中药活性成分调控血管新生的研究进展

杨 婷[1], 张莉君[1], 黄 睿[1], 兰海月[1], 张 宏[1], 栾 鑫[1*], 张卫东[1,2*]

(1. 上海中医药大学交叉科学研究院, 上海 201203; 2. 海军军医大学药学院, 上海 200433)

摘要: 血管新生已成为临床上治疗多种疾病的靶点, 一方面可通过抑制血管新生治疗癌症、动脉粥样硬化和糖尿病视网膜病变等多种血管生成过度的疾病; 另一方面通过促进血管新生改善由于血管生成不足而造成的心肌梗死、心肌缺血/再灌注损伤、脑卒中和伤口久愈不合等缺血性疾病症状。研究表明, 许多中药有效成分可通过不同途径调节血管新生从而有效治疗相关疾病。因此, 本文从抗血管与促血管两方面, 总结了中药活性成分对血管新生的调控, 并对其作用机制进行归纳, 为与血管新生相关疾病的治疗提供依据。

关键词: 中药; 活性成分; 血管新生调控; 血管内皮生长因子; 血管内皮细胞

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Research progress in the regulation of angiogenesis by active ingredients of traditional Chinese medicine

YANG Ting[1], ZHANG Li-jun[1], HUANG Rui[1], LAN Hai-yue[1], ZHANG Hong[1], LUAN Xin[1*], ZHANG Wei-dong[1,2*]

(*1. Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China; 2. School of Pharmacy, Naval Medical University, Shanghai 200433, China*)

Abstract: Angiogenesis is the formation of new capillaries from pre-existing vasculature, which plays a critical role in several diseases. Under the normal physiological conditions, only about 0.5% of endothelial cells (ECs) undergo mitosis, while the most ECs are in a resting state. Angiogenesis is a dynamic process in which ECs shift from resting to activated state, including three basic steps: ① excessive vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), platelet-derived endothelial growth factor (PDGF) and other pro-angiogenic factors secreted by ECs can promote the germination of ECs in the original blood vessels; ② the sprouts are continuously elongated through the proliferation of ECs and the degradation and migration of basement membrane. At this time, the ECs present two phenotypes with filamentous feet and strong proliferation ability; ③ the buds are continuously elongated to form a tubular structure and connect with adjacent blood vessels, and the junction is wrapped by wall cells and basement membrane to form new blood vessels. Nowadays, angiogenesis has become a target for clinical treatment of multifarious diseases. On one hand, anti-angiogenesis is used to treat various diseases with excessive angiogenesis, such as cancer, atherosclerosis, and diabetic retinopathy, etc. On the other hand, the diseases caused by insufficient angiogenesis, including myocardial infarction, myocardial ischemia/reperfusion injury, stroke, wound long-term healing and other ischemic diseases can be improved by pro-angiogenesis therapy. Large numbers of researches have shown that many active ingredients of traditional Chinese medicine can effec-

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*通讯作者 Tel / Fax: 86-21-81871244, E-mail: wdzhangy@hotmail.com; luanxin@shutcm.edu.cn

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tively treat the previously mentioned diseases by regulating angiogenesis in different ways. Therefore, the anti- and pro-angiogenesis effects of some active ingredients derived from traditional Chinese medicine and their mechanism were summarized in this manuscript, arming to provide theoretical basis for the development of new drugs for the treatment of angiogenesis-related diseases.

Key words: traditional Chinese medicine; active ingredient; angiogenic regulation; vascular endothelial growth factor; endothelial cell

“血管新生”最早由英国外科医生约翰•亨特于1787年提出[1], 指原有血管的基础上生成新血管的过程。研究表明血管新生与组织生长、伤口修复和女性生殖周期等生理过程密切相关[2]。在正常生理条件下, 仅有约0.5%的内皮细胞发生有丝分裂, 其余内皮细胞均处于静息状态[3]。血管新生是内皮细胞从静息状态转变到激活状态的动态过程。血管生成分为3个基本步骤: 首先, 内皮细胞被机体分泌的大量血管内皮生长因子 (vascular endothelial growth factor, VEGF)、碱性成纤维细胞生长因子 (fibroblast growth factor, FGF) 和血小板源性内皮细胞生长因子 (platelet-derived growth factor, PDGF) 等促血管生成因子激活使其在原有血管处“发芽”; 然后, 新芽通过内皮细胞增殖、基膜降解和迁移而不断伸长, 且内皮细胞呈现出具有丝状足的顶端细胞和增殖能力较强的干细胞两种表型; 最后, 芽不断伸长形成管状结构, 并与邻近的血管连接, 连接处被壁细胞和基膜包裹从而形成新的血管[1,4]。

研究表明, 血管生成异常与70多种疾病的发生、发展密切相关, 随着研究的不断深入, 该数值还在逐年递增[2]。一旦体内促血管生成因子和抗血管生成因子的动态平衡被打破, 不受机体控制的病理性血管过度生成将导致恶性肿瘤、动脉粥样硬化、视网膜病变和子宫内膜异位症等疾病发生。而心肌梗死、脑卒中和伤口久愈不合等缺血性疾病发生的主要原因是内皮细胞功能紊乱, 造成血管畸形或衰退, 从而阻碍新的血管形成。

《素问•脉要精微论》提出“脉”乃是气血运行的通道。络脉是经脉的细小分支, 络主血, 发挥运行气血, 濡养、滋润脏腑肢体的功能[5]。血管生成相关的疾病与络脉阻滞、络脉空虚和络脉损伤等密切相关。络脉病变初始时表现为气滞于经, 久而入血伤络。络脉中气血津液运行不畅, 无法濡养脏腑肢体, 从而导致肿瘤、缺血性心脑血管疾病等的发生[6]。辛味通络、虫类通络和络虚通补等是络病治疗的有效方法, 临床上首选药物多为人参、黄芪、姜黄、川芎、丹参和苦参等具有补气养血、活血化瘀活性的中药[7]。因此, 本文介绍了血管生成相关疾病, 总结了来源于活血化瘀、补气养血、清热养阴和清热解毒类中药活性成分对血管生成的调控, 从抗血管与促血管两方面进行论述, 并归纳其作用机制 (图1)。

1 血管生成相关疾病

在已发育完全的成年个体中, 绝大部分血管生成过程受到抑制, 处于静息状态, 体内抗血管与促血管因子之间实现平衡。当机体受到某些刺激时, 血管生成过程会被激活。过度促血管因子刺激会导致病理性的血管过度新生, 其与肿瘤、视网膜病变和动脉粥样硬化 (atherosclerosis, AS) 等疾病的发生、发展密切相关[2]; 当血管生成严重不足时, 则可能诱发严重的心肌梗死、心肌缺血/再灌注损伤、脑卒中或伤口久愈不合等疾病[2]。

