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综 述
Review

补骨脂黄酮治疗骨关节疾病的研究现状

Current research status on psoralen flavonoids for treating bone and joint diseases

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摘要：骨关节疾病涵盖骨质疏松症、骨关节炎、类风湿关节炎、痛风性关节炎等，患病率高、致残负担重，已成为全球重要公共卫生问题。现有治疗手段主要依赖药物干预与手术治疗，整体干预手段相对有限。补骨脂(*Psoralea corylifolia L.*)为我国传统中药材，富含多种黄酮类小分子化合物，具有多靶点、多环节调控优势，在骨与关节疾病中的防治中备受关注。现有证据显示，该类化合物兼具成骨促进、破骨抑制、抗炎、抗氧化及代谢调节等综合效应，但其关键活性物质基础及作用网络尚未系统阐明。基于此，本文旨在系统阐述补骨脂黄酮在骨关节疾病治疗中的药理作用及分子机制，以期为骨关节疾病的临床防治提供新的研究思路及潜在策略，并进一步探讨其临床转化应用前景及面临的主要挑战。

关键词：补骨脂；黄酮类；骨质疏松；骨关节炎；类风湿关节炎；痛风性关节炎

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Abstract: Bone and joint diseases encompass conditions such as osteoporosis, osteoarthritis, rheumatoid arthritis, and gouty arthritis. With high prevalence rates and a significant burden of disability, they have become a major global public health issue. Current treatment approaches primarily rely on drug interventions and surgical procedures, with relatively limited options for comprehensive intervention strategies. *Psoralea corylifolia L.* (Buguzhi), a traditional Chinese medicinal herb, is rich in various flavonoid small-molecule compounds. Its multi-targeted, multi-step regulatory advantages have drawn significant attention in the prevention and treatment of bone and joint diseases. Existing evidence indicates that these compounds exhibit comprehensive effects including osteogenesis promotion, osteoclast inhibition, anti-inflammation, antioxidant activity, and metabolic regulation, However, its key active substances and functional networks have yet to be systematically elucidated. Based on this, this paper aims to systematically elucidate the pharmacological actions and molecular mechanisms of psoralen flavonoids in the treatment of osteoarthritis, with the goal of providing novel research perspectives and potential strategies for the clinical prevention and treatment of this condition. Furthermore, it explores the prospects for clinical translation and the primary challenges encountered.

Key words: *Psoralea corylifolia L.*; flavonoids; osteoporosis; osteoarthritis; rheumatoid arthritis; gouty arthritis

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人体骨骼系统主要由骨骼与关节构成,作为机体的重要运动与支撑结构,其功能不仅在于维持形态与实现多样化运动,还为内部器官提供有效的机械防护和缓冲作用[1]。骨骼与关节疾病涵盖多种疾病,包括骨折、骨关节炎、类风湿关节炎、骨质疏松、痛风性关节炎和骨相关恶性肿瘤等。根据 2019 年全球疾病负担研究的综合分析结果,骨骼肌肉系统疾病在全球非传染性疾病中位居患病率首位,受累人群高达约 17.1 亿人。其中,仅骨关节炎患者人数就达到约 3.4 亿人,而骨折患者更是超过 4.3 亿[2],而且在 2021 年全球疾病负担研究中发现,除腰痛和骨关节炎外的其他骨骼肌肉疾病是全球第 5 位致残年长的原因[3]。进一步表明此类疾病已构成全球公共健康巨大挑战。尽管如此,目前提供的治疗选择有限,主要依赖于传统药物和手术治疗[4],主要的管理方式为生活方式改变、教育、锻炼和疼痛控制[5]。

补骨脂为豆科植物补骨脂 *Psoralea corylifolia L.* 的干燥成熟果实,已鉴定化学成分约 163 种,主要包括香豆素类、黄酮类、单萜类、苯并呋喃类及糖苷类等[6]。其药理活性丰富,包括抗炎、抗菌、抗病毒、抗氧化、抗肿瘤、抗骨质疏松、心脏保护、神经保护及免疫调节等多方面效应[7]。目前,从补骨脂中分离并鉴定出 72 种类黄酮,在加工方面,盐渍加工与油炸等传统工艺仍为补骨脂加工的主流方式[8]。补骨脂富含的多种黄酮类小分子化合物,已被证实具有抗氧化、抗炎、雌激素样等生物活性[9]。近年来,多项基础与临床研究发现这类黄酮类化合物在骨关节疾病的防治中作用显著,因此本文旨在系统综述补骨脂黄酮类小分子在治疗骨关节疾病中的分子作用机制,以期为该类疾病的预防和治疗提供理论参考。

