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严悦梅, 胡东艳, 曹滇誉, 王强

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· 综 述 ·

# 活血化癥类中药在硬皮病中的应用及机制研究进展

严悦梅<sup>1,2</sup>, 胡东艳<sup>1</sup>, 曹滇誉<sup>1</sup>, 王 强<sup>1\*</sup>

1. 复旦大学附属中山医院皮肤科, 上海 200032

2. 嘉兴市第一医院皮肤科, 嘉兴 314000

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**〔摘要〕** 硬皮病是一种复杂的多器官累及的自身免疫性疾病, 以皮肤和内脏器官结缔组织发生进行性纤维化为特征。中医认为硬皮病属于“痹症”范畴, 具有血瘀证征象, 故活血化癥治疗贯穿全程; 而西医则认为, 硬皮病是由血管病变、胶原合成异常、免疫紊乱等导致的结缔组织细胞外基质过度沉积。近年来, 越来越多的学者发现活血化癥类中药成功改善硬皮病动物模型的炎症、纤维化、血管病变等, 并逐渐将这类中药应用于临床患者。这类动物试验结果符合西医对硬皮病发病机制的认识, 也为活血化癥类中药的应用提供了客观实验证据。

**〔关键词〕** 硬皮病; 活血化癥; 中药; 机制

**〔中图分类号〕** R 593.25 **〔文献标志码〕** A

## Progression of mechanism research and application of traditional Chinese medicine for promoting blood circulation and removing blood stasis in the treatment of scleroderma

YAN Yue-mei<sup>1,2</sup>, HU Dong-yan<sup>1</sup>, CAO Dian-yu<sup>1</sup>, WANG Qiang<sup>1\*</sup>

1. Department of Dermatology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

2. Department of Dermatology, the First Hospital of Jiaxing, Jiaxing University, Jiaxing 314000, Zhejiang, China

**〔Abstract〕** Scleroderma is a complex, multiorgan, autoimmune disease that is characterized by the progressive fibrosis mainly involving the connective tissue of the skin and internal organs. Based on the traditional Chinese medicine, scleroderma belongs to the category of “Bi Zheng” with blood stasis symptom, which leads to a throughout treatment of promoting blood circulation and removing blood stasis. However, Western medicine believes that scleroderma is excessive deposition of extracellular matrix (ECM) of connective tissue caused mainly by vasculopathy, abnormal collagen synthesis and autoimmune disorder. In recent years, an increasing number of researchers have found that some of traditional Chinese herbs for promoting blood circulation and removing blood stasis can successfully improve the inflammation, fibrosis and vasculopathy in the animal models of scleroderma, and these herbs have been gradually applied to scleroderma patients. These results from animal trials accord with Western medicine’s understanding of the pathogenesis of scleroderma and provide objective experimental evidence for application of traditional Chinese herbs for promoting blood circulation and removing blood stasis in the treatment of scleroderma.

**〔Key Words〕** scleroderma; promoting blood circulation and removing blood stasis; traditional Chinese medicine; mechanism

硬皮病是一种免疫介导的风湿性疾病, 表现为皮肤和内脏器官的纤维化以及血管病变<sup>[1]</sup>。尽管硬皮病总体患病率和发病率较低, 但其致死率

在所有风湿性疾病中最高<sup>[2-5]</sup>。近年来, 关于硬皮病的发病机制有免疫学说、胶原合成异常学说、血管学说等。这些理论与中医学对硬皮病发病的

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**〔作者简介〕** 严悦梅, 硕士生. E-mail: yuemeiyan1210ha@163.com

\* 通信作者 (Corresponding author). Tel: 021-64041990, E-mail: wang.qiang@zs-hospital.sh.cn

阐释相似。中医学认为,硬皮病属“痹症”范畴,多由寒凝血瘀,痰瘀痹阻于皮肤肌肉,皮肉失养所致<sup>[6]</sup>。近代医家完善了硬皮病中医病因病机,提出了本病的两大理论,即“血瘀发病论”<sup>[7]</sup>和“肾阳不足论”<sup>[8]</sup>。根据兼有血瘀证的病理特点,本文从中医、西医两方面论述活血化瘀类中药治疗硬皮病的依据。

