DOI:10.13193/j.issn.1673-7717.2025.08.048

黄芪甲苷在肺部疾病防治中的作用和机制研究进展

叶敏[1,2,3],何光亮[1,4],刘磊[5],王丹心[5]
(1.海南科技职业大学,海南 海口 571126;2.海南医科大学,海南 海口 570100;
3.合江县中医医院,四川 合江 646200;4.西南医科大学合江医院,四川 合江 646200;
5.海南医学院第一附属医院,海南 海口 570102)

摘要:肺部疾病严重影响患者的生活质量,但治疗方法有限。黄芪甲苷(Astragaloside Ⅳ,AS-Ⅳ)具有潜在的抗炎、抗衰老和抗癌特性,在中药中已有数千年的应用历史且越来越受欢迎。大量证据表明AS-Ⅳ的保护效应可以防治肺部疾病。介绍目前AS-Ⅳ在防治肺部疾病中的作用和机制。讨论该药物在抑制氧化应激、细胞增殖和上皮-间质转化、减轻炎症反应和调节程序性细胞死亡的能力。综述当前肺部疾病面临的挑战和新策略。

关键词:黄芪甲苷;呼吸系统疾病;氧化应激;炎症反应
中图分类号:R282.71 **文献标志码**:A **文章编号**:1673-7717(2025)08-0240-06

Research Progress of Role and Mechanism about Astragaloside Ⅳ in Prevention and Treatment of Pulmonary Diseases

YE Min[1,2,3],HE Guangliang[1,4],LIU Lei[5],WANG Danxin[5]
(1. Hainan Vocational University of Science and Technology,Haikou 571126,Hainan,China;
2. Hainan Medical University,Haikou 570100,Hainan,China;
3. Hejiang County Hospital of Traditional Chinese Medicine,Hejiang 646200,Sichuan,China;
4. Hejiang Hospital,Southwest Medical University,Hejiang 646200,Sichuan,China;
5. The First Affiliated Hospital of Hainan Medical University,Haikou 570102,Hainan,China)

Abstract:Pulmonary diseases seriously affect the quality of life of patients,but the treatment methods are limited. Astragaloside Ⅳ(AS-Ⅳ) has been applied in traditional Chinese medicine for thousands of years and is becoming increasingly popular due to its potential anti-inflammatory,anti-aging and anti-cancer properties. A large amount of evidence suggests that the protective effect of AS-Ⅳ can prevent and treat lung diseases. This article introduced the current progress of role and mechanism of AS-Ⅳ in the prevention and treatment of lung diseases. The ability of the drug to inhibit oxidative stress,promote cell proliferation and epithelial mesenchymal transition,alleviate inflammatory response and regulate programmed cell death was discussed. It also summarized the challenges and new strategies faced by current lung diseases.

Keywords:astragaloside Ⅳ;respiratory system diseases;oxidative stress;inflammatory reaction

近年来,肺部疾病的高发病率日益引起人们的关注。哮喘影响2.7亿人;慢性阻塞性肺疾病(chronic obstructive pulmonary disease,COPD)是全球第三大死亡原因,每年导致约323万人死亡[1-2]。而肺癌是世界上癌症相关死亡的主要原因,每年有200万新病例和176万患者死亡[3]。肺纤维化(pulmonary fibrosis,PF)和肺动脉高压(pulmonary hypertension,PH)与患者死亡风险升高有关[4]。然而,上述疾病的可用治疗方法有限,很难治愈[5]。为了改善患者的生活质量,预防与高发病率和医疗保健使用增加有关的不良后果,我们仍然需要进一步探讨肺部疾病发病机制,期望获得新的诊断和治疗方法。

天然植物是发现和开发新药的重要来源。因此,草药作为一种肺部疾病的治疗方法正在受到科学界的关注。新出现的天然化合物之一是黄芪甲苷(Astragaloside Ⅳ,AS-Ⅳ),是从黄芪中提取的具有多靶点治疗特性的天然皂苷[6]。AS-Ⅳ的药理作用有抗衰老、抗炎、抗纤维化、抗癌等[7]。也是大脑局部缺血、动脉粥样硬化、癌症等临床疾病的推荐治疗方法[7-8]。在过去20年中,AS-Ⅳ在细胞和动物模型中改善了肺部疾病的症状[6,9]。然而,关键的药理机制仍然不清楚和有争议。在此,本文综述了AS-Ⅳ在呼吸系统疾病中的作用以及现有文献中潜在的治疗效果。

1 AS-Ⅳ在肺部疾病治疗中的作用和机制

1.1 AS-Ⅳ在肺纤维化中的作用和机制 上皮-间充质转化(Epithelial-mesenchymal transition,EMT)是将完全分化的上皮细胞转化为间充质表型的过程[10]。EMT是纤维化的主要驱动因素,并参与肺纤维化(PF)的病理过程[11]。转化生长因子-β1(Transforming growth factor -β1,TGF-β1)是一种必需的促纤维化因子,通过Smad依赖性或Smad非依赖性途径诱导EMT[12]。AS-Ⅳ通过抑制TGF-β1/磷脂酰肌醇3-激酶(PI3K)/蛋白激酶B(AKT)诱导的叉形头转录因子FOXO3α过度磷酸化,在博莱霉素(Bleomycin,BLM)诱导的大鼠肺纤维

基金项目:海南省卫生厅项目(WSJK2024QN008);海南省高等学校科学研究项目(Hnky2021ZD-15)
作者简介:叶敏(1986-),女,四川泸州人,副教授,硕士,研究方向:肺部疾病发病机制及治疗。
通讯作者:王丹心(1973-),女,海南海口人,教授,硕士研究生导师,学士,研究方向:中药在肺部疾病中的药效物质基础及作用机制。E-mail:13807588257@126.com。

变性中显示出对 EMT 的保护作用[13]。AS－Ⅳ 也通过抑制转移相关基因 1 表达来阻断 TGF－β1 诱导的肺泡Ⅱ型上皮细胞中的 EMT[14]。AS－Ⅳ 可以通过调节 NLRP3/TGF－β1 信号通路来减弱 BLM 治疗的肺泡上皮细胞中的 EMT[15]。AS－Ⅳ 治疗还可以通过抑制其他疾病模型(如糖尿病性肾病、肾纤维化、胃癌)中的 EMT 来延缓病理进展[16]。