1 黄酮类小分子化合物的化学组成与药理特性

来源于补骨脂的黄酮类小分子化合物是一类骨架结构为 2-苯基色烯-4-酮的化合物,其按母核结构可分为黄酮类、黄酮醇类、二氢黄酮类、异黄酮类、查尔酮类等[10]。补骨脂黄酮整体呈现出多靶点、多层面的药理效应特征。在炎症调控方面,已有研究表明其可下调炎性介质释放并减轻炎症相关组织损伤,如在高脂饮食诱导的 LDL 受体基因敲除(LDLR$^{-/-}$)小鼠中,补骨脂黄酮可显著改善脂质谱并抑制血清炎症细胞因子[11];在氧化应激效应方面,如新补骨脂异黄酮通过抑制过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor alpha, PPARα)信号通路诱导肝脂质代谢障碍和氧化应激,从而逆转肝损伤[12],补骨脂二氢黄酮也可通过抑制氧化应激和增强线粒体功能,从而改善糖尿病肾病[13]。更重要的是,补骨脂黄酮在骨代谢调控方面显示出骨关节保护效应。部分黄酮类化合物的分类及化学式见表 1。

表 1 部分黄酮类化合物的分类及化学式

Table 1 Classification and chemical formulas of selected flavonoids

主要成分类型	化学成分名称	化学式
黄酮类	补骨脂异黄酮 D	$C_{20}H_{16}O_5$
	补骨脂异黄酮 C	$C_{20}H_{18}O_5$
	4′-甲氧基黄酮	$C_{16}H_{12}O_3$
黄酮醇类	黄芪苷	$C_{21}H_{20}O_{11}$
	3,5,3′,4′-四羟基-7-甲氧基黄酮	$C_{32}H_{38}O_{20}$
二氢黄酮类	补骨脂二氢黄酮	$C_{19}H_{19}O_4$
	异补骨脂二氢黄酮	$C_{20}H_{19}O_4$
	补骨脂二氢黄酮甲醚	$C_{20}H_{21}O_4$
异黄酮类	补骨脂异黄酮	$C_{20}H_{16}O_4$
	新补骨脂异黄酮	$C_{20}H_{18}O_4$
	corylifol A	$C_{15}H_{26}O_4$
查尔酮类	异补骨脂查尔酮	$C_{20}H_{20}O_4$

2 黄酮类小分子化合物治疗骨质疏松及机制

骨质疏松症(osteoporosis, OP)是一种全身代谢性骨病,主要特征为骨量减少、骨小梁微结构破坏,导致骨脆性增加和骨折风险升高[14]。其分子机制普遍认为与骨重塑过程失衡密切相关,表现为破骨细胞活性增强、成骨细胞活性减弱,或两者兼有,从而加速骨吸收并抑制骨形成[15]。OP 的发生涉及多条关键信号通路的异常调控,包括 Wnt/β-连环蛋白(Wnt/β-catenin)[16]、核因子 κB 受体活化因子配体/核因子 κB 受体活化因子(receptor activator of nuclear factor kappa-B ligand/receptor activator of nuclear factor kappa-B, RANKL/RANK)[17]、磷脂酰肌醇-3-激酶/蛋白激酶 B/糖原合成激酶 3β(phosphatidylinositol 3-kinase/protein kinase B/glycogen synthase kinase 3β, PI3K/Akt/GSK3β)[18]以及核因子红细胞-2 相关因子 2/血红素加氧酶-1(nuclear factor erythroid 2-related factor 2/heme oxygenase-1, Nrf2/HO-1)[19]等。

近年来,有研究发现[20]补骨脂异黄酮(corylin)可通过激活 Wnt/β-catenin 信号通路,显著上调成骨细胞中骨形成相关关键转录因子和基质蛋白的表达,如 Runt 相关转录因子 2(runt-related transcription factor 2, Runx2)、成骨细胞特异性转录因子(osterix)、I 型胶原蛋白(type I collagen, Col-1)和碱性磷酸酶(alkaline phosphatase, ALP),从而增强骨形成能力。在双侧卵巢切除(ovariectomy, OVX)模型大鼠中,高浓度补骨脂二氢黄酮(bavachin)处理显著提升 Wnt3a、低密度脂蛋白受体相关蛋白 5(low-density lipoprotein receptor

