疗联合丹参、茯苓和甘草等单味药, 对结直肠癌的疗效同样优于单纯卡培他滨方案<sup>[21]</sup>。

### 2.2 对细胞的影响

单味药是由多种化学成分组成的复合体, 其有效成分可以通过促进凋亡、诱导细胞周期阻滞、改善肿瘤耐药、维持肠道屏障完整性、抑制炎症和增强机体免疫反应, 全面抑制结直肠癌肿瘤的生长、侵袭和转移<sup>[77,78]</sup>。

**2.2.1 对肿瘤细胞的影响** 夏枯草乙醇提取物通过抑制 STAT3 通路激活, 提高 Bax/Bcl-2 比率, 诱导细胞凋亡, 减低 Cyclin D1 和 CDK4 表达阻碍细胞增殖, 下调 VEGF-A 和 VEGFR-2 抑制肿瘤血管生成, 从而抑制体内结直肠癌的生长<sup>[79]</sup>。西洋参可以增加 HCT116 人结

直肠癌细胞 p53 和 p21 蛋白表达,降低 MEK 磷酸化水平,使细胞周期被阻滞在 G0/G1 期,同时西洋参可以降低 p21 缺失的 HCT116 的细胞活性,提高 Bax 和裂解的 caspase-3 蛋白的水平,诱导细胞凋亡<sup>[80]</sup>。据报道,西洋参可抑制促癌上皮损伤和异常隐窝病灶的形成,抑制潜在或已知的具有促瘤作用的蛋白质的活化,保持结肠环境代谢平衡,预防 CAC<sup>[81]</sup>。除了直接影响肿瘤的生长,中药还可以逆转肿瘤耐药表型,增强化疗敏感性,研究表明穿心莲、丹参、白花蛇舌草、槐花、莪术和蟾蜍等中药可降低结直肠癌的耐药性,增强 5-FU、奥沙利铂等化疗药物的细胞毒性<sup>[82]</sup>。单味药中的有效成分具有不同的组织依赖性,这使得单味药的靶点过于分散,无法在特定疾病中预测其作用机制。对于多成分、多靶点药物来说,很难确定其与结直肠癌治疗靶点互作的最终效果。钩吻常用于治疗胃肠道癌症,通过基于网络药理学的分析,研究人员获得了其与结直肠癌相关的 53 个活性化合物和 136 个潜在靶点,并确定了其潜在的中心靶点和影响结直肠癌的主要生物学过程。分析表明钩吻主要通过调控不同的靶点 (MAPK3、HSP90AA1、JUN、表皮生长因子受体、CDK1、TNFCCND1、ESR1、PRKACA 和 CCNA2),以及 FoxO、PI3K-Akt 等信号通路,影响机体磷酸化功能,抑制结直肠癌<sup>[83]</sup>。

**2.2.2 对肿瘤免疫的影响** 一项基于网络药理学的研究发现,人参的 22 种活性成分和 202 个与结直肠癌肿瘤微环境 (TME) 密切相关的靶点。通过蛋白质-蛋白质相互作用 (PPI) 网络分析,确定了 SRC、STAT3、PIK3R1、HSP90AA1 和 Akt1 为可能的核心靶点,并通过基因表达谱交互分析 (GEPIA) 和人类蛋白质图谱 (HPA) 数据库验证了核心目标靶点在结直肠癌组织中的 mRNA 水平的显著变化。分子对接表明,人参皂苷 Rh2 等人参的主要化学成分对核心靶点具有稳定的结合活性,表明人参可能通过作用于 SRC、STAT3、PIK3R1、HSP90AA1 和 Akt1 等核心靶点,调节 T 细胞共刺激、淋巴细胞共刺激、生长激素反应和蛋白质摄入等生物学过程,从而调节结直肠癌的肿瘤微环境<sup>[84]</sup>。广藿香精油可以显著增加杯状细胞和 Paneth 细胞的数量,上调紧密连接和黏附分子的表达,加强肠道上皮屏障。此外,广藿香精油及其衍生物广藿香醇和广藿香油,可以将 M1 型巨噬细胞转变为 M2 型巨噬细胞,并重塑 APC<sup>Min/+</sup> 小鼠的炎症微环境。同时,抑制小鼠的脾脏、血液、肠系膜淋巴结 (MLNs) 和 Peyer's 斑 (PPs) 中 CD4<sup>+</sup>CD25<sup>+</sup> 细胞,刺激 CD4<sup>+</sup>CD8<sup>+</sup> 细胞<sup>[85]</sup>。