1.1 血管生成过度相关疾病

1.1.1 肿瘤 在正常生理过程中, 新生血管会迅速成熟并趋于稳定。而在肿瘤生长过程中, 肿瘤就如同一个“永远不会愈合的伤口”[8], 通过不断地过度分泌促血管生长因子, 诱导现有血管出芽, 形成新的血管结构, 为其生长提供氧气与营养, 同时新生的肿瘤血管也成为肿瘤细胞转移的重要通道。但是这些血管在结构上是不规则、扭曲和杂乱无章的, 它们没有静脉、动脉和毛细血管的分化[9], 而且血管周围细胞与内皮细胞之间的黏附在VEGF的影响下变得不那么紧密, 导致肿瘤中所形成的血管网络是渗漏和出血的。随着肿瘤肿块的增大, 血管渗漏增加了间质压力, 阻碍了肿瘤组织内氧气与营养物质的供给。受此种不利情况刺激, 肿瘤细胞会进一步加剧血管生成, 形成恶性循环[10]。通过抑制肿瘤内部血管新生有望打破该恶性循环过程, 阻滞肿瘤生长, 诱使肿瘤细胞凋亡或者坏死。1971年, 美国福克曼教授首次提出通过抑制血管生成实现“饥饿”肿瘤的目的[11], 其后一系列包括贝伐单抗在内的抗血管治疗药物已经得到批准上市, 抗血管生成治疗已成为除手术治疗、放疗和化疗以外的重要抗肿瘤治疗方法。

1.1.2 动脉粥样硬化 AS是炎症反应在体内缓慢发展的过程。在该过程中, 动脉壁结构发生改变导致AS斑块的形成。在AS斑块内存在大量不成熟的病理性

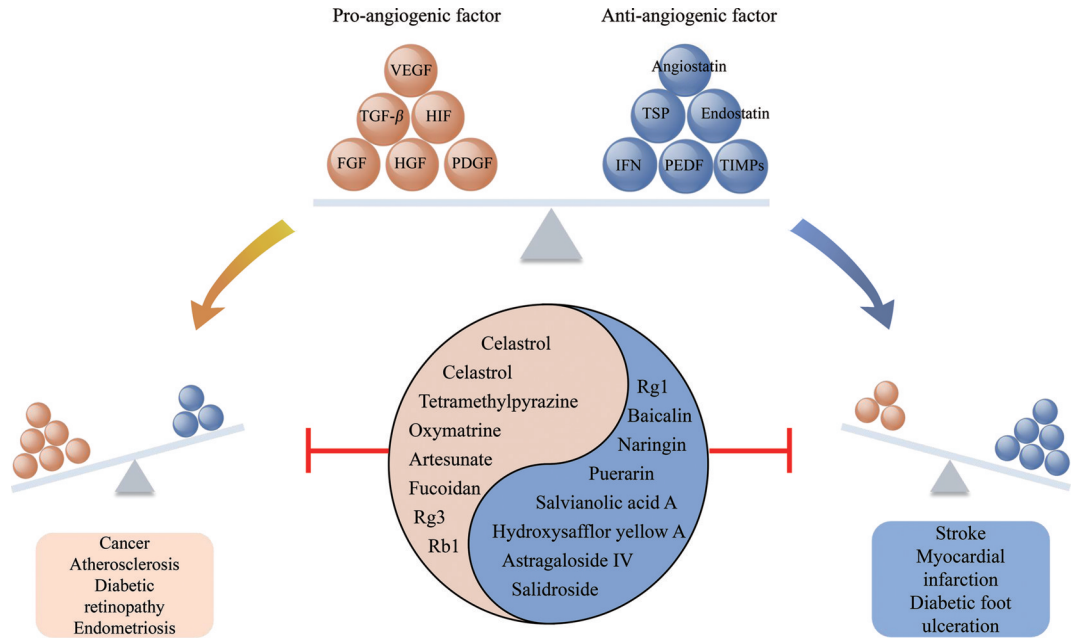

Figure 1　The active ingredients of traditional Chinese medicine (TCM) regulate angiogenesis. VEGF: Vascular endothelial growth factor; FGF: Fibroblast growth factor; PDGF: Platelet-derived growth factor; HIF: Hypoxia inducible factor; TGF-β: Transforming growth factor-β; HGF: Hepatocyte growth factor; TSP: Thrombospondin; IFN: Interferon; PEDF: Pigment epithelium-derived factor; TIMPs: Tissue inhibitors of metalloproteinases

新生血管, 这些新生血管为血液中炎症细胞、脂质和红细胞的渗漏提供便利条件。此外, 这些血管仅有单层内皮细胞构成, 极不稳定, 一旦斑块内血管破裂将会导致出血甚至整个斑块破裂, 加重管腔狭窄, 增加诱发冠心病、卒中和心肌梗死等急性心脑血管疾病的风险[12]。据报道, 多种抑制肿瘤血管生成的药物用于治疗AS取得了良好的效果。例如, VEGFR抑制剂阿西替尼 (anxitinb) 能有效地抑制 ApoE$^{-/-}$Fbn1$^{C1039G+/-}$小鼠AS斑块内的血管生成继而增加AS斑块稳定性, 降低斑块内出血的发生率, 同时小鼠心功能得到改善, 心肌梗死小鼠数量大大减少[13]。首个具有知识产权的国产抗血管药物恩度 (Endostar) 能抑制血管内皮细胞生长因子受体2 (vascular endothelial growth factor receptor 2, VEGFR-2) 磷酸化而减少非小细胞肺癌患者颈动脉斑块中血管的生成[14]。通过抑制斑块内血管生成降低患者恶化风险有望成为未来治疗AS有效治疗策略之一。

1.1.3　糖尿病视网膜病变　糖尿病视网膜病变 (diabetic retinopathy, DR) 是糖尿病的主要微血管并发症之一。当机体长期处于高血糖状态时, 将会造成微循环障碍、血流速度缓慢和视网膜中出现供氧不足的情况。视网膜组织为改善缺氧状态, 会诱导大量新生血管的形成。然而, 这些新生血管可能会渗入玻璃体甚至导致牵引性视网膜脱离, 导致视力降低甚至失明的严重后果[15-17]。目前临床上治疗DR的有效方案是通过向玻璃体内注射抗VEGF药物, 阻碍VEGF信号通路介导的人视网膜内皮细胞和脉络膜视网膜内皮细胞的增殖与迁移, 抑制视网膜血管生成, 从而防止DR恶化[18]。