-related protein 5, LRP5)和 β-catenin 的表达水平，LRP5 进一步与 Wnts 和卷曲蛋白(frizzled)结合促进信号转导，此过程可被 Wnt 抑制剂 Dkk1 明显阻断，证实 Bavachin 可特异性激活典型 Wnt 通路，促进成骨分化[21]。LI 等[22]的实验表明，Corylifol A 能显著抑制 PI3K、AKT 及 GSK-3β 的磷酸化，并通过激活 Nrf2 信号减少 ROS 生成及抑制线粒体氧化磷酸化，从而缓解氧化应激并改善 OP 病理表型。

在破骨细胞调控方面，LIU 等[23]指出，异补骨脂查尔酮(isobavachalcone, IBC)可通过抑制核因子 κB(nuclear factor κB, NF-κB)信号传导并下调 *miR*-193-3*p* 表达，抑制破骨细胞分化与骨吸收。既往研究证实[24]，异补骨脂二氢黄酮(isobavachin)可降低破骨细胞内铁积累，并抑制线粒体生物合成和功能，减少 ROS 生成，从而有效抑制 RANKL 诱导的骨髓来源单核细胞(bone marrow-derived macrophages, BMMs)及 RAW264.7 细胞向破骨细胞分化。新补骨脂异黄酮(neobavaisoflavone, NBIF)则表现出剂量依赖性抑制作用，其机制为阻断 RANKL 与肿瘤坏死因子受体相关因子 6(tumor necrosis factor receptor-associated factor 6, TRAF6)/原癌基因酪氨酸-蛋白激酶(oncogene tyrosine protein kinase, c-Src)的结合，进一步抑制下游 NF-κB、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPKs)及 Akt 信号通路的活化，在双侧 OVX 小鼠模型中表现出显著的抗骨吸收效应[25]。此外，与 RANKL 诱导的 BMMs 相比，Corylifol A(7.5, 15 μM)处理组细胞内活性氧(reactive oxygen species, ROS)水平明显降低，同时过氧化氢酶(catalase, CAT)、超氧化物歧化酶(superoxide dismutase, SOD1)和 Nrf2 蛋白表达上调，该结果提示，提示其可通过激活 Nrf2/HO-1 轴并增强抗氧化酶表达，促进 ROS 清除，从而减弱 RANKL 诱导的破骨细胞生成与功能[17]。补骨脂来源黄酮类化合物在 OP 防治中表现出双重作用，实现骨重塑的重建并降低骨吸收。部分黄酮类小分子化合物治疗 OP 的作用机制见图 1[26]。