AS－Ⅳ可调节 PF 的炎症和氧化应激[17]。AS－Ⅳ 可显著下调大鼠中白细胞介素－1β(Interleukin－1β,IL－1β),肿瘤坏死因子－α(Tumor necrosis factor－α,TNF－α)和白细胞介素－6(Interleukin－6,IL－6)的水平,抑制炎症和氧化应激来减轻 BLM 诱导的 PF 大鼠的肺组织损伤[18]。AS－Ⅳ通过阻断二氧化硅诱导的 PF 大鼠的 NF－κB 通路来抑制炎症反应。AS－Ⅳ 联合阿魏酸通过上调 BLM 诱导的 PF 小鼠的核因子－E2 相关因子 2(Nuclear factor－erythroid 2－related factor 2,Nrf2)来保护肺组织免受氧化应激[19]。

众所周知,肺成纤维细胞的不受控制地增殖和成纤维细胞向肌成纤维细胞的过度分化会产生细胞外基质(Extracellular matrix,ECM)蛋白,从而导致肺纤维化[20]。AS－Ⅳ 通过 TGF－β1/Smads 信号通路抑制成纤维细胞胶原合成和肌成纤维细胞转化[21]。此外,AS－Ⅳ可降低 BLM 诱导的 PF 大鼠肺组织中 ECM 蛋白的Ⅲ型胶原、层粘连蛋白的血液水平[22]。

ECM 蛋白的过度沉积、炎症、氧化应激和治疗药物抵抗是 PF 进展的主要因素[23]。虽然吡非尼酮和尼达尼布被批准用于 IPF 治疗,但其临床应用受到有不良反应的限制,例如胃肠道问题、光敏度和皮肤反应[24]。因此,AS－Ⅳ 单独或与其他药物联合应用是 IPF 治疗的有希望的选择,需要进一步的研究来满足日益增长的临床需求。

1.2 AS－Ⅳ 在辐射诱发肺癌中的作用和机制 癌症是拥有免疫逃逸和免疫抑制的微环境属性。因此,肿瘤微环境(Tumor microenvironment,TME)重塑已成为当前辐射诱发的肺癌治疗的一个重要研究方向[25]。AS－Ⅳ 在癌症治疗中的免疫调节作用和通过多种途径拮抗辐射诱发的肺癌的发展,如抑制细胞增殖、迁移和侵袭,以及增强化疗和靶向治疗的敏感性[26－27]。吲哚胺 2,3－双加氧酶(indoleamine 2,3－dioxygenase,IDO)是一种色氨酸分解代谢酶,可诱导辐射诱发的肺癌细胞免疫逃逸[28]。AS－Ⅳ 通过抑制 IDO 表达来上调细胞毒性 T 淋巴细胞和下调调节性 T 细胞活性来减少辐射诱发的 Lewis 肺癌小鼠模型中的肿瘤生长[29]。AS－Ⅳ 通过阻断 IDO1 与鸟苷酸结合蛋白 1 的相互作用,减少 T 细胞耗竭及抑制辐射诱发的肺癌进展,从而减少 IDO1 的细胞外分泌[30]。

肿瘤相关巨噬细胞(Tumor－associated macrophage,TAM)或 M2 极化 TAM 是 TME 中必不可少的免疫抑制细胞,其在肿瘤组织中的浸润增加往往与不良预后相关[31]。AS－Ⅳ 通过抑制单磷酸腺苷(Adenosine monophosphate,AMP)激活蛋白激酶 α 活化,显著降低 IL－13 和 IL－4 诱导的 M2 TAM 极化,并减弱 M2－CM 诱导的 A549 和 H1299 细胞中的侵袭、迁移和血管生成[32]。因此,抑制 M2 极化的 TAM 活性成为一种有希望的治疗辐射诱发的肺癌的策略[33]。AS－Ⅳ 也可抑制辐射诱发的 Lewis 肺癌小鼠模型中的肿瘤生长,并减少肿瘤组织中的 M2 TAM 浸润[34]。因此,TME 重塑可能是探索 AS－Ⅳ 抗肿瘤作用机制的一个新途径。

AS－Ⅳ可提高辐射诱发的肺癌对化疗和靶向治疗的敏感性[29]。顺铂耐药是辐射诱发的肺癌化疗失败的最主要原因[35]。AS－Ⅳ 通过抑制自噬和辐射诱发的肺癌内质网应激,增强了非小细胞肺癌(Non－small cell lung cancer,NSCLC)细胞对顺铂的敏感性[29]。此外,AS－Ⅳ 通过抑制 B7－H3 蛋白的表达,提高了 A549、HCC827 和 H1299 辐射诱发的肺癌细胞对顺铂的敏感性[29]。靶向治疗也是 NSCLC 的一种重要治疗方法,在治疗耐药性方面面临着与化疗类似的挑战。而 AS－Ⅳ 可能通过抑制自噬和激活 AKT/mTOR 信号通路来增强 A549 细胞对贝伐单抗靶向治疗的敏感性[36]。此外,吉非替尼联合 AS－Ⅳ 治疗比单独使用吉非替尼更有效地抑制 NSCLC 细胞增殖[37]。

人们越来越认识到,化疗药物抵抗和免疫逃逸对辐射诱发的肺癌的治疗管理构成重大障碍。现有的证据表明 AS－Ⅳ 改善了化疗药物抵抗,重塑了肿瘤免疫微环境,并可能为辐射诱发的肺癌的治疗带来新的曙光。