### 2.3 对肠道菌群的影响

单味药与肠道菌群间相互作用构成复杂的交互网

络,一方面单味药可以调节菌群的组成,影响菌群代谢;另一方面,肠道菌群对单味药的代谢可产生更多的活性成分。西洋参可对肿瘤产生免疫抑制作用,但体内摄入后生物利用度较低。通过肠道菌群的生物转化,西洋参可被转化为人参皂苷化合物 K,调节与细胞凋亡相关的蛋白质,对肿瘤细胞产生促凋亡作用<sup>[86-89]</sup>。西洋参能减少西式饮食饲养、AOM 诱导小鼠中的软壁菌门 (Tenericutes),增加拟杆菌门 (Bacteroidetes),促进西洋参向化合物 K 等生物活性分子的生物转化<sup>[90]</sup>。西洋参通过增加厚壁菌门和亚麻酸丰度,减少拟杆菌目 (Bacteroidales)、疣微菌门 (Verrucomicrobia)、苹果酸和 2-羟基丁酸,西洋参可恢复 AOM/DSS 处理小鼠健康的代谢组和微生物群谱,减少炎症细胞因子,如 IL-1 $\alpha$ 、IL-1 $\beta$ 、IL-6、G-CSF 和 GM-CSF 的释放,延缓 CAC 的形成<sup>[91]</sup>。研究发现,APC 突变的结肠癌小鼠血清中 4 种尿毒症毒素 (硫酸甲酚、硫酸甲酚葡萄糖苷酸、硫酸吲哚酚和苯磺酸) 积累。这些尿毒症毒素很可能是由肠道菌群产生,与促炎细胞因子 IL-6 的表达增加和脂质代谢紊乱相关。肉豆蔻能够调节肠道菌群降低血清中尿毒症毒素和 IL-6 的水平,恢复紊乱的脂质代谢,减少 APC<sup>Min/+</sup> 小鼠的肠道肿瘤发生<sup>[92]</sup>。木耳可恢复由 AOM/DSS 处理引起的 CAC 小鼠中梭菌属 (*Clostridium*)、苏黎世杆菌属 (*Turicibacter*)、螺旋体属 (*Oscillospira*)、脱硫弧菌属 (*Desulfovibrio*)、阿克曼菌属和拟杆菌属 (*Parabacteroides*) 的丰度变化,通过 NF- $\kappa$ B 途径减轻肠道炎症<sup>[93]</sup>。通过微生物群和代谢组学的联合分析显示,螺旋体属与 2'脱氧尿苷之间存在正相关,而拟杆菌属、肌酐和 1-棕榈酰溶血磷脂胆碱 (1-palmitoyl lyso-phosphatidyl choline) 之间存在负相关,表明木耳通过调节肠道菌群和血清代谢物,上调游离脂肪酸受体 2 (free fatty acid receptor 2) 和  $\beta$ -抑制蛋白 ( $\beta$ -arrestin 2),抑制 NF- $\kappa$ B 途径,减少炎症细胞因子,缓解 CAC 小鼠的炎症反应。

单味药是连接中药复方与中药单体的枢纽,整体认知单味药的治疗效果和作用机制,是研究人员深入研究中药复方及其配伍思路的基础,数百种化学分子组成的单味药与机体复杂的生物调控网络间的相互作用既是中药疗效的物质基础,也是解释中医治疗理念的关键。

### 3 中药单体

中药单体是中药体系的最后一级,是发挥药效的最小单元,但中药单体仍具有多重药理活性和多靶点效应的特点,这使得中药单体在药物研究领域受到了广泛关注,许多中药单体已被证明对结直肠癌具有治疗作用,同时这一多靶点特性使整体认知单体的药理