3 黄酮类小分子化合物治疗骨关节炎及机制

骨关节炎(osteoarthritis, OA)是最常见的慢性关节疾病，其主要特征为软骨下骨重塑为主要特征，临床表现包括活动后疼痛、关节僵硬、摩擦音、活动受

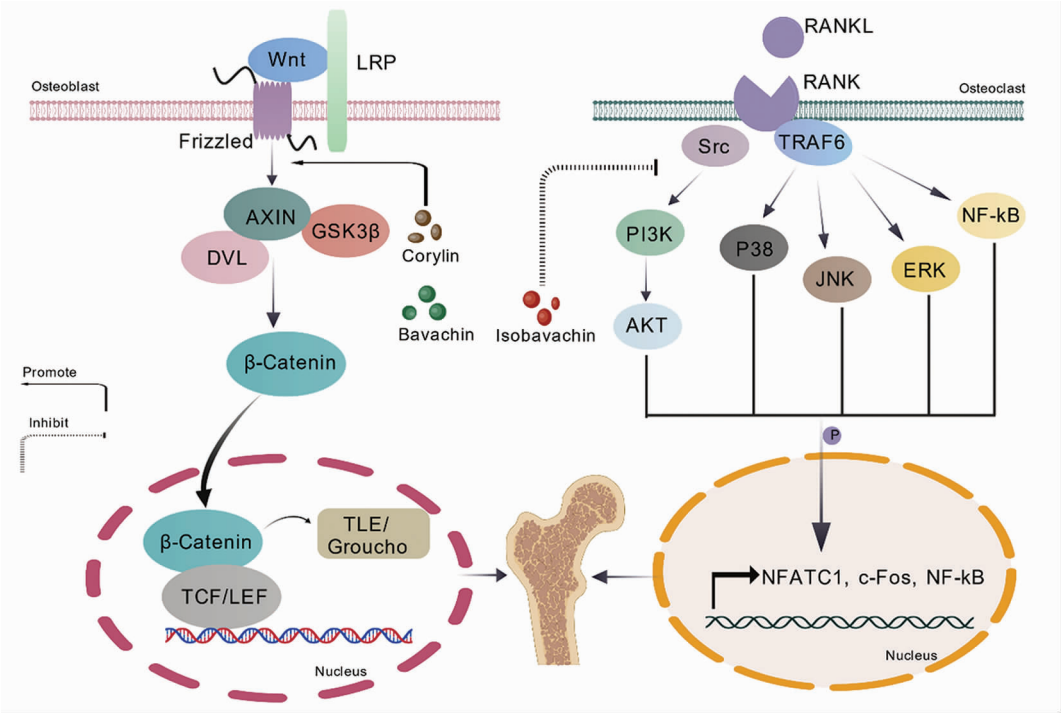

图 1 部分黄酮类小分子化合物治疗骨质疏松症(OP)的作用机制

Figure 1 Mechanisms of action of certain flavonoid small molecules in the treatment of osteoporosis (OP)

LRP: Low-density lipoprotein receptor-related protein; AXIN: Axis inhibitor; DVL: Dishevelled; GSK3β: Glycogen synthase kinase 3β; TCF/LEF: T-cell factor/lymphoid enhancer-binding factor; RANKL: Receptor activator of nuclear factor kappa-B ligand; RANK: Receptor activator of nuclear factor kappa-B; TRAF6: Tumor necrosis factor receptor-associated factor 6; Src: Steroid receptor coactivator; PI3K: Phosphatidylinositol-3-kinase; Akt: Protein kinase B; JNK: c-Jun N-terminal kinase; ERK: Extracellular regulated protein kinases; NF-κB: Nuclear factor κB; NFATC1: Nuclear factor of activated T cells 1; c-Fos: Cellular fos.

限,严重者可出现关节畸形,该病好发于膝、髋和手指等关节[27]。OA的主要病理改变可涉及关节软骨破坏与侵蚀、滑膜增生与炎症反应、异常血管生成、软骨下骨紊乱以及韧带与肌腱结构不稳定等,这些改变可能共同或分别驱动疾病发生与进展[28]。

既往实验研究中,GUO等[29]和FAN等[30]分别采用前交叉韧带离横断(anterior cruciate ligament transection, ACLT)及半月板不稳定(destabilization of the medial meniscus, DMM)建立大鼠OA模型,并给予IBC治疗,结果显示,与对照组相比,IBC组软骨形状更加规整,骨关节炎软骨损伤分级(osteoarthritis research society international, OARSI)评分显著降低,基质金属蛋白酶13(matrix metallopeptidase 13, MMP13)表达减少,提示IBC可有效改善大鼠软骨退变,减缓OA进程。

OA的发生机制涉及多条信号通路的激活,如PI3K/AKT/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)[31],Janus激酶2/信号转导和转录激活因子3(janus kinase 2/signal transducer and activator of transcription 3, JAK2/STAT3)[32],成纤维细胞生长因子2-成纤维细胞生长因子受体2(fibroblast growth factor 2-fibroblast growth factor receptor 2, FGF2-FGFR2)[33]以及NF-κB[34]等。CHENG等在OA患者来源的软骨细胞中发现,Bavachin(10~20 μM)可抑制人核因子κB抑制蛋白α(inhibitor of nuclear factor kappa Bα, IκBα)降解及kappa-B抑制因子激酶(inhibitor of kappa B kinase, IKK)和NF-κB的转录活性,同时显著降低白细胞介素-1β(interleukin-1β,IL-1β)诱导的趋化因子如调节激活正常T细胞表达分泌因子(regulated on activation, normal T cell expressed and secreted, RANTES)、单核细胞趋化蛋白2(monocyte chemoattractant protein-2, MCP-2)、巨噬细胞炎性蛋白1α(macrophage Inflammatory protein-1 alpha, MIP-1α)及MIP-1β的水平,其作用机制可能与抑制IL-1β诱导的IKK-IκBα-NF-κB途径有关[35]。MA等则报道,紫云英苷(Astragalin)可剂量依赖性抑制人OA软骨细胞中IL-1β诱导的一氧化氮(nitric oxide, NO)、前列腺素E2(prostaglandin E2,PGE2)、诱导型一氧化氮合酶(inducible nitric oxide synthase,iNOS)和环氧化酶2(oxygenase 2,COX-2)表达,并通过激活过氧化物酶体增殖物激活受体γ(peroxisome proliferator-activated receptor γ,PPAR-γ)下调炎症介质,从而抑制NF-κB和MAPK通路的活化[36]。