1.3 AS－Ⅳ 在肺动脉高压中的作用和机制 肺动脉平滑肌细胞(Pulmonary artery smooth muscle cells,PASMCs)的过度增殖在 PH 中肺动脉重塑的发病机制中是至关重要的[38]。AS－Ⅳ 是一种有效的 PASMCs 增殖抑制剂,可以抑制肺动脉重塑,并导致缺氧诱导的 PH 大鼠平均肺动脉压显著下降[39]。50 μm 的 AS－Ⅳ 对体外缺氧诱导的 PASMC 增殖有明显的抑制作用[40]。Notch 信号通路是一种高度进化的保守信号通路,在 PASMCs 增殖中起着重要作用[41]。Notch－3 靶向 hes 家族的 bHLH 转录因子 5(Hairy and enhancer of split 5,Hes－5)在成年人的平滑肌细胞(Smooth muscle cell,SMC)中专门表达,并且可能与 SMC 的成熟和增殖有关[42]。已经在体外和活体内证明,AS－Ⅳ 可以通过抑制 Jag－1、Notch－3 和 Hes－5 的表达来逆转缺氧诱导的 PASMCs 增殖[43]。此外,AS－Ⅳ 通过在蛋白质水平下调 RhoA 和上调 p27 来抑制缺氧条件下 PASMCs 的增殖、迁移和黏附[44]。同时,AS－Ⅳ 通过下调 Bcl－2,磷酸化 ERK 和缺氧诱导因子－1α 的表达,改善了 PASMCs 的抗凋亡病理生理学凋亡[45]。

另外,越来越多的证据表明,炎症在肺血管重塑中的作用[46]。AS－Ⅳ 治疗减弱了由 NLRP－3/calpain－1 介导的炎症反应,从而减轻野百合碱(Monocrotaline,MCT)诱导的 PH 大鼠肺血管重塑[47]。AS－Ⅳ 降低了 MCT 诱导的 PH 大鼠血液中 TNF－α 和 IL－1β 的水平[46]。此外,AS－Ⅳ 还降低了缺氧诱导的 PH 大鼠血清中内皮素－1、血管紧张素Ⅱ、TNF－α 和 IL－6 的水平[48]。

在治疗这种疾病的过程中,PH 和 AS－Ⅳ 靶点或途径有多种致病因素。因此,AS－Ⅳ 抗 PH 的临床前机制尚未完全阐明。尽管如此,文献表明,AS－Ⅳ 作为 PH 的治疗成分或预防药物的潜力,特别是在缺乏良好的临床选择的 PH 患者。

1.4 AS－Ⅳ 在肺损伤中的作用和机制 AS－Ⅳ 可能通过降低炎症反应和调节细胞程序性死亡(Programmed cell death,PCD)而成为肺损伤的保护剂[49]。细颗粒物(Fine Particulate Matter,PM2.5)、百草枯(Paraquat,PQ)、肺组织的缺氧/复氧(Hypoxia/Reoxygenation of lung tissue,H/R)等多种病理因素均可引起肺损伤,损害肺功能。

PM2.5 诱导的肺损伤与多种 PCD 途径的活化有关,包括铁浓缩、细胞焦亡和自噬等。

铁浓缩拥有脂质过氧化氢的铁依赖性堆积属性,可以诱发各种呼吸系统疾病[50]。这种 PCD 机制可能参与了与慢性阻塞性肺病、PH 和肺损伤有关的病理细胞死亡[51－52]。谷胱甘肽过氧化酶 4 是铁浓缩症的已知威慑因素[53]。在 PM2.5 诱导的小鼠模型中,AS－Ⅳ 通过 Nrf2/SLC7a11/GPX4 信号通路抑

制铁浓缩、炎症和氧化应激,导致肺组织出现保护效应[52]。

自噬作为一种进化上保守的细胞内降解途径,对于细胞稳态至关重要[54]。自噬在肺损伤的发病机制中起关键作用[55]。AS-Ⅳ可通过抑制自噬在 PM2.5 诱导的大鼠肺损伤中发挥保护作用,主要通过 PI3K/AKT 信号通路下游的哺乳动物雷帕霉素靶蛋白(Mammalian target of rapamycin,mTOR)[49]。同时 AS-Ⅳ也通过激活自噬 AMP 活化蛋白激酶 AMPK/mTOR 信号通路来减轻 PM2.5 诱导的大鼠肺毒性[56]。这些结果表明,自噬在 PM 2.5 诱导的肺损伤中起双刃剑的作用,AS-Ⅳ通过自噬诱导或自噬通量抑制在肺损伤中发挥治疗作用。

细胞焦亡是由炎症小体复合物内 Caspase-1 的活化和细胞内脂多糖识别后引起的 PCD 的促炎症形式[57]。AS-Ⅳ通过抑制 NLRP3 炎性体介导的细胞焦亡通过 NLRP3/Caspase-1 轴抑制对 PM2.5 诱导的肺毒性的保护作用[9]。因此,PM2.5 诱导的肺部炎症和氧化损伤被阻止,导致小鼠存活时间延长。此外,AS-Ⅳ可通过抑制 TLR4/MyD88/NF-κB 信号通路和炎症来预防 PM2.5 诱导的大鼠肺损伤,并延缓肺组织损伤[58]。

PQ 可引起多系统损伤,尤其是严重的肺组织损伤[59]。AS-Ⅳ在 PQ 损伤的小鼠中减少了 Txnip/Trx 的表达并抑制了 Rho/ROCK/NF-κB 信号通路,从而减轻了肺组织损伤[60]。

H/R 也能诱发肺泡上皮细胞的凋亡,导致肺损伤[61]。AS-Ⅳ通过上调 miR-21-5p 抑制 TLR4/NF-κB 途径,从而在体外减弱 H/R 损伤诱导的Ⅱ型肺泡上皮细胞凋亡[62]。此外,肺缺血/再灌注(Ischemia/Reperfusion,I/R)肺损伤可严重限制术后肺功能的恢复,并导致并发症,如 PH、肺水肿和呼吸衰竭,最终导致患者死亡[63]。AS-Ⅳ通过降低肺组织过氧化物酶水平和肺湿干比(D/W)来减轻大鼠的 I/R 肺损伤[64]。

肺和肺泡损伤引起的肺功能受损是许多急性和慢性肺部疾病的特征。由于 AS-Ⅳ抗衰老和抗炎作用,其可以减轻各种病理因素引起的肺损伤。然而,大多数相关的研究只是基于动物实验,未来还需要相关的临床试验。