1.1.4　子宫内膜异位症　子宫内膜异位症 (endometriosis, EMs) 是一种血管生成依赖性疾病。在EMs患者的异位病灶组织中, 多种促血管生成因子 (VEGF、FGF) 表达明显增高, 病灶周围有大量的新生微血管形成, 这些血管为EMs病变的发展提供必要的氧气和营养供应[19,20]。因此, 通过减少甚至抑制血管生成可有效减缓病灶的生长。

1.2　血管生成不足相关疾病

1.2.1　糖尿病足溃疡　糖尿病足溃疡 (diabetic foot ulceration, DFU) 在中晚期糖尿病人群中发病率较高。这类患者通常表现为末梢血管血液供应不足, 肢体组织因局部缺血引起感染、溃疡, 伤口长期受到高血糖的影响而无法愈合, 进一步对深部组织造成不可逆转的损伤[21]。有研究表明, 通过激活PI3K/AKT和MAPK信号通路、促进VEGF分泌能够诱导血管新生而促进创面愈合[22]。Lin等[23]进一步证明miRNA-217抑制剂促进DFU大鼠溃疡创面愈合的作用机制与调节大鼠体内缺氧诱导因子-1α (hypoxia inducible factor-1α, HIF-1α)/VEGF和炎症因子的表达有关。由此可知, 通

过促进溃疡组织内微血管生成而促进末梢血管循环, 使组织得到充足的血液供应, 修复病变部位是治疗DFU的有效方法之一[24]。

1.2.2 心肌梗死 心肌梗死 (myocardial infarction, MI) 是一种常见的缺血性心脏病, 诱发该疾病的主要原因是冠状动脉粥样硬化斑块破裂而形成继发性血栓, 导致冠状动脉闭塞、心肌细胞持续缺血最终造成心肌细胞大量死亡[25,26]。治疗MI的关键在于增加心脏血液灌注, 满足心肌组织氧气和营养供应, 进一步恢复缺血区血液供应。目前, 促进血管新生已成为缺血性心脏病的研究热点。多项研究证明, 若增加HIF-1α、VEGF-A和bFGF等促血管生长因子的表达就能够促进血管新生、提高心肌修复水平并减轻心梗后大鼠的心衰程度[27]。此外, 启动血管内皮细胞的活性氧 (reactive oxygen species, ROS)-内质网应激-自噬轴也可诱导急性心肌缺血后的代偿性血管生成, 恢复心脏正常功能[25]。

1.2.3 脑卒中 脑卒中俗称中风, 是由于大脑前动脉 (脑动脉) 发生闭塞或出血而阻碍局部脑组织供血, 病灶内神经元大量坏死而引起脑功能障碍[28]。根据卒中患者脑部梗死灶的受损程度可分为完全梗死脑组织区域和处于缺血状态但未完全梗死的缺血半暗带[29]。研究表明, 在动物模型和患者中, 卒中后新血管的形成不仅可以补充脑缺血区的血流量, 增加缺血半暗带的血流灌注, 还可以促进神经发生, 改善神经功能[30]。

2 抑制血管新生中药活性成分及其作用机制

中医常选用具有活血化瘀、祛痰除湿功效的中药祛除瘀血、痰浊以疏通脉络, 并配伍清热解毒中药消除热性病因, 同时配伍补虚类中药扶助正气, 恢复脉络环境[31]。大量研究表明, 抑制血管生成的中药多具有活血化瘀、祛痰除湿、清热解毒或补气养血的功效, 这些中药的活性成分能够通过不同途径调控血管生成, 抑制血管新生, 对临床治疗异常血管生成性疾病有重要意义。

2.1 来源于活血化瘀类中药的活性成分

2.1.1 姜黄素和β-榄香烯 姜黄中的主要活性物质分为姜黄素和挥发油成分β-榄香烯两大类。多项研究证实姜黄素和β-榄香烯对血管生成均具有显著的抑制作用。姜黄素不仅能够通过影响miR-1275和miR-1246的靶基因 *VEGFB* 和核因子κB (nuclear factor κB, NF-κB) 作用蛋白表达来抑制NF-κB活性, 减少角膜内血管生成[32]; 而且高剂量的姜黄素还能抑制内皮素-1和VEGF表达而减少肝窦内皮细胞外基膜的形成, 显著减轻肝窦的毛细血管化, 延缓肝纤维化的发展[33]。

肿瘤干细胞可以产生大量“血管干细胞来源的内皮前体细胞”, 诱导肿瘤血管生成因子分泌, 具有较强的促血管生成能力。β-榄香烯具有靶向CD44$^+$胃癌干细胞 (gastric cancer stem-like cells, GCSCs) 同时下调Notch-1和Hes1的表达的能力, 从而抑制GCSCs增殖, 减少胃癌内血管生成[34]。不仅如此, β-榄香烯还能显著抑制VEGF诱导的大鼠主动脉环和鸡胚尿囊膜血管生成; 且经β-榄香烯治疗后, 原发性黑色素瘤中血管生成标志物CD34表达相对较少, 肿瘤生长及肺转移均受到抑制[35]。

2.1.2 川芎嗪 川芎嗪是活血化瘀药川芎的活性成分, 在抑制肿瘤生长、转移方面具有良好的应用前景。研究表明, 川芎嗪既能通过直接促进内皮细胞凋亡, 还能下调环氧化酶-2 (cyclooxygenase-2, COX-2) 表达、打破“血栓素A_2-前列环素”平衡来破坏血管壁的完整性, 从而达到抑制胃癌、黑素瘤、结直肠癌及其他恶性肿瘤血管生成的目的[36]。另外, 川芎嗪抑制血管生成的作用机制还与阻断BMP/Smad/ID-1信号通路有关。骨形态发生蛋白 (bone morphogenetic proteins, BMP) 是转化生长因子β (transforming growth factor-β, TGF-β) 家族分泌的细胞外信号配体, 当BMP与I型和II型跨膜丝氨酸/苏氨酸激酶受体结合后会触发Smads的磷酸化, 磷酸化的Smad1/5/8与Smad4结合形成异源复合物进入细胞核内进而促进DNA结合抑制剂ID-1 (DNA-binding protein inhibitor ID-1, ID-1) 的转录, 进一步刺激内皮细胞促血管生成基因的表达, 促进血管新生[37]。

川芎嗪还可与其他药物联合通过多靶点、多途径达到抗血管生成作用。川芎嗪和化疗药紫杉醇联合使用不仅能抑制A2780小鼠移植瘤血管生成, 诱导细胞凋亡, 还可降低紫杉醇的毒性增强其抗肿瘤作用[38]。川芎嗪和芍药苷联合使用则能够同时阻断VEGF/VEGFR2和Jagged1/Notch1信号通路传导来抑制血管生成, 有效减少由氧化型低密度脂蛋白引起的动脉硬化斑块破裂和降低血管内血栓形成的风险[39]。