学作用,进行不同单体间的组合成为可能<sup>[94]</sup>。

### 3.1 临床疗效

中药单体药效物质基础和药理作用机制比较明确,质量稳定,可以更好地应用于临床。梓醇具有抗炎和抗增生活性<sup>[95,96]</sup>。一项三臂随机盲法对照临床试验显示,与贝伐珠单抗相比,梓醇可降低结直肠癌手术患者血清中 CA19-9、CEA、MMP-2 和 MMP-9 的水平、延长 OS,且无严重并发症<sup>[97]</sup>。结肠上皮细胞在环境或遗传因素的作用下发生表型变化,通过不同的细胞途径经历一系列分子事件后从正常细胞转化为中间腺瘤(或息肉),并最终转化为晚期腺癌<sup>[98,99]</sup>。一项多中心双盲随机对照研究调查了小檗碱对预防息肉切除术后结直肠腺瘤复发的影响。1 108 名参与者被随机分配到小檗碱组和安慰剂组。结果显示,与对照组相比,服用小檗碱的试验对象腺瘤复发率降低了 23%<sup>[100]</sup>。中药单体仍具有类似中药的多靶点性质,单体配伍具有潜在的治疗潜力。姜黄素能改善结直肠癌患者的生活质量,槲皮素的摄入可以降低结直肠癌的发病率,一项研究发现,姜黄素和槲皮素联合使用可延缓家族性息肉病患者回肠和直肠腺瘤的发展,且无明显不良反应<sup>[101-105]</sup>。中医的体质学说认为,个人禀赋会影响疾病的转化,因患者的体质选择适合的中药,可以提高治疗效果。有研究表明,基因可能影响机体对药物的敏感性<sup>[106]</sup>。一项流行病学研究发现,饮食中黄酮类化合物摄入在结直肠癌发生过程中的作用可能因不同的黄酮亚类和与致癌物代谢相关的个体遗传变异而有所不同,饮食中黄酮类化合物的摄入,特别是黄酮醇(flavonols)和儿茶素(catechins),与降低结直肠癌的风险相关,CYP1A1 rs4646903 基因变异似乎会影响黄酮醇对结直肠癌的抑制作用。CC 纯合子携带者摄入较高黄酮醇时,结直肠癌的发病率显著降低<sup>[107]</sup>。

### 3.2 对细胞的影响

中药单体是中药药理作用的最终执行者,它与不同靶标分子结合并激活相应通路来抑制肿瘤生长,调节肿瘤微环境,多靶点协同治疗疾病。中药单体针对生命活动的全过程进行调控,影响复制、转录、翻译、表观遗传及翻译后修饰调节机体生命活动全过程。

**3.2.1 对肿瘤细胞的影响** 芹菜素通过上调 TAGLN 降低 Akt 在 Ser473 和 Thr308 处的磷酸化以及 MMP-9 的表达,降低结直肠癌细胞的增殖迁移能力<sup>[108]</sup>。在 HCT116 细胞中,广藜香酮通过上调 LC3-II 的表达、抑制 mTOR 磷酸化和 PI3K/Akt/mTOR 信号通路中的 Akt 激活,诱导细胞自噬和凋亡<sup>[109]</sup>。白藜芦醇可通过上调 SET 域含赖氨酸甲基转移酶 7/9 (SET7/9) 的表达激活 p53 介导的细胞凋亡,抑制 HCT116、CO115 和 SW48 等

结直肠癌细胞活力<sup>[110]</sup>。在 HT-29 细胞中,苍术内酯 I 可激活 caspases 和促凋亡 Bcl-2 家族蛋白,从而对结直肠癌起到抗增殖作用<sup>[111]</sup>。小檗碱具有明显的抗结直肠癌活性,可通过上调 PTEN 抑制 PI3K-Akt-mTOR 信号通路,降低 aquaporins (1、3 和 5) 的表达,抑制结直肠癌的生长和迁移<sup>[112]</sup>。黄芩苷通过影响细胞周期停滞、p53 依赖性凋亡以及内源性和外源性 TGF $\beta$ 1 诱导的结直肠癌细胞 EMT,抑制 TGF $\beta$ /Smad 通路阻止结直肠癌细胞的生长和转移,并减少 CSC 的标记蛋白,抑制结直肠癌细胞中 CSC 样细胞团的形成<sup>[113]</sup>。据报道,吴茱萸碱可抑制结直肠癌 CSC 中控制 Wnt 和 Notch 信号通路的基因表达,从而消除 CSC<sup>[114,115]</sup>。组蛋白去乙酰化酶调节多种疾病,山柰酚通过抑制人类组蛋白去乙酰化酶诱导组蛋白复合物 H3 的高乙酰化,介导 HCT116 肿瘤存活率的浓度依赖性下降<sup>[116,117]</sup>。