1.5 AS-Ⅳ在慢性阻塞性肺病中的作用和机制 慢性阻塞性肺病(Chronic obstructive pulmonary disease,COPD)是一种常见的气道慢性炎症性疾病,不可逆转的气流受限为特征,是全球第三大死亡原因[65]。尽管对慢性阻塞性肺病的病理机制知之甚少,但气道炎症和氧化损伤涉及疾病病理生理学的许多方面[66]。COPD 患者长时间的气流受限会导致呼吸肌疲劳,进一步加重病情。例如,膈肌功能受损往往会引起呼吸衰竭[67]。AS-Ⅳ在体外通过抑制 AKT 凋亡,Caspase-3 和 Caspase-9 蛋白表达,ROS 和炎症反应产生来减弱 IL-8 诱导的膈肌细胞中的磷酸化和炎症因子[68]。

香烟烟雾(Cigarette smoke,CS)仍然是 COPD 最关键的危险度[69]。因此,长期接触香烟烟雾是目前 COPD 啮齿动物模型的最佳方法。对小鼠的研究表明,AS-Ⅳ通过抑制 JAK3/STAT3/NF-κB 途径以剂量依赖性方式减轻 CS 诱导的肺组织病理损伤[70]。同样,AS-Ⅳ可显著抑制香烟烟雾提取物诱导的人支气管上皮细胞中 JAK3/STAT3/NF-κB 途径中的蛋白质水平[71]。此外,AS-Ⅳ已被证明是一种有效的 NF-κB 途径抑制剂,并且通过对 CS 诱导的 COPD 大鼠气道炎症施加保护效应[72]。

1.6 AS-Ⅳ在哮喘中的作用和机制 哮喘是一种具有多种潜在炎症途径和结构性气道异常的异质性疾病[73]。AS-Ⅳ可以通过调节各种炎症细胞和介质(如嗜中性粒细胞,IL-4 和 IL-10)来抑制气道炎症和减少气道超敏反应(Airway hyperresponsiveness,AHR)[74]。AS-Ⅳ通过抑制 Janus 激酶 2/STAT6(JAK2/STAT6)信号传导途径改善了卵清蛋白(Ovalbumin,OVA)致敏的哮喘小鼠模型中的气道炎症和 AHR[58]。另外,AS-Ⅳ通过下调 IL-4 和 IL-10,上调干扰素-γ和增强 OVA 诱导的哮喘小鼠模型中的 $CD4^+CD25^+Foxp3T$ 细胞来减弱变应性炎症[75]。

支气管上皮细胞非特异性炎症在哮喘病情恶化的病理特征中极其重要[76]。AS-Ⅳ通过阻断 NF-κB 和丝裂原活化蛋白激酶信号传导途径来抑制人类支气管上皮细胞中的炎症和氧化应激[77]。AS-Ⅳ通过抑制雷帕霉素复合物 1 信号传导途径的机制靶点来改善 AHR,减轻肺部炎症,并减少炎症介质如 IL-4、IL-5 和 IL-17 的产生[77]。

嗜酸性粒细胞参与哮喘病情进展,包括气道重塑、高反应性和气道变应性炎症[78]。因此,减少嗜酸性粒细胞在气道的浸润将有效地治疗这种疾病。AS-Ⅳ抑制气道中的嗜酸性粒细胞浸润,从而抑制过敏原致敏和过敏原激发的小鼠的黏液分泌过多、气道炎症和反应过度[79]。同样,50 μg/mL AS-Ⅳ在体外显著抑制由尘螨诱导的嗜酸性粒细胞[78]。总之,AS-Ⅳ的抗炎和防老化特征为哮喘患者提供了潜在的治疗选择。

2 AS-Ⅳ应用面临的挑战与新策略

尽管 AS-Ⅳ对肺部疾病有很好的治疗效果,但有几个问题限制了其临床应用。例如,这种天然皂苷是一种相对较大的分子(分子量=784.97 g/mol),在水中的可溶性较差,导致目标部位的生物利用度较低,特别是通过口服给药[80]。在灌注的大鼠肠道模型中,AS-Ⅳ表现出较低的吸收率,而口服生物利用度只有 2.2%[81]。在比格犬中 AS-Ⅳ的绝对口腔生物利用度只有 7.4%[82]。虽然研究显示 AS-Ⅳ的潜在毒性较低,但亦有其他研究报告了该化合物的生殖毒性[83]。AS-Ⅳ对大鼠的母体毒性为 1 mg/kg,胎儿毒性>0.5 mg/kg[83]。

脂质体是疏水性药物的有效载体,具有增效、减毒的作用。有研究者开发了一种新型多功能脂质体,用于装载 AS-Ⅳ药物输送,显著提高了该化合物的生物利用度和疗效[81]。此外,由于能够大大提高天然药物的功效,利用纳米材料开发新药正在成为趋势。有趣的是,最近的一项研究表明,甘草衍生的蛋白质纳米颗粒通过包封可增溶不溶性 AS-Ⅳ[84]。此外,载有 AS-Ⅳ的脂质纳米胶囊可以有效地管理干性老年黄斑变性[85]。尽管如此,AS-Ⅳ纳米制剂离临床翻译还有好几年的时间,需要药理学家、化学家和材料科学家的共同努力来开发一种稳定、可扩展和有效的产品。天然产物的结构修饰可提高药效并使毒性最小化。然而,现有文献对 AS-Ⅳ的结构修饰缺乏研究。

虽然多靶点调控是 AS-Ⅳ在肺部疾病中的一个治疗特点,但是这种方法对临床翻译造成了很大的障碍。如果不同的生理状况和复杂的信号传导途径导致药物不能准确定位,可能会出现多种药物副作用,从而降低药物的体内活性。因此,确定肺疾病中 AS-Ⅳ的特定治疗靶点是目前的重要研究方向之一。有研究表明,AS-Ⅳ通过转录组学技术阻断 NLR 信号传导,从而减轻了糖尿病性肾病大鼠的肾纤维化[86]。此外,也有研究证实,通过转录组筛选和实验确证 miR-26b-5p/ATF3/JUN 是 AS-Ⅳ心脏保护作用的主要介质[86]。另外,有学者利用定量蛋白质组学显示 AS-Ⅳ通过靶向 DCP1A 和 TMSB4X 诱导自噬来抑制子宫颈癌细胞侵袭[87]。因此,转录组学、蛋白质组学和代谢组学等现代生物技术可能是探索 AS-Ⅳ对肺疾病特异性治疗靶点的可靠方法。