## 1 活血化瘀类中药治疗硬皮病的中医依据

根据历代中医典籍的记载,硬皮病归入中医“痹症”范畴,亦称为“皮痹”。即硬皮病是风、寒、湿外邪侵袭,人体气血运行受阻,经脉雍闭,皮肤肌肉营养失职,久则入内而伤脏气,导致的“痹症”。血瘀不仅是硬皮病形成的主要病机之一,形成的瘀血可使肌肤失去血液濡养,进而导致其他部位症候的出现。上海市名中医秦万章等<sup>[7,9]</sup>指出,硬皮病有雷诺氏现象(肢端动脉痉挛症),皮肤肿胀、发硬、皮下硬结及瘀斑,肢体血流缓慢,微循环障碍等血瘀征象,提出了“血瘀发病论”,并采用活血化瘀法治疗。赵党生等<sup>[10]</sup>也认为,硬皮病的病理机制与瘀血内阻有关,较为系统地提出了硬皮病属皮痹血瘀证这一观点,将本病归纳为“因虚致瘀、外邪致瘀、寒凝致瘀、气痰致瘀”四大病因,瘀血阻滞在皮肤、肌肉、脉络、筋骨、脏腑,而表现出不同的辨证指征。国医大师熊继柏等<sup>[11]</sup>则运用补阳还五汤治疗硬皮病,此药益气活血通络,药方中川芎、赤芍、红花、桃仁、当归尾活血祛瘀;黄芪补气,气行则血行,祛瘀而通络;当归尾补血活血而不伤血。通过检索1989年1月至2021年4月知网、万方数据库中中药治疗硬皮病相关文献,发现补虚药与活血化瘀药是最常用的两类中药,应用频次位于前10位者分别为当归、黄芪、桂枝、甘草、丹参、熟地黄、白芍、鸡血藤、红花、川芎,其中当归、川芎、丹参、红花、鸡血藤均为活血化瘀药,当归虽为补虚药,亦有活血祛瘀之功效<sup>[12]</sup>。可见活血化瘀类中药在治疗硬皮病中广泛应用。

## 2 活血化瘀类中药治疗硬皮病的西医依据

### 2.1 抗纤维化 硬皮病的特征在于胶原合成增加

和胶原沉积,引起皮肤以及各种内脏器官广泛纤维化。软皮热敷散与“热敷药”具有相似的药理作用,可能通过抑制Wnt1诱导的Wnt/ $\beta$ -catenin信号通路活化和Wnt5a诱导的Wnt/ $Ca^{2+}$ 非经典信号通路活化发挥作用,从而显著减小硬皮病模型小鼠的皮肤厚度,减少胶原沉积<sup>[13]</sup>。

成纤维细胞是合成胶原纤维的主要细胞,体外实验<sup>[14]</sup>发现17味活血化瘀中药具有抑制人类皮肤成纤维细胞增殖的作用,其中9味中药效果最为显著。为进一步研究这9味中药对皮肤成纤维细胞胶原合成的影响,该团队测定了细胞上清液中羟脯氨酸含量,发现4味活血化瘀中药(积雪草、丹参、茜草、当归)能不同程度抑制硬皮病患者真皮成纤维细胞合成胶原蛋白的能力;另外4味(丹皮、苏木、赤芍、川芎)的作用不明显;红花对皮肤成纤维细胞合成胶原有促进作用<sup>[15]</sup>。该团队后续研究<sup>[16]</sup>证实,丹参的4种有效成分(丹参酮II A、丹参素、丹参多酚酸盐、原儿茶醛)能有效抑制硬皮病患者真皮成纤维细胞的增殖能力,以及I、III型前胶原的mRNA表达水平,显示出较强的抗纤维化作用。此外,孙春斌等<sup>[17]</sup>发现,中药三七及其有效成分三七总皂苷可减少细胞外基质以及胶原纤维沉积,缓解肺纤维化进程,可能与抑制PI3K/AKT/mTOR信号通路,激活细胞自噬,从而缓解肺纤维化有关。积雪草苷是活血化瘀中药积雪草的有效提取物。李晶冰等研究<sup>[18]</sup>发现,积雪草苷能抑制硬皮病患者皮肤成纤维细胞增殖,减少成纤维细胞自分泌转化生长因子 $\beta 1$ (TGF- $\beta 1$ ),从而抑制胶原合成,减少细胞外基质沉积。

### 2.2 调节免疫炎症 免疫功能异常与炎症因子水平失控是硬皮病发病的重要机制。胶原纤维的过度产生也与免疫密切相关。血府逐瘀汤能显著降低硬皮病患者血清中可溶性白介素2受体(sIL-2R)、肿瘤坏死因子 $\alpha$ (TNF- $\alpha$ )水平,显示出抗炎效果<sup>[19]</sup>。当归四逆汤治疗后,硬皮病小鼠外周血CD4<sup>+</sup>、CD8<sup>+</sup>T细胞的数目增多,腹腔巨噬细胞的活力也提高,证明当归四逆汤对免疫应答有较好地调节作用<sup>[20]</sup>。魏慧玲等<sup>[21-22]</sup>研究发现,当归四逆汤能下调硬皮病模型小鼠Toll样受体4(TLR4)/核因子 $\kappa B$ (NF- $\kappa B$ )炎症信号通路活性,以及