2.2 来源于祛痰除湿类中药的活性成分

2.2.1 雷公藤红素 雷公藤红素是一种从雷公藤根皮中提取的五环三萜类化合物, 具有很强的抗炎和抗血管生成活性[40]。研究表明, 肿瘤的增殖、转移、血管生成与HIF-1α高表达密切相关。而雷公藤红素在常氧和缺氧条件下均可降低HIF-1α的表达水平, 并抑制缺氧诱导的HIF-1α的核转位, 减少HIF-1α的核积聚。这些作用都与雷公藤红素能阻止热休克蛋白90与HIF-1α结合, 继而促进HIF-1α降解有关[41]。雷公藤红素还能减少血管内皮祖细胞, 胞内VEGF的分泌, 进而抑制血管内皮祖细胞的活性、黏附性及迁移能力, 进一步减少新生血管的形成[42]。

2.2.2　岩藻多糖　岩藻多糖是从昆布中提取的一种复杂的分枝硫酸化多糖混合物, 具有良好的抗血管生成作用, 其可抑制 VEGF 的表达, 且与多种信号通路有关。首先, 岩藻多糖能够靶向信号转导和转录激活因子 3 (signal transducer and activator of transcription 3, STAT3), 阻碍 Janus 激酶 (Janus kinase, JAK) 磷酸化, 使 STAT3 不能被激活形成同源或异源二聚体而抑制 VEGF 表达[43]; 其次, 岩藻多糖能通过下调膀胱癌细胞中 HIF-1α 的表达抑制 VEGF 的表达[44]。即使在经过贝伐单抗治疗后, 岩藻多糖仍可降低视网膜色素上皮细胞内 VEGF 的分泌, 为治疗视网膜病变提供另一种安全有效的辅助疗法[45]。

2.3　来源于清热解毒类中药的活性成分

2.3.1　苦参碱和氧化苦参碱　苦参是豆科苦参属植物苦参的干燥根, 其主要成分为两种四环喹啉类生物碱—苦参碱和氧化苦参碱。近年来研究显示, 苦参碱可以显著降低 MDA-MB-231 细胞中 NF-κB 与 DNA 结合的活性, 降低基质金属蛋白酶-9/-2 (matrix metallopeptidase-9/-2, MMP-9/-2)、表皮生长因子 (epidermal growth factor, EGF) 和 VEGFR-1 的表达水平, 抑制乳腺癌细胞增殖、侵袭与血管生成[46]。碱烧伤角膜大鼠模型经苦参碱治疗后, 角膜内新生血管数随着苦参碱浓度增加而减少[47]。胰腺癌移植瘤小鼠模型经氧化苦参碱治疗后, 显著降低了肿瘤的血氧饱和度, 表明其具有良好的抑制胰腺癌的血管生成能力, 且其抗血管生成机制与降低 VEGF 的表达有关但与受体 VEGFR-2 表达无关[48]。

2.3.2　靛玉红和甲异靛蓝　青黛具有清热解毒、凉血消肿之效, 靛玉红与甲异靛蓝是中药青黛的活性成分。在临床上, 甲异靛蓝已被广泛用于治疗慢性粒细胞白血病。众所周知, 白血病细胞自身可产生大量 VEGF, 这些 VEGF 通过旁分泌途径促进内皮细胞的活化和增殖, 而激活的内皮细胞又可以释放细胞因子, 促进白血病细胞生长, 如此恶性循环从而加重病情。甲异靛蓝治疗白血病除了能促进癌细胞凋亡外, 还与下调血管细胞黏附分子 1 表达、抑制人静脉内皮细胞系 EVC304 细胞的黏附活性、阻断上述内皮细胞和白血病细胞之间的自分泌和旁分泌环路、减少血管形成有关[49]。靛玉红也具有良好的抗肿瘤效果, 它可通过阻断血管内皮细胞中 VEGFR-2 介导的 JAK/STAT3 信号通路抑制血管生成来抑制前列腺癌生长, 还能抑制肿瘤来源内皮细胞的细胞增殖、迁移、侵袭和血管生成, 为治疗肿瘤提供新途径[50]。

2.3.3　青蒿琥酯　青蒿素是从传统中草药青蒿中分离得到的一种倍半萜内酯, 青蒿琥酯 (artesunate, ART) 是青蒿素的水溶性衍生物, 在治疗疟疾方面比青蒿素疗效更佳[51]。除了抗疟疾作用外, ART 还具有很强的抗肿瘤活性。ART 在治疗多发性骨髓瘤方面具有双重活性, 即抑制骨髓瘤细胞的增殖和延缓骨髓瘤细胞诱导的血管生成。在骨髓瘤血管形成过程中, 血管生成素-1 (angio-poietin-1, Ang-1) 与 VEGF 发挥着重要作用, 二者相互协调、共同促进内皮细胞激活和萌芽。而 VEGF 和 Ang-1 的活性均受到细胞外调节蛋白激酶 1/2 (extracellular regulated protein kinases 1/2, ERK1/2) 通路的影响。若抑制 ERK1/2 的活性, 则会减少 VEGF 的分泌, 同时下调 Ang-1 的表达。Chen 等[52]发现 ART 具有阻断 ERK1/2 活化的能力从而抑制人多发性骨髓瘤 RPMI8226 细胞诱导的血管生成。另外, ART 还能通过降低癌细胞内 VEGF 和 MMP-9 水平延长结直肠癌患者的生存期[53], 下调 VEGF 的表达抑制高糖环境下人视网膜微血管内皮细胞增殖, 为糖尿病视网膜病变提供潜在的治疗方案[54]。

2.4　来源于补虚类中药的活性成分

2.4.1　人参皂苷 Rg3 和人参皂苷 Rb1　《神农本草经》中称人参为“上品”, 可“主补五脏, 除邪气”, 具有大补元气、养血生津之效。人参皂苷 Rg3 (ginsenoside Rg3, Rg3) 是人参中主要的活性成分, 是一种天然的血管抑制剂, 已经用于临床抗肿瘤治疗。研究表明, Rg3 对黑色素瘤有良好的抑制作用, 既可通过降低组蛋白去乙酰化酶 3 和增加 p53 乙酰化来抑制黑色素瘤细胞的增殖, 同时还能降低细胞外信号调节激酶和蛋白激酶 B 的表达, 下调 MMP-2、MMP-9 和 VEGF 表达从而抑制黑色素瘤内血管新生[55]。内皮祖细胞 (endothelial progenitor cells, EPC) 在早期肿瘤的生长中起关键作用, 它通过在肿瘤增殖过程中产生血管生成细胞因子来促进肿瘤新生血管的形成。Rg3 能有效地抑制 EPC 的多种生物活性, 能通过延缓 G1 期细胞周期素 E 和周期蛋白依赖性激酶 (cyclin-dependent kinases, CDK2) 的积聚而影响 EPC 增殖水平, 同时 Rg3 还可在蛋白质水平降低 EPC 中 VEGFR-2 的表达, 并阻断 VEGF 诱导的多条信号通路, 从而抑制肿瘤生长和新生血管的形成[56]。