临床试验表明,200 mL 黄芪静脉注入健康的中国志愿者中是安全和耐受性良好的,表明 AS－Ⅳ 具有很好的临床应用潜力[88]。尽管如此,大多数应用 AS－Ⅳ 治疗肺疾病的研究都集中在临床前模型上。因此,有必要进行临床研究,以确认 AS－Ⅳ 在预防和治疗肺部疾病方面的有效性和安全性。长期的研究发现,应用药物组合是实现最佳效果的关键,为 AS－Ⅳ 的临床翻译提供了一个新的思路。例如,AS－Ⅳ 和阿魏酸组合在各种纤维化疾病模型中表现出协同作用,因此是一种有希望的抗纤维化治疗[88]。此外,AS－Ⅳ 与阿托伐他汀,贝伐单抗,丹参酮 IIA 和人参皂苷 Rg1 的组合已被用于临床前研究以治疗各种疾病[89－90]。综上所述,AS－Ⅳ 复合治疗在肺部疾病的应用是值得未来研究的。

3 结论与展望

AS－Ⅳ 是一种具有多种有益生物活性的天然皂苷,在预防肺部疾病的作用和机制研究方面取得了重大进展。这种天然皂苷通过抗炎、防老化、细胞增殖、EMT 抑制和 PCD 调节来抑制肺部疾病的进展。确切地说,AS－Ⅳ 联合阿魏酸、顺铂和贝伐单抗显示出协同作用,并显著提高药物疗效。更重要的是,AS－Ⅳ 活体内显示出低毒性,从而促进了未来的临床翻译。尽管 AS－Ⅳ 在多种肺部疾病的临床前模型中具有良好的治疗作用,但其作用机制和直接靶点仍有待阐明。现代生物技术,如转录组学、表面等离子共振和蛋白质微阵列技术,提供了填补 AS－Ⅳ 研究知识空白的新策略。然而,AS－Ⅳ 应用于肺部疾病的一个主要障碍是缺乏临床资料。因此,未来的研究应着眼于临床试验,以确认 AS－Ⅳ 治疗肺部疾病的有效性和安全性。此外,AS－Ⅳ 的高分子量导致低生物利用度,进一步限制了其临床应用。新型的药物输送系统,如纳米胶囊,改善了 AS－Ⅳ 生物利用度。总之,AS－Ⅳ 是治疗肺部疾病的潜在候选药物,在未来的研究中有待进一步开发。

参考文献

[1] YAN Q, FORNO E, HERRERA－LUIS E, et al. A genome－wide association study of asthma hospitalizations in adults[J]. J Allergy Clin Immunol, 2021, 147(3): 933－940.
[2] ZHANG Y C, SHENG Y X, GAO Y R, et al. Exploration of the pathogenesis of chronic obstructive pulmonary disease caused by smoking－based on bioinformatics analysis and *in vitro* experimental evidence[J]. Toxics, 2023, 11(12): 995.
[3] DING D X, WANG L B, ZHANG Y Q, et al. Machine learning developed a programmed cell death signature for predicting prognosis and immunotherapy benefits in lung adenocarcinoma[J]. Transl Oncol, 2023, 38: 101784.
[4] RIGATO M, MONAMI M, FADINI G P. Autologous cell therapy for peripheral arterial disease: systematic review and meta－analysis of randomized, nonrandomized, and noncontrolled studies[J]. Circ Res, 2017, 120(8): 1326－1340.
[5] ZHANG Y P, WANG L Y, WANG Z D, et al. Surface－anchored microbial enzyme－responsive solid lipid nanoparticles enabling colonic budesonide release for ulcerative colitis treatment[J]. J Nanobiotechnology, 2023, 21(1): 145.
[6] WANG Q, XU J C, LI M M, et al. Nrf2 knockout attenuates the astragaloside IV therapeutic effect on kidney fibrosis from liver cancer by regulating pSmad3C/3L pathways[J]. Naunyn Schmiedebergs Arch Pharmacol, 2024, 397(3): 1687－1700.
[7] LU L, CHEN B, ZHANG X Y, et al. The effect of phytochemicals in N－methyl－N－nitro－N－nitroguanidine promoting the occurrence and development of gastric cancer[J]. Front Pharmacol, 2023, 14: 1203265.
[8] HU LC, DING M Y, HE W C. Emerging therapeutic strategies for attenuating tubular EMT and kidney fibrosis by targeting Wnt/β－catenin signaling[J]. Front Pharmacol, 2022, 12: 830340.
[9] SUN Y, LU M L, SUN T R, et al. Astragaloside IV attenuates inflammatory response mediated by NLRP－3/calpain－1 is involved in the development of pulmonary hypertension[J]. J Cell Mol Med, 2021, 25(1): 586－590.
[10] FAN Y, ZHAO X X, MA J F, et al. LncRNA GAS5 competitively combined with miR－21 regulates PTEN and influences EMT of peritoneal mesothelial cells *via* Wnt/β－catenin signaling pathway[J]. Front Physiol, 2021, 12: 654951.