在体外模型研究中,研究人员利用脂多糖(lipopolysaccharide, LPS)1 μg·mL^{-1}刺激原代大鼠软骨细胞模拟炎症性OA状态,IBC处理可显著抑制iNOS、COX-2、基质金属蛋白酶3(matrix metallopeptidase, MMP3)、MMP13和血小板反应蛋白解整合素金属肽酶5(recombinant a disintegrin and metalloproteinase with thrombospondin 5, ADAMTS5)表达,同时逆转LPS诱导的Ⅱ型胶原蛋白(Collagen type II)和聚集蛋白(Aggregin)减少,其机制与抑制NF-kB通路活化密切相关[29]。相似地,IL-1β(10 ng·mL^{-1})刺激小鼠膝关节软骨细胞并给予IBC后,可剂量依赖性抑制IL-1β诱导的IκBα和P65磷酸化,进一步证实了PI3K/Akt/NF-kB信号通路在IBC治疗OA中的重要作用[30]。BAI等在内侧副韧带切除术大鼠OA模型中发现,新补骨脂异黄酮(neobavaisoflavone, NBIF)可减少软骨基质降解与软骨细胞凋亡;在IL-1β诱导的大鼠软骨细胞体外模型中,新补骨脂异黄酮抑制NF-κB磷酸化与低氧诱导因子-2α(hypoxia-inducible factor-2α, HIF-2α)表达,通过阻断NF-κB/HIF-2α通路发挥抗凋亡、抗炎及抗氧化应激作用[37]。黄酮类小分子化合物在多种OA模型中均表现出显著的抗炎、抗氧化和软骨保护作用,其分子机制主要涉及NFκB、PI3K/AKT、MAPK及PPARγ等关键信号通路的调控,为其在OA预防与治疗中的潜力提供了实验学依据。部分黄酮类小分子化合物治疗OA的作用机制见图2[26]。

4 黄酮类小分子化合物治疗类风湿关节炎及机制

类风湿关节炎(rheumatoid arthritis, RA)是一种常见的系统性炎症性自身免疫疾病,其病理特征包括滑膜组织过度增生、赘生物形成、软骨与骨骼破坏,临床上以对称性关节疼痛、肿胀及晨硬为主要表现[38]。RA的发病涉及自身免疫系统的多重失调,包括自身反应性CD4$^+$T细胞与致病性B细胞异常活化、巨噬细胞浸润,以及炎症细胞因子、趋化因子和多种自身抗体水平异常升高[39]。

在动物模型研究中,JIA等[40]采用牛Ⅱ型胶原蛋白诱导法建立RA小鼠模型,并给予Astragalin治疗,结果明显抑制了肿瘤坏死因子-α(tumour necrosis factor-α, TNF-α)、IL-1β、IL-6和IL-8等炎症因子的产生,并下调滑膜细胞和软骨细胞中MMP-1、MMP-3及MMP-13的表达,从而减轻了小鼠的滑膜炎症和关节结构破坏。在细胞水平研究中[41],补骨脂二氢黄酮可上调维生素D受体(vitamin D receptor, VDR)和类视黄醇X受体α(retinoid X