高迁移率族蛋白 B1 (HMGB1)、微管相关蛋白 1A/1B 轻链 3 (MAP1LC3) 等信号蛋白的表达, 抑制多种炎症因子的表达, 从而发挥抗炎作用。卢海松等<sup>[23]</sup>在《永类铃方》中补肺汤的基础上, 加用牡丹皮、凌霄花等活血化瘀药, 组成加味补肺汤, 应用于硬皮病患者后发现, 其 CD3<sup>+</sup>、CD4<sup>+</sup>T 细胞水平升高, CD4<sup>+</sup>/CD8<sup>+</sup>T 细胞比值增加, CD8<sup>+</sup>T 细胞水平降低。红花水煎液能改善硬皮病小鼠皮肤炎症评分, 并显著降低维甲酸相关孤儿核受体  $\gamma$ t (ROR- $\gamma$ t) 蛋白表达量, 说明红花可能通过抑制 ROR- $\gamma$ t 的表达, 进而调节 Th17 细胞, 发挥抑制免疫炎症反应的作用<sup>[24]</sup>。采用积雪草苷片口服以及地龙提取液外洗后, 硬皮病患者血清 S100 钙结合蛋白 A8 (S100A8) 和 S100 钙结合蛋白 A9 (S100A9) 水平明显下降, 证明积雪草可发挥抗炎作用, 进而改善症状<sup>[25]</sup>。

**2.3 改善血管损伤** 内皮细胞功能障碍和损伤是硬皮病血管病变的基础, 可导致血管壁的纤维增生性改变及毛细血管减少, 影响微循环。因此, 治疗硬皮病时使用活血化瘀类药物可以扩张外周血管, 降低血液黏度, 防止血栓形成<sup>[26]</sup>, 从而改善微循环, 减少血管损伤<sup>[27]</sup>。一项体外实验<sup>[28]</sup>从大鼠骨髓单核细胞分离出内皮祖细胞管, 并给以含血清的血府逐瘀汤刺激, 发现血府逐瘀汤可诱导血管生成并加速管形成 (尤其是毛细血管); 对人微血管内皮细胞 (HMEC-1) 的体外实验发现, 血府逐瘀汤这种促进管形成的作用可能仅发生在血管生成的早期<sup>[29]</sup>。活血化瘀方的促血管新生作用可能是通过上调血管内皮生长因子 (VEGF) 及 VEGFR1 的 FMS 相关酪氨酸激酶 1 (FLT1)、编码 VEGFR2 的激酶插入区受体 (KDR) 的基因表达实现的<sup>[30-31]</sup>。活血化瘀方还可通过下调 c-Jun 氨基末端激酶 (JNK) 信号通路、上调 Bcl-2 基因及蛋白表达水平, 改善主动脉内皮细胞凋亡, 明显降低 TNF- $\alpha$ 、IL-6 含量, 发挥保护内皮细胞的功能<sup>[32]</sup>。服用红花水煎液硬皮病小鼠的皮肤组织中纤溶酶原激活物抑制物 1 (PAI-1)、血栓调节蛋白 (TM)、VEGF 的表达下调, 血管病变减轻, 硬皮病症状改善<sup>[33-34]</sup>。同样, 川芎素是活血化瘀中药川芎的有效成分, 能较好地改善内皮细胞损伤,

从而缓解硬皮病症状<sup>[35]</sup>。

### 3 小结与展望

硬皮病是发病率低, 而致死率最高的风湿性疾病。青霉素、糖皮质激素、免疫抑制剂和生物制剂等药物治疗疗效不理想或不良反应大。中药治疗硬皮病不仅具有较好的临床疗效, 且药性温和、不良反应小, 适合长期应用。活血化瘀类中药广泛应用于硬皮病的治疗, 且从中医理论及西医客观病变指标角度都显示出了抗炎、抗纤维化、改善血管病变的作用。然而, 目前在分子水平和信号通路方面对活血化瘀类中药的作用研究较少, 可能与中药复方成分复杂, 表现出多层次、多途径、多靶点的作用特点有关。因此, 今后研究具有挑战性:

(1) 从人体临床试验、动物模型验证、细胞体外实验更为全面地研究活血化瘀类中药的作用机制, 尤其须加强基因水平的深层次研究; (2) 不仅须对中药复方整体进行研究, 更应着眼于单味中药、有效单体, 明确药物的有效成分及作用机制, 为改良中药剂型奠定基础, 也使中药治疗硬皮病更具有针对性、科学性, 进而造福硬皮病患者。

**利益冲突:** 所有作者声明不存在利益冲突。

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