[11] LI J P, LIU J, YUE W F, et al. Andrographolide attenuates epithelial－mesenchymal transition induced by TGF－β1 in alveolar epithelial cells[J]. J Cell Mol Med, 2020, 24(18): 10501－10511.
[12] TOMA T, TATEISHI H, KAWAKAMI K, et al. Novel inhibitor for downstream targeting of transforming growth factor－β signaling to suppress epithelial to mesenchymal transition and cell migration[J]. Int J Mol Sci, 2022, 23(9): 5047.
[13] WEI S C, QI F, WU Y P, et al. Overexpression of KLF4 suppresses pulmonary fibrosis through the HIF－1α/endoplasmic reticulum stress signaling pathway[J]. Int J Mol Sci, 2023, 24(18): 14008.
[14] HE H J, JI X Y, CAO L H, et al. Medicine targeting epithelial－mesenchymal transition to treat airway remodeling and pulmonary fibrosis progression[J]. Can Respir J, 2023, 2023: 3291957.
[15] HU Y H, TANG W N, LIU W J, et al. Astragaloside IV alleviates renal tubular epithelial－mesenchymal transition *via* CX3CL1－RAF/MEK/ERK signaling pathway in diabetic kidney disease[J]. Drug Des Devel Ther, 2022, 16: 1605－1620.
[16] GUAN Y Q, QUAN D L, CHEN K, et al. Kaempferol inhibits renal fibrosis by suppression of the sonic hedgehog signaling pathway[J]. Phytomedicine, 2023, 108: 154246.
[17] LIU S S, LI Y, WU C J. Paeoniflorin suppresses the apoptosis and inflammation of human coronary artery endothelial cells induced by oxidized low－density lipoprotein by regulating the Wnt/β－catenin pathway[J]. Pharm Biol, 2023, 61(1): 1454－1461.
[18] SINGH J, PHOGAT A, PRAKASH C, et al. N－acetylcysteine reverses monocrotophos exposure－induced hepatic oxidative damage via mitigating apoptosis, inflammation and structural changes in rats[J]. Antioxidants (Basel), 2021, 11(1): 90.
[19] TONG J H, WU Z S, WANG Y C, et al. Astragaloside IV synergizing with ferulic acid ameliorates pulmonary fibrosis by TGF－β 1/Smad3 signaling[J]. Evid Based Complement Alternat Med, 2021, 2021: 8845798.
[20] RAGURAMAN R, SRIVASTAVA A, MUNSHI A, et al. Therapeutic approaches targeting molecular signaling pathways common to diabetes, lung diseases and cancer[J]. Adv Drug Deliv Rev, 2021, 178: 113918.
[21] PAPAKONSTANTINOU E, ROTH M, TAMM M, et al. Hypoxia differentially enhances the effects of transforming growth factor－beta isoforms on the synthesis and secretion of glycosaminoglycans by human lung fibroblasts[J]. J Pharmacol Exp Ther, 2002, 301(3): 830－837.
[22] BAI Y, LIANG C, GAO L, et al. Celastrol pyrazine derivative alleviates silicosis progression *via* inducing ROS－mediated apoptosis in activated fibroblasts[J]. Molecules, 2024, 29(2): 538.
[23] RESENDE V Q, REIS－GOES K H, FINATO A C, et al. Combined silymarin and cotrimoxazole therapy attenuates pulmonary fibrosis in experimental paracoccidioidomycosis[J]. J Fungi (Ba-