**3.2.2 对肿瘤免疫的影响** 淫羊藿次苷 I [icariside I (ICA-I)] 可以靶向 TRPV4,浓度依赖性诱导线粒体超氧阴离子产生,促进线粒体 ROS 生成,引发线粒体功能障碍、氧化磷酸化和电子传递链损伤,导致线粒体产生和释放过量的线粒体活性氧,诱导细胞内钙离子增加和线粒体 DNA 释放,触发癌细胞中胞质 DNA 感应的 STING/IFN-I 通路,促进肿瘤相关巨噬细胞的 M1 极化。同时,细胞内的氧化线粒体 DNA 片段被肿瘤微环境中的免疫细胞吸收,放大了免疫反应,提高树突状细胞的交叉启动能力并增强肿瘤特异性免疫细胞的激活,ICA-I 和抗- $\alpha$ -PD-1 单克隆抗体的序贯给药有助于克服肿瘤的抗-PD-1 阻断剂耐药<sup>[118]</sup>。牡荆素(vitexin)通过 VDR 调节吩嗪生物合成样结构域蛋白(PBLD)的转录激活,使其易位到细胞核中以发挥转录活性,促进巨噬细胞向 M1 型极化,从而缓解从慢性结肠炎到结直肠癌的转变<sup>[119]</sup>。双氢青蒿素(dihydroartemisinin)可以抑制 AOM/DSS 诱导的结肠炎相关结直肠癌模型早期阶段的炎症反应和随后的肿瘤形成,在结肠炎相关结直肠癌晚期,双氢青蒿素通过增强肿瘤细胞周期阻滞和凋亡来抑制肿瘤生长,并通过 TLR4 信号通路来抑制巨噬细胞的激活逆转结肠黏膜巨噬细胞浸润,降低促炎细胞因子的表达,全周期给予双氢青蒿素提高了双氢青蒿素对结肠炎相关结直肠癌的治疗效果并呈时间依赖性<sup>[120]</sup>。