人参中的另一种活性成分人参皂苷 Rb1 则可通过与过氧化物酶体增殖物激活受体-γ (peroxisome proliferator-activated receptor-γ, PPAR-γ) 相互作用, 降低人脐静脉内皮细胞 (human umbilical vein endothelial cells, HUVEC) 中 miRNA-33a 的水平, 并以浓度和时间依赖的方式增加诱导色素上皮衍生因子蛋白表达从而抑制血管生成[57]。

以上中药活性成分抑制血管新生的机制见表 1。

Table 1 Mechanism of anti-angiogenesis of TCM components. VEGFB: Vascular endothelial growth factor B; NKAP: Nuclear transcription factor kappa B acting protein; NF-κB: Nuclear factor κB; VEGF: Vascular endothelial growth factor; COX-2: Cyclooxygenase-2; BMP: Bone morphogenetic proteins; ID-1: DNA-binding protein inhibitor ID-1; HIF-1α: Hypoxia inducible factor-1α; HSP90: Heat shock protein 90; STAT3: Signal transducer and activator of transcription 3; JAK: Janus kinase; MMP-9/-2: Matrix metallopeptidase-9/-2; EGF: Epidermal growth factor; VCAM1: Vascular cell adhesion molecule 1; Ang-1: Angio-poietin-1; ERK1/2: Extracellular regulated protein kinases 1/2; CDK2: Cyclin-dependent kinases; EPC: Endothelial progenitor cells; PPAR-γ: Peroxisome proliferator-activated receptor-γ

Classification	Source	Active ingredient	Mechanism of anti-angiogenesis	Ref.
Promoting blood circulation and removing blood stasis	*Curcuma Longa* L	Curcumin	Inhibition of VEGFB and NKAP expression further inhibits the activation of NF-κB, and inhibits the expression of VEGF and endothelin-1	[32, 33]
		β-Elemene	Targeting gastric cancer stem cells and down-regulating the expression of Notch-1 and Hes1	[34]
	Ligusticum Chuanxiong Hort	Tetramethylpyrazine	Promote endothelial cell apoptosis; down-regulate the expression of COX-2 and break the balance of thromboxane A2 -prostacyclin to destroy the integrity of blood vessel wall; blocking BMP/Smad/ID-1 signal pathway	[36−39]
Eliminating phlegm and dampness	*Tripterygium Wilfordii* Hook. F	Celastrol	Inhibit the activity of HSP90, prevent the binding of HSP90 and HIF-1α, and then promote the degradation of HIF-1α; reduce the secretion of VEGF in vascular endothelial progenitor cells	[41, 42]
	Ecklonia Kurome	Fucoidan	Targeting STAT3, inhibit the phosphorylation of JAK, down-regulate the expression of HIF-1α and inhibit the expression of VEGF	[43, 44]
Clearing heat and detoxification	*Sophorae Flavescentis Radix*	Matrine	Decrease the binding activity of NF-κB to DNA, and decrease the expression level of MMP-9, MMP-2, EGF and VEGFR1	[46]
		Oxymatrine	Down-regulate the expression of VEGF	[48]
	Indigo Naturalis	Meisoindigo	Down-regulate the expression of VCAM1, then block the autocrine and paracrine circuits between endothelial cells and leukemic cells	[49]
		Indirubin	Inhibition of JAK/STAT3 signal pathway	[50]
	Artemisiae Annuae Herba	Artesunate	Inhibit the activation of ERK1/2 and thus inhibit the activity of VEGF and Ang-1; reduce the expression level of VEGF and MMP-9; inhibition of vascular endothelial cell proliferation	[52−54]
Tonify deficiency	*Ginseng Radix et Rhizoma*	Ginsenoside Rg3	Down-regulate the expression of MMP-2, MMP-9 and VEGF; delaying the accumulation of cyclin E and CDK2 in G1 phase inhibits the proliferation of EPC and inhibits the expression of VEGFR2	[55, 56]
		Ginsenoside Rb1	Interaction with PPAR-γ increases the expression of induced pigment epithelium-derived factor protein	[57]

3 促进血管新生中药活性成分及其作用机制

络脉之病变可引起心血管疾病, 主要表现为浊物沉积于脉络之中, 导致脉络壁增厚, 脉络淤阻, 血瘀气滞, 如此恶性循环。现代药理表明, 活血化瘀药 (红花、丹参、银杏叶等) 具有良好的抗凝、降低血液黏度、抑制血栓形成、促进毛细血管新生的功效[58]。气为血之帅, 血为气之母, 气能生血, 血能载气。气血不足, 运行不畅, 瘀血阻滞, 脉络失去濡养, 营养代谢失调。益气补血药可增强五脏之气血, 为血管新生提供保障。心阴肾阴亏虚, 水火不济, 导致阴血亏虚, 血行涩滞, 脉络淤阻[59]。清热滋阴类药补阴益气, 稳定脉络平衡, 促进脉络的良性循环。肾阴不足, 心脉失养, 血行不利; 肾阳亏虚, 心阳不足, 血行无力。两者均可导致瘀血阻滞, 心脉不通。补肾固本类药能补肾阴肾阳, 先天之精, 促进气血运行, 脉络通畅, 保护心血管[60]。

促进血管生成是临床治疗心血管疾病常用的方法之一。上述来源于活血化瘀、益气补血、清热滋阴和补肾固本类中药的活性成分能够通过不同作用机制促进血管生成, 有效治疗各种由于血管生成不足导致的缺血性疾病。