sel), 2022, 8(10): 1010.
[24] GHUMMAN M, DHAMECHA D, GONSALVES A, et al. Emerging drug delivery strategies for idiopathic pulmonary fibrosis treatment [J]. Eur J Pharm Biopharm, 2021, 164: 1-12.
[25] PENG H J, LI X Q, LUAN Y C, et al. A novel prognostic model related to oxidative stress for treatment prediction in lung adenocarcinoma[J]. Front Oncol, 2023, 13: 1078697.
[26] TOYOMASU Y, MATSUI K, OMORI K, et al. Tenascin C in radiation-induced lung damage: Pathological expression and serum level elevation[J]. Thorac Cancer, 2022, 13(20): 2904-2907.
[27] LIU J T, CHEN L, ZHANG J L, et al. AS-IV enhances the antitumor effects of propofol in NSCLC cells by inhibiting autophagy [J]. Open Med (Wars), 2023, 18(1): 20230799.
[28] YANG X Y, ZHANG W Z, JIANG W, et al. Nanoconjugates to enhance PDT-mediated cancer immunotherapy by targeting the indoleamine-2, 3-dioxygenase pathway[J]. J Nanobiotechnology, 2021, 19(1): 182.
[29] ZHANG L L, LI Q, ZHONG D S, et al. MCM5 aggravates the HDAC1-mediated malignant progression of lung cancer[J]. Front Cell Dev Biol, 2021, 9: 669132.
[30] NETH B J, WEBB M J, PARNEY I F, et al. The current status, challenges, and future potential of therapeutic vaccination in glioblastoma[J]. Pharmaceutics, 2023, 15(4): 1134.
[31] YANG Y C, TIAN Q, WU S Q, et al. Blue light-triggered Fe^{2+}-release from monodispersed ferrihydrite nanoparticles for cancer iron therapy[J]. Biomaterials, 2021, 271: 120739.
[32] XIA D Q, LI W J, TANG C, et al. Astragaloside IV, as a potential anticancer agent[J]. Front Pharmacol, 2023, 14: 1065505.
[33] ZHAO X P, WANG X Y, YOU Y, et al. Nogo-B fosters HCC progression by enhancing Yap/Taz-mediated tumor-associated macrophages M2 polarization [J]. Exp Cell Res, 2020, 391(1): 111979.
[34] QIN Y, ZHANG L F, LIANG X, et al. Venous and arterial thromboembolism in patients with metastatic lung cancer[J]. Clin Appl Thromb Hemost, 2023, 29: 10760296231159121.
[35] XIE M Y, DING K, JING X M, et al. Identification and verification of hub genes associated with the progression of non-small cell lung cancer by integrated analysis[J]. Front Pharmacol, 2022, 13: 997842.
[36] YOU X J, WU Y R, LI Q X, et al. *Astragalus*-scorpion drug pair inhibits the development of prostate cancer by regulating GDPD4-2/PI3K/AKT/mTOR pathway and autophagy[J]. Front Pharmacol, 2022, 13: 895696.
[37] ZHANG X W, LI L, HU W Q, et al. Neurokinin-1 receptor promotes non-small cell lung cancer progression through transactivation of EGFR[J]. Cell Death Dis, 2022, 13(1): 41.
[38] XIAO X H, LUO F M, FU M Y, et al. Evaluating the therapeutic role of selected active compounds in *Plumula Nelumbinis* on pulmonary hypertension *via* network pharmacology and experimental analysis[J]. Front Pharmacol, 2022, 13: 977921.
[39] XI J, MA Y, LIU D M, et al. Astragaloside IV restrains pyroptosis and fibrotic development of pulmonary artery smooth muscle cells to ameliorate pulmonary artery hypertension through the PHD2/HIF1α signaling pathway[J]. BMC Pulm Med, 2023, 23(1): 386.
[40] HOU X H, CHEN J, LUO Y J, et al. Silencing of STIM1 attenuates hypoxia-induced PASMCs proliferation *via* inhibition of the SOC/Ca^{2+}/NFAT pathway[J]. Respir Res, 2013, 14(1): 2.
[41] O'HARE M, ARBOLEDA-VELASQUEZ J F. Notch signaling in vascular endothelial and mural cell communications [J]. Cold Spring Harb Perspect Med, 2022, 12(9): a041159.
[42] LING X T, MA X Q, KUANG X L, et al. Lidocaine inhibits myoblast cell migration and myogenic differentiation through activation of the Notch pathway[J]. Drug Des Devel Ther, 2021, 15: 927-936.
[43] WANG A P, YANG F, TIAN Y, et al. Pulmonary artery smooth muscle cell senescence promotes the proliferation of PASMCs by paracrine IL-6 in hypoxia-induced pulmonary hypertension[J]. Front Physiol, 2021, 12: 656139.
[44] ZENG Z M, WANG X Y, CUI L D, et al. Natural products for the treatment of pulmonary hypertension: mechanism, progress, and future opportunities [J]. Curr Issues Mol Biol, 2023, 45(3): 2351-2371.
[45] YANG C K, PAN Q Q, JI K, et al. Review on the protective mechanism of astragaloside IV against cardiovascular diseases[J]. Front Pharmacol, 2023, 14: 1187910.
[46] TANG Y, TAN S Y, LI M Q, et al. Dapagliflozin, sildenafil and their combination in monocrotaline-induced pulmonary arterial hypertension[J]. BMC Pulm Med, 2022, 22(1): 142.
[47] YU W D, XIE D J, WANG Y, et al. Apolipoprotein A1 is associated with pulmonary vascular resistance and adverse clinical outcomes in patients with pulmonary hypertension secondary to heart failure [J]. Pulm Circ, 2022, 12(3): e12096.
[48] DAI Y, QIU Z H, MA W R, et al. Long-term effect of a vaccine targeting endothelin-1 receptor type A in pulmonary arterial hypertension[J]. Front Cardiovasc Med, 2021, 8: 683436.
[49] PEI C X, WANG F, HUANG D M, et al. Astragaloside IV Protects from $PM_{2.5}$-Induced Lung Injury by Regulating Autophagy *via* Inhibition of PI3K/Akt/mTOR Signaling *in vivo* and *in vitro*[J]. J Inflamm Res, 2021, 14: 4707-4721.
[50] CAO Y M, PAN H Q, YANG Y W, et al. Screening of potential key ferroptosis-related genes in Chronic Obstructive Pulmonary Disease [J]. Int J Chron Obstruct Pulmon Dis, 2023, 18: 2849-2860.
[51] GHOSH A J, SAFERALI A, LEE S, et al. Blood RNA sequencing shows overlapping gene expression across COPD phenotype domains [J]. Thorax, 2022, 77(2): 115-122.
[52] TRIVEDI A, KHAN M A, BADE G, et al. Orchestration of neutrophil extracellular traps (nets), a unique innate immune function during chronic obstructive pulmonary disease (COPD) development [J]. Biomedicines, 2021, 9(1): 53.
[53] PARK J S, KIM D H, CHOI H I, et al. 3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) induces cell death through ferroptosis and acts as a trigger of apoptosis in kidney cells[J]. Cell Death Dis, 2023, 14(2): 78.
[54] HUANG X, YAO J, LIU L, et al. Atg8-PE protein-based *in vitro* biochemical approaches to autophagy studies[J]. Autophagy, 2022, 18(9): 2020-2035.
[55] TING L, FENG Y Y, ZHOU Y, et al. IL-27 induces autophagy through regulation of the DNMT1/lncRNA MEG3/ERK/p38 axis to reduce pulmonary fibrosis[J]. Respir Res, 2023, 24(1): 67.
[56] WANG X M, WANG Y L, HUANG D M, et al. Astragaloside IV regulates the ferroptosis signaling pathway *via* the Nrf2/SLC7A11/GPX4 axis to inhibit $PM_{2.5}$-mediated lung injury in mice[J]. Int Immunopharmacol, 2022, 112: 109186.
[57] SHI Z J, YUAN S Y, SHI L L, et al. Programmed cell death in spinal cord injury pathogenesis and therapy[J]. Cell Prolif, 2021, 54(3): e12992.
[58] YUAN F Y, YANG Y, LIU L, et al. Research progress on the mechanism of astragaloside IV in the treatment of asthma[J]. Heliyon, 2023, 9(11): e22149.