### 3.3 对肠道菌群的影响

中药单体可以影响肠道内细菌的丰度与占比,改变菌群代谢谱,发挥抗癌作用。

一些人参多糖可影响细菌产物,如短链脂肪酸和多胺代谢物,在肠道产生局部效应,从而为宿主带来健康益处。研究表明,人参多糖通过改变肠道菌群的结

构,增加细菌代谢产物戊酸,降低L-犬尿氨酸和Kyn/Trp的比例,抑制调节性T细胞,刺激 $T_{eff}$ 细胞,从而增强 $\alpha$ -PD-1单克隆抗体的抗肿瘤作用<sup>[121]</sup>。肠道菌群的失调会降低肠黏膜屏障的功能,并增强细菌的转运,导致炎症和感染,小檗碱可通过重塑肠道菌群上调产生短链脂肪酸的细菌数量,抑制TLR4/p-NF- $\kappa$ Bp65/IL6/p-STAT3炎症-癌症转化途径,增加occludin和ZO-1,治疗CAC<sup>[122]</sup>。上皮细胞的快速增殖和肠道菌群与免疫系统间相互作用会导致肠道受损,进而诱发结肠炎。5-FU是临床上常用的化疗药物,但5-FU和甲氨蝶呤常引起黏膜炎症<sup>[123]</sup>。隐丹参酮通过改变与脂质代谢密切相关的穆里杆菌(*Muribaculaceae*)和乳酸杆菌(*Lactobacillus*)的丰度,可以缓解5-FU/CPT11诱导的CAC小鼠结肠炎<sup>[124]</sup>。羧甲基苜蓿多糖(carboxymethyl pachyman)能保护CT26肿瘤小鼠免受5-FU引起的肠黏膜炎的影响,通过NF- $\kappa$ B、MAPK/p38和Nrf2途径改善肠黏膜炎,并恢复正常的肠道菌群,增加拟杆菌、乳酸菌(*Lactobacilli*)、丁酸菌和乙酸菌的丰度,以及短链脂肪酸的浓度<sup>[125]</sup>。肠道菌群可直接干扰中药单体在体内的吸收和代谢,介导生物转化,改变中药单体的药理和生物活性,并将中药单体代谢为特定分子,影响其吸收和药效<sup>[126]</sup>。细菌定向酶原药疗法是通过表达转化酶的肿瘤特异性富集细菌在肿瘤组织周围激活毒性较低的前体药物,以更好地靶向肿瘤以减轻药物对健康组织损伤的一种技术<sup>[127]</sup>。Jafari等<sup>[128,129]</sup>利用大肠杆菌DH5 $\alpha$ -lux/ $\beta$ G的 $\beta$ -葡糖醛酸酶过表达能力,通过微生物将黄芩苷转化为毒性更强的苷元黄芩素,治疗携带CT26肿瘤的小鼠。结果表明,大肠杆菌DH5 $\alpha$ -lux/ $\beta$ G增强了黄芩苷的细胞毒性和抗肿瘤作用,且无不良反应。

寻找中药中的活性中药单体可以使中药研究更加细化和准确,但解析事物是为了更好地理解整体,中药的临床疗效通常是通过中药复方加减单味药实现的,中药复方通过多种成分的协同作用,对结直肠癌患者进行精准调控,从而更好地发挥疗效,恢复身体机能,体现了精准医学和整体医学的理念。从多维度、整体性的角度认识中药的治疗机制,将中药看成一个有机整体,系统全面地研究其对机体的药理作用,有助于从中药中发现更多有效的抗癌药物。

#### 4 总结与展望

单靶点药物只能控制或缓解疾病进展,很难彻底治愈复杂的结直肠癌<sup>[130]</sup>。临床应用广泛、安全性高的中药在治疗结直肠癌上具有独特优势,尽管许多试验缺乏盲法可能导致治疗结果有偏差,但中药治疗结直肠癌的作用已得到越来越多的认可。正常肠道在遗传

及表观遗传改变的逐步积累中发展成结直肠癌,这一漫长的过程受到诸如炎症、饮食、肠道菌群等多种因素的影响<sup>[131]</sup>。与传统细胞毒性药物直接杀伤肿瘤细胞,造成正常机体损害,伴随明显的不良反应不同,中药具有多靶点、多成分、多功能的特点,符合结直肠癌发生和演变的复杂机制。中药通过整体调节身体机能,改善机体内稳态,去除诱发癌变的病理因素,清除促进肿瘤生成的微环境,改善肠道菌群,恢复正常的基因表达谱,预防甚至逆转肿瘤的进程,这是中医未病先治,即病防变思想的集中体现。中药药理研究从最初的中药复方到单味药,再到中药单体,逐步阐明了中药治疗结直肠癌的物质基础和分子机制,但是这些研究往往局限于特定化合物及信号通路,不能全面系统地解释中药,尤其是中药复方在治疗疾病时的整体作用和对机体的综合影响。随着人工智能及生物信息学的发展,通过数学模型及机器学习去模拟中药与机体间的复杂作用网络,构建一个药效系统的整体结构及其对个体扰动的反应的数学模型将更好地解释中药治疗结直肠癌的作用机制<sup>[132]</sup>。

针对中药单体的作用机制的研究非常重要,这是构建中药复方治疗疾病宏观模型的基础,只有从分子层面揭示作用机制,中医药才能真正融入现代医学,使古老的中药在确凿的证据基础上得到更合理的应用。但是,中药机制研究不能仅仅停留于单一化合物作用机制的解析,更应继续探讨中药整体调控网络,挖掘中药配伍背后的科学内涵。随着生物信息学的发展,高通量生物信息学检测使研究者更全面地了解中药治疗涉及的分子靶点和信号通路,为整体认知中药药理作用,模拟构建药物机体互作网络提供了可能性。

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