3.1 来源于活血化瘀类中药的活性成分

3.1.1 丹参素、丹酚酸 A 和丹酚酸 B 丹参是临床上常用的活血化瘀类中草药之一, 具有较强的抗氧化作用, 常用于治疗心肌梗死、心肌缺血/再灌注损伤、心律失常和心肌纤维化等心血管疾病。丹参的亲水性成分 (丹参素、丹酚酸 A 和丹酚酸 B) 具有抗氧化、抗炎、抗缺氧、抗动脉粥样硬化和抗凋亡等作用[61,62]。丹参素是丹参中各种丹酚酸的基本化学结构, 其表现出良好的心血管活性。一方面, 丹参素可通过增强内皮祖细胞活性、上调 Akt 磷酸化而抑制心肌细胞凋亡, 进一步降低缺氧导致的心肌细胞损伤; 另一方面, 丹参素能够显著降低内皮祖细胞内基质细胞源性因子-1α (stromal

cell-derived factor-1α, SDF-1α) 水平及C-X-C趋化因子受体4 (C-X-C chemokine receptor type 4, CXCR4) 表达, 激活SDF1α/CXCR4轴, 使内皮祖细胞迁移并在局部缺血区聚集, 进一步诱导心肌组织内新生血管形成, 增加缺血组织灌注, 从而减轻心肌缺血性损伤、恢复心脏功能[63]。

丹酚酸A也能作用于内皮祖细胞, 促进其增殖与迁移, 使内皮祖细胞在受损的血管中聚集并重新内皮化形成成熟的内皮细胞, 同时促进心肌组织内VEGF/VEGFR-2和MMP-9表达, 诱导损伤心肌内新生血管的形成[64]。而丹酚酸B除了能够增加VEGF表达、保护内皮细胞和减少大鼠急性心肌梗死面积之外[65], 还能改善糖尿病小鼠左心室功能障碍, 减少心脏胶原沉积, 同时增强缺氧条件下HUVEC细胞内胰岛素样生长因子结合蛋白3 (insulin-like growth factor-binding protein 3, IGFBP3) 启动子的甲基化, 诱导IGFBP3核移位, 激活VEGFR-2/VEGFA信号转导通路, 促进新生血管形成, 改善糖尿病性心肌病小鼠的心脏功能[66]。

3.1.2　银杏内酯B和银杏内酯K　银杏叶具有清除自由基的能力, 能够减轻心肌缺血再灌注损伤、缺血性脑损伤和抑制神经细胞凋亡。银杏叶内酯是银杏叶的主要萜类化合物, 是一种天然的血小板活化因子拮抗剂, 其中银杏内酯B生物活性最高, 具有广泛的药理作用, 常用于治疗心肌梗死、脑卒中和缺血性心脏病等疾病。银杏内酯B不仅能使内皮祖细胞免受H_2O_2诱导的细胞凋亡, 还能以剂量与时间依赖的方式上调AKT/eNOS和MAPK/P38信号通路的传导, 促进内皮祖细胞增殖、迁移和黏附, 进一步促进血管生成[67]。

银杏内酯K是从银杏叶中提取的一种新化合物, 它与银杏内酯B结构相似。但是, 相较于银杏内酯B, 银杏内酯K具有更强的抗氧化应激和神经保护活性, 它能通过促进JAK2/STAT3信号通路的传导上调HIF-1α/VEGF的表达, 进一步促进损伤侧皮质和纹状体内微血管生成, 改善脑血流, 为脑神经提供充足的葡萄糖和氧气, 从而减轻小鼠脑部神经功能损伤[68]。

3.1.3　羟基红花黄色素A　羟基红花黄色素A (hydroxysafflor yellow A, HSYA) 是红花属植物红花中具有代表性的水溶性成分, 表现出显著的抗凝和促血管生成活性。据报道, HSYA可通过多种途径治疗缺血性心血管疾病。首先, HSYA能明显改善缺血心肌的血流动力学, 促进缺血心肌中核仁蛋白、VEGF-A和MMP-9的表达, 增加心肌组织内血管新生, 进一步减轻心肌损伤, 提高存活率[69]; 其次, HSYA能提高血红素氧合酶1 (heme oxygenase-1, HO-1) 活性。HO-1一方面能催化血红素生成一氧化碳从而刺激心肌细胞合成VEGF, 促进骨髓内皮祖细胞进入外周循环; 另一方面可直接激活SDF-1/CXCR4信号传导, 促进内皮祖细胞分化、黏附、归巢和募集, 进而促进心肌血管形成, 减轻心肌损伤, 恢复心脏功能[70]。此外, HSYA还能上调HUVEC细胞内Ang-1和Tie-2的表达, 增强Tie-2、Akt和ERK1/2磷酸化, 促进血管新生[71]。

3.2　来源于益气补血类中药的活性成分

3.2.1　人参皂苷Rg1和人参皂苷F1　人参皂苷Rg1 (ginsenoside Rg1, Rg1) 是人参中含量最丰富的原人参三醇之一, 已被证明具有调节血压、抗炎和神经保护等多种生物活性。Rg1可激活卒中后PI3K/Akt/mTOR信号通路, 进而诱导促血管生成因子VEGF上调, 促进脑缺血模型小鼠的血管生成, 恢复卒中后神经功能[72]。Rg1通过抑制miR-23a的表达, 激活肝细胞生长因子(hepatocyte growth factor, HGF)/调节肝细胞生长因子受体 (hepatocyte growth factor receptor, MET) 信号通路传导, 进而促进血管生成[73], 同时解除miR-23a对IRF-1的抑制作用, 增强iNOS活性, 刺激细胞内NOx和VEGF的表达, 促进糖尿病足溃疡伤口愈合[74]。然而, 促进细胞内VEGF表达既能刺激血管生成, 也会增加血管通透性造成血管渗漏。人参中的另一种原人参三醇型皂苷人参皂苷F1 (ginsenosides F1, GF1) 不仅能通过促进内皮细胞的胰岛素样生长因子1 (insulin-like growth factor 1, IGF-1) 自分泌, 激活IGF-1/胰岛素样生长因子1受体 (insulin-like growth factor 1 receptor, IGF1R) 信号传导及其下游蛋白Akt、FAK和MEK1/2表达, 从而促进脑部治疗性血管生成, 增加大鼠大脑中动脉闭塞模型的脑微血管密度, 增强脑血流灌注, 减轻脑部缺氧缺血损伤[75]; 而且还能直接抑制核受体4 A1 (nuclear receptor 4 A1, NR4A1) 的转录活性, 降低NR4A1的基因表达来削弱对内皮连接蛋白的抑制作用, 从而减少血管渗漏的发生[76]。

3.2.2　黄芪甲苷IV　黄芪甲苷IV是黄芪中的主要活性成分, 具有较强的促组织新生活性, 能够促进伤口愈合和心肌梗死后心肌功能恢复。皮肤伤口愈合是一个复杂的动态过程, 需要多种细胞参与, 并协调细胞增殖、血管生成和细胞外基质沉积等过程[77]。EGF/表皮生长因子受体 (epidermal growth factor receptor, EGFR) 信号通路是最具特征性的信号通路之一, 参与伤口愈合的多个阶段, 包括炎症、增殖、伤口收缩、角质形成、细胞迁移和血管生成。黄芪甲苷IV能促进EGFR和ERK1/2的表达, 激活EGF/EGFR信号通路传导, 诱导组织内血管生成, 进一步促进肉芽组织的形成[78]。黄芪甲苷IV还能够抑制抑癌基因磷酸酶和张力蛋白同源物的表达, 激活PI3K/Akt信号通路, 促进HIF-1α蛋