[59] SHI M D, ZENG M, JIAN T Z, et al. A mass event of paraquat poisoning *via* inhalation [J]. Front Public Health, 2023, 11: 1309708.
[60] LARKI-HARCHEGANI A, FAYAZBAKHSH F, NOURIAN A, et al. Chlorogenic acid protective effects on paraquat-induced pulmonary oxidative damage and fibrosis in rats[J]. J Biochem Mol Toxicol, 2023, 37(7): e23352.
[61] AI L, LI Y X, LIU Z J, et al. Tempol attenuates chronic intermittent hypoxia-induced lung injury through the miR-145-5p/Nrf2 signaling pathway[J]. Cell Mol Biol (Noisy-le-grand), 2023, 69(13): 225-234.
[62] WANG J, KE J, WU X, et al. Astragaloside prevents UV-induced keratinocyte injury by regulating TLR4/NF-κB pathway [J]. J Cosmet Dermatol, 2022, 21(3): 1163-1170.
[63] LI H, YAO C, SHI K H, et al. Astragaloside IV attenuates hypoxia/reoxygenation injury-induced apoptosis of type II alveolar epithelial cells through miR-21-5p[J]. Bioengineered, 2021, 12(1): 7747-7754.
[64] LV X J, LU X M, ZHU J P, et al. Lipopolysaccharide-induced acute lung injury is associated with increased ran-binding protein in microtubule-organizing center (RanBPM) molecule expression and mitochondria-mediated apoptosis signaling pathway in a mouse model[J]. Med Sci Monit, 2020, 26: e923172.
[65] MASJEDY A, SALESI M, AHMADI A, et al. Association between single-nucleotide polymorphism of cytokines genes and chronic obstructive pulmonary disease: a systematic review and meta-analysis [J]. Cytokine, 2023, 171: 156352.
[66] FENG X Y, DONG H, LI B B, et al. Integrative analysis of the expression profiles of whole coding and non-coding RNA transcriptomes and construction of the competing endogenous RNA networks for chronic obstructive pulmonary disease[J]. Front Genet, 2023, 14: 1050783.
[67] GANASSI M, MUNTONI F, ZAMMIT P S. Defining and identifying satellite cell-opathies within muscular dystrophies and myopathies [J]. Exp Cell Res, 2022, 411(1): 112906.
[68] REARDON P M, WONG J, FITZPATRICK A, et al. Diaphragm function in acute respiratory failure and the potential role of phrenic nerve stimulation [J]. Curr Opin Crit Care, 2021, 27(3): 282-289.
[69] WARE S A, KLIMENT C R, GIORDANO L, et al. Cell-free DNA levels associate with COPD exacerbations and mortality[J]. Respir Res, 2024, 25(1): 42.
[70] LI L Y, ZHANG C T, ZHU F Y, et al. Potential natural small molecular compounds for the treatment of chronic obstructive pulmonary disease: an overview[J]. Front Pharmacol, 2022, 13: 821941.
[71] ZHANG Y, XUE X M, MENG L H, et al. Roles of autophagy-related genes in the therapeutic effects of Xuanfei Pingchuan capsules on chronic obstructive pulmonary disease based on transcriptome sequencing analysis[J]. Front Pharmacol, 2023, 14: 1123882.
[72] LI L, GUAN J, LIN R J, et al. Astragaloside IV alleviates lung inflammation in *Klebsiella* pneumonia rats by suppressing TGF-β1/Smad pathway[J]. Braz J Med Biol Res, 2023, 56: e12203.
[73] GEORAS S N, WRIGHT R J, IVANOVA A, et al. The precision interventions for severe and/or exacerbation-prone (PrecISE) asthma network: an overview of network organization, procedures, and interventions[J]. J Allergy Clin Immunol, 2022, 149(2): 488-516.
[74] HSIEH H L, LIU S H, CHEN Y L, et al. Astragaloside IV suppresses inflammatory response *via* suppression of NF-κB, and MAPK signalling in human bronchial epithelial cells[J]. Arch Physiol Biochem, 2022, 128(3): 757-766.
[75] YANG Q Q, ZHANG H Y, DUAN X H, et al. Astragaloside IV targeting autophagy of T cells improves inflammation of asthma[J]. J Asian Nat Prod Res, 2024, 26(6): 699-713.
[76] CAI X J, HUANG L H, ZHU Y K, et al. LncRNA OIP5-AS1 aggravates house dust mite-induced inflammatory responses in human bronchial epithelial cells *via* the miR-143-3p/HMGB1 axis[J]. Mol Med Rep, 2020, 22(6): 4509-4518.
[77] JING W B, JI H J, JIANG R, et al. Astragaloside positively regulated osteogenic differentiation of pre-osteoblast MC3T3-E1 through PI3K/Akt signaling pathway[J]. J Orthop Surg Res, 2021, 16(1): 579.
[78] YAMAGUCHI M, NISHIMURA Y, TAKUMI Y, et al. Real-world safety and effectiveness of benralizumab in Japanese patients with severe asthma: a multicenter prospective observational study [J]. J Asthma Allergy, 2024, 17: 45-60.
[79] SÁNCHEZ G B, BUNN K E, PUA H H, et al. Extracellular vesicles: mediators of intercellular communication in tissue injury and disease[J]. Cell Commun Signal, 2021, 19(1): 104.
[80] HU J F, PAN D, LI G, et al. Regulation of programmed cell death by Brd4[J]. Cell Death Dis, 2022, 13(12): 1059.
[81] YUE Y, LIU X J, PANG L, et al. *Astragalus* polysaccharides/PVA nanofiber membranes containing astragaloside IV-loaded liposomes and their potential use for wound healing[J]. Evid Based Complement Alternat Med, 2022, 2022: 9716271.
[82] DENNINGER A, BECKER T, WESTEDT U, et al. Advanced *in vivo* prediction by introducing biphasic dissolution data into PBPK models[J]. Pharmaceutics, 2023, 15(7): 1978.
[83] QIU S D, LIU Y, PAN Y H, et al. Developmental and reproduction toxicity studies of Biolimus A9 in SD rats[J]. Reprod Toxicol, 2023, 116: 108338.
[84] ZHOU J W, ZHANG J, GAO G Z, et al. Boiling licorice produces self-assembled protein nanoparticles: a novel source of bioactive nanomaterials [J]. J Agric Food Chem, 2019, 67(33): 9354-9361.
[85] SUN R, ZHANG A N, GE Y, et al. Ultra-small-size Astragaloside-IV loaded lipid nanocapsules eye drops for the effective management of dry age-related macular degeneration[J]. Expert Opin Drug Deliv, 2020, 17(9): 1305-1320.
[86] WANG M Z, SHI Y N, YAO L, et al. Identification of hub genes in protective effect of astragaloside IV on aconitine-induced cardiac damage in zebrafish based on bioinformatics analysis [J]. Front Pharmacol, 2020, 11: 957.
[87] XIA C L, HE Z H, CAI Y T. Quantitative proteomics analysis of differentially expressed proteins induced by astragaloside IV in cervical cancer cell invasion[J]. Cell Mol Biol Lett, 2020, 25: 25.
[88] QUE R F, ZHENG J L, CHANG Z H, et al. Dl-3-n-butylphthalide rescues dopaminergic neurons in Parkinson's disease models by inhibiting the NLRP3 inflammasome and ameliorating mitochondrial impairment[J]. Front Immunol, 2021, 12: 794770.
[89] HE G N, CHEN G F, LIU W D, et al. Salvianolic acid B: a review of pharmacological effects, safety, combination therapy, new dosage forms, and novel drug delivery routes[J]. Pharmaceutics, 2023, 15(9): 2235.
[90] ZHANG J J, GUO F F, WU H W, et al. Yixin-Shu facilitated cardiac-like differentiation of mesenchymal stem cells *in vitro*[J]. RSC Adv, 2018, 8(18): 10032-10039.