白聚集和VEGF表达, 发挥心肌梗死后血管生成和心脏保护作用[79,80]。

3.2.3 红景天苷 红景天苷 (salidroside, SAL) 是从红景天属植物根部提取的生物活性化合物, 具有多种药理作用, 包括抗缺氧、促血管生成和抗骨质疏松作用。虽然SAL可以下调HIF-1α表达并抑制其转位, 但却能促进缺氧环境中HIF-1α与HIF-1β的结合来提高HIF-1α转录活性, 显著上调VEGF的表达, 进一步诱导在骨髓间充质干细胞中血管形成, 调节成骨和成脂分化之间的平衡, 避免骨质疏松症的发生[81]。脯氨酰羟化酶结构域3 (prolyl-hydroxylase domain 3, PHD3) 是SAL的一个作用靶点。SAL能通过雌激素受体α (estrogen receptor α, ERα) 特异性抑制PHD3在骨骼肌细胞中转录活性, 促进骨骼肌细胞的运动和EGF、HGF、PDGF-BB、FGF2、Ang-1等血管生成因子的分泌, 激活FGF2/FGF2R和PDGF-BB/PDGFR-β信号通路传导进而增强内皮细胞和平滑肌细胞的运动, 促进后肢缺血小鼠的新生血管形成[82]。

3.3 来源于补肾固本类中药的活性成分

3.3.1 柚皮苷 骨碎补具有补肾强骨、活血疗伤的功效, 为伤科之要药。现代药理研究证明, 其主要活性成分柚皮苷具有抗氧化、抗炎、抗凋亡、抗溃疡和抗骨质疏松等药理作用, 常用于治疗骨质疏松和口溃疡等疾病。柚皮苷是通过抑制内质网应激以及线粒体去极化介导的血管内皮细胞凋亡, 促进血管内皮细胞增殖, 并调节内皮细胞中内皮素的分泌进而促进一氧化氮的表达, 促进血管生成, 恢复骨微循环与骨代谢, 使血液中的营养物质进入骨组织, 发挥其抗骨质疏松作用的。在去卵巢大鼠骨质疏松症模型中, 柚皮苷治疗后大鼠骨髓内微血管数量明显增加, 进一步证明了柚皮苷治疗骨质疏松症的潜力[83]。在促进伤口愈合方面, 柚皮苷也具有显著疗效。它不仅能通过促进VEGF和VEGFR-2的表达促进骨折骨痂的血管化从而提高骨折处的骨强度[84], 而且还能诱导炎症因子和生长因子合成, 增加毛细血管密度, 促进糖尿病大鼠足部溃疡伤口愈合[85]。此外, 低剂量的柚皮苷还能作用于内皮祖细胞, 通过CXCL12/CXCR4介导的PI3K-Akt信号通路促进内皮祖细胞增殖, 增强其管状形成能力, 促进血管形成[86]。

3.4 来源于清热滋阴类中药的活性成分

3.4.1 葛根素 葛根来源于豆科多年生藤本植物葛根的干燥根, 用于治疗发热、腹泻、头痛和心血管疾病。葛根素是评价葛根质量的标志化合物, 具有降血压、降血脂和抗炎等生物活性。葛根素能通过舒张小动脉和p42/44MAPKs介导的血管生成增加脑血流灌注, 减轻由自发性高血压所引起脑组织小动脉重构、水肿和缺血等症状, 促进脑微循环, 降低发生脑卒中的风险[87]。葛根素还能显著增加缺氧性脑缺血再灌注后HIF-1α蛋白水平, 抑制脑血管内皮细胞凋亡, 促进脑部血管新生和神经再生[88]。

3.4.2 黄芩苷 黄芩是治疗心血管疾病的常用药, 黄芩苷是黄芩的主要有效成分, 能通过升高ERα水平, 进一步促进ERα与PGC-1α的相互作用, 激活VEGF启动子的转录因子结合位点, 有效地诱导VEGF的表达和血管生成[89]。黄芩苷还可作为糖尿病相关血管并发症的潜在治疗药物, 能够减少高糖条件下人脐静脉内皮细胞死亡。其主要原因是黄芩苷能在不改变HUVECs细胞内Nrf2蛋白的情况下, 显著增加Nrf2的核积聚和下游抗氧化基因的表达, 促进Akt和GSK3B的磷酸化, 进而保护HUVEC免受高血糖诱导的氧化损伤[90]。

以上中药活性成分促进血管生成的机制见表2。

4 结语与展望

血管生成是一个复杂的过程, 需要内皮细胞、成纤维细胞、平滑肌细胞、血小板和炎症细胞等多种细胞共同参与。这些细胞能分泌大量促血管生成生长因子和细胞因子, 如VEGF、PDGF、FGF、TGF-β、基质金属蛋白酶和血管生成素-2。这些因子与基底膜降解、壁细胞脱落、内皮细胞萌发和管状形成密切相关[10,91]。这些促血管生成因子可作为治疗病理性血管生成过度或不足导致的恶性肿瘤或缺血性疾病的潜在靶点。

临床上使用的抗血管生成药物基本上可以分为3大类: 针对VEGF及其膜受体酪氨酸激酶的抗体、受体酪氨酸激酶的小分子抑制剂及针对参与血管生成信号通路的蛋白的小分子抑制剂[92]。然而, 当这些药物投入临床使用后发现抑制VEGF信号通路会干扰内皮细胞的再生能力, 使内皮层缺损和基质外露, 同时还可能降低NO和前列环素活性, 改变血管舒张能力, 导致出血、高血压和血栓形成等不良反应发生[93-95]。

与现有的单克隆抗体和小分子抑制剂相比, 从中药获得的活性成分除能调节血管生成过程外, 还具有抗炎、抗氧化和提高机体免疫功能等多重活性, 可从多方面协同治疗血管生成相关疾病。研究表明, 炎症与癌症、动脉粥样硬化、心肌梗死等血管生成相关疾病之间存在密切联系。正常细胞发生突变是形成肿瘤的开端, 炎症反应所形成的炎性微环境不仅能增加突变率, 还能促进突变细胞的增殖。随着肿瘤体积不断增加, 其核心部分会因无法得到足够的氧气和营养而发生坏死, 并释放大量炎症因子诱导炎症反应发生。这类炎症反应会在肿瘤部位招募更多的免疫细胞, 为肿瘤细胞提供大量生长因子, 诱导新生血管生成[96]。另外, 活

Table 2　Mechanism of pro-angiogenesis of TCM components. Akt: Protein kinase B; SDF1α: Stromal cell-derived factor-1α; CXCR4: C-X-C chemokine receptor type 4; IGFBP3: Insulin-like growth factor-binding protein 3; HUVEC: Human umbilical vein endothelial cells; HGF: Hepatocyte growth factor; MET: Hepatocyte growth factor receptor; IGF-1: Insulin-like growth factor 1; IGF1R: Insulin-like growth factor 1 receptor; EGFR: Epidermal growth factor receptor; PTEN: Phosphatase and tensin homolog; PHD3: Prolyl-hydroxylase domain 3; ERα: Estrogen receptor α; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1α; Nrf2: NF-E2-related factor 2

Classification	Source	Active ingredient	Mechanism of pro-angiogenesis	Ref.
Promoting blood circulation and removing blood stasis	*Salviae Miltiorrhizae* Radix et Rhizoma	Danshensu	Enhance the activity of endothelial progenitor cells and up-regulate Akt phosphorylation to inhibit cardiomyocyte apoptosis; activating the SDF1α/CXCR4 axis to make endothelial progenitor cells migrate and gather in the local ischemic area	[63]
		Salvianolic acid A	Promote the expression of VEGF/VEGFR-2 and MMP-9 in myocardial tissue	[64]
		Salvianolic acid B	IGFBP3 promoter methylation induces IGFBP3 nuclear translocation and activates VEGFR2/VEGFA signal transduction pathway	[66]
	Ginkgo Biloba	Ginkgolide B	Up-regulate the transduction of Akt/eNOS and MAPK/P38 signal pathways and promote the proliferation, migration and adhesion of endothelial progenitor cells	[67]
		Ginkgolide K	Promote the transduction of JAK2/STAT3 signal pathway and up-regulate the expression of HIF-1α/VEGF	[68]
	Carthami Flos	Hydroxysafflor yellow A	Promote the expression of nucleolar protein, VEGF-An and MMP-9 in ischemic myocardium and increase the activity of heme oxygenase 1; up-regulate the expression of Ang1 and Tie-2 in HUVEC cells and enhance the phosphorylation of Tie-2, Akt and ERK1/2	[69−71]
Replenishing qi and tonifying blood	*Ginseng Radix et Rhizoma*	Ginsenoside Rg1	Activate PI3K/Akt/mTOR signal pathway and up-regulate the expression of VEGF; inhibit the expression of miR-23a, activate HGF/MET signal pathway, enhance the activity of iNOS, and stimulate the expression of NOx and VEGF in cells	[72−74]
		Ginsenoside F1	Promote IGF-1 autocrine of endothelial cells, activate IGF-1/IGF1R signal transduction and the expression of its downstream proteins Akt, FAK and MEK1/2	[75]
	Astragali Radix	Astragaloside IV	Promote the expression of EGFR and ERK1/2, activate EGF/EGFR signal transduction pathway; inhibit PTEN expression, activate PI3K/Akt signal pathway, and promote HIF-1α protein aggregation and VEGF expression	[78−80]
	Rhodiola rosea L	Salidroside	Promote the binding of HIF-1α and HIF-1β, increase the transcriptional activity of HIF-1α, and significantly up-regulate the expression of VEGF; inhibit the transcriptional activity of PHD3 and activate FGF2/FGF2R and PDGF-BB/PDGFR-β signaling pathways	[81, 82]
Tonifying the kidney and strengthening the foundation	*Drynariae Rhizoma*	Naringin	Regulate the secretion of endothelin in endothelial cells to promote NO expression and activate CXCL12/CXCR4-mediated PI3K-Akt signal pathway; promote the expression of VEGF and VEGFR-2 and induce the synthesis of inflammatory factors and growth factors	[83−86]
Clearing heat and nourishing yin	*Puerariae Lobatae Radix*	Puerarin	Activate p42/44MAPKs signal pathway and increase the level of HIF-1α protein	[87, 88]
	Scutellariae Radix	Baicalin	Promote the interaction between ERα and PGC-1α and induce the expression of VEGF; increase the nuclear accumulation of Nrf2 and promote the expression of Akt and GSK3B	[89, 90]

化的炎症细胞是ROS的重要来源[97]。当机体组织内ROS产生和清除之间稳态发生偏离, 导致超氧化物、过氧化氢和其他产物 (过氧亚硝酸盐和次氯酸) 在体内蓄积时, 会直接造成心肌细胞、内皮细胞等多种细胞损伤, 甚至使其坏死或凋亡, 进而引发或加重动脉粥样硬化和心肌梗死等心血管疾病[98-100]。

然而, 将这些中药活性成分成功地应用于临床, 仍存在很多问题亟待解决。首先, 许多中药活性成分水溶性差, 其生物利用度低, 严重阻碍其临床应用。而使用纳米载体已成为提高生物利用度的有效方法之一。

将中药活性成分包装于可生物降解的纳米载体中, 既保留了药物的活性, 又增加了其对病灶部位的靶向性, 极大地提高了治疗效果。例如, 姜黄素与低分子量肝素通过酯化反应所形成的纳米粒能显著增加姜黄素的溶解度 (从 0.006 mg·mL^{-1} 提高至 0.12 mg·mL^{-1}), 并且在较低剂量下就能有效抑制血管新生, 表现出优异的抗肿瘤活性[101]; 其次, 目前针对中药调控血管生成的报道大多停留在药物筛选初级阶段, 对其作用机制的研究也仅限于某一信号通路中的 1 个或几个信号蛋白的检测, 并且还可能放大该信号通路在血管生成的重要性, 这与中医药治疗疾病的多靶点、多途径、整体性和系统性不相吻合[102-104]。另外, 成分多样和作用复杂是中药所具备的特点, 这也给阐明其如何影响血管生成带来挑战。一味中药可同时具有促进血管生成与抑制血管生成双重活性成分 (人参中 Rg3 和 Rb1 对血管生成具有抑制作用, 而 Rg1 和 GF1 则促进血管生成), 甚至是同一活性成分在不同剂量、疾病发展的不同阶段都可能表现出截然相反的调节作用。

因此, 系统科学地诠释中药活性成分对血管生成调控及其作用机制, 仍需要与现代科学技术相结合深入研究, 为其应用提供科学的依据。

作者贡献: 该文章主要由杨婷、张莉君撰写, 兰海月、黄睿二人收集整理了文献资料。张卫东、栾鑫提供了文章的总体思路, 张卫东、栾鑫、张宏为文章提供了重要的指导和意见。

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