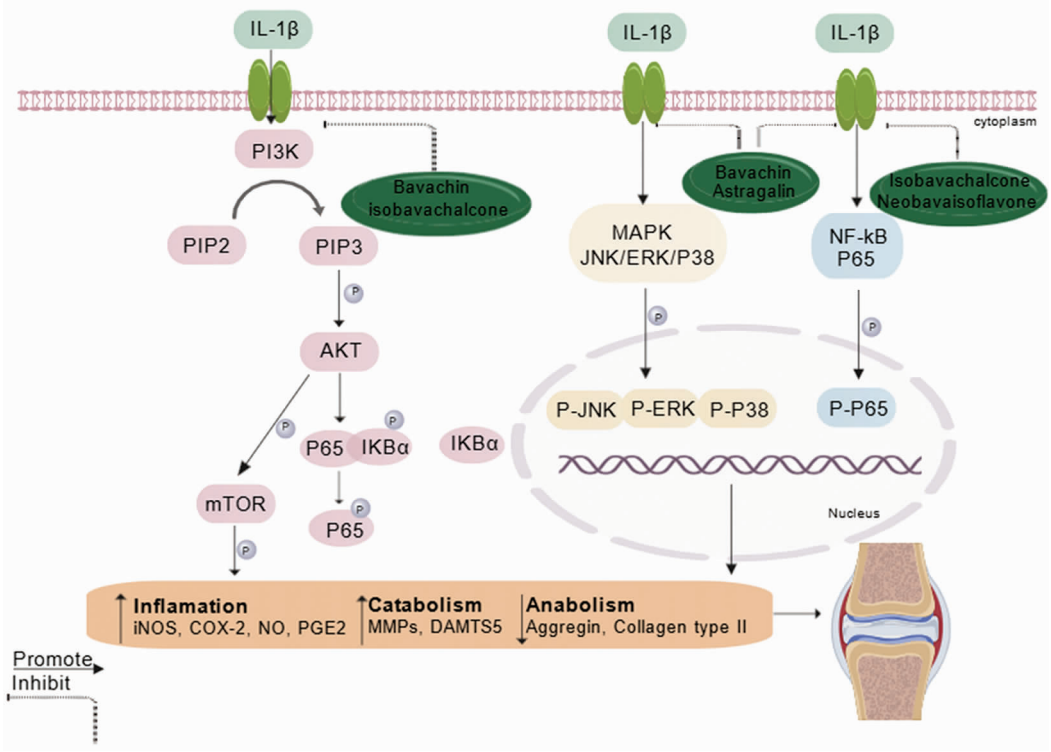

图 2 部分黄酮类小分子化合物治疗骨关节炎(OA)的作用机制

Figure 2 Mechanisms of action of some flavonoid small molecules in the treatment of osteoarthritis (OA)

IL-1β: Interleukin-1β; PIP2: Phosphatidylinositol 4,5-bisphosphate; IκBα: Inhibitor of nuclear factor kappa Bα; mTOR: Mammalian target of rapamycin; MAPK: Mitogen-activated protein kinase; JNK: c-jun n-terminal kinase; iNOS: Inducible nitric oxide synthase; COX-2: Oxygenase 2; PGE2: Prostaglandin E2; MMPs: Matrix metalloproteinases; DAMTS5: Disintegrin and metalloproteinase with thrombospondin motifs 5

receptor alpha, RXRα)的 mRNA 及蛋白质表达,并增强了二者之间的结合,从而激活维生素 D 信号通路。此外,补骨脂二氢黄酮还可调节相关钙信号,减少成纤维样滑膜细胞(fibroblast-like synoviocytes, FLS)中的钙沉积,从而减缓 RA 的病理进展。

现有证据显示,RA 的病理过程涉及多条信号通路异常激活,包括 PI3K/AKT[42], JAK/STAT[43], MAPK[44]以及 NF-κB 通路[45]等。IBC 在 TNF-α 刺激的 MH7A 细胞中显著下调 PI3K、AKT、JAK1、STAT3 及细胞因子信号传导抑制因子 3(suppressor of cytokine signaling 3, SOCS3)的磷酸化水平,抑制 PI3K/AKT 和 JAK/STAT 通路的激活,并在 RA 大鼠模型中明显改善大鼠爪部肿胀症状[46]。此外,异补骨脂查尔酮还可显著抑制 TNF-α 预刺激人类风湿性关节炎成纤维细胞 MH7A 的增殖和迁移,降低 MMP-1、MMP-3、IL-1β、IL-2、IL-6、IL-17、γ-干扰素(interferon-γ, IFN-γ)和单核细胞趋化蛋白 1(monocyte chemoattractant protein-1, MCP-1)等炎症介质的表达[46]。Astragalin 同样能抑制 TNF-α 诱导的 MH7A 细胞中 MMPs 的表达及 p38 与 JNK 的磷酸化,其作用机制可能与阻断 JNK/p38/AP-1 和 MAPK 信号通路有关[40]。补骨脂黄酮类小分子化合物可调控 VDR/RXRα 及抑制 PI3K/AKT、JAK/STAT、MAPK 和 NF-kB 等关键炎症通路,显著抑制滑膜细胞的炎症反应与关节破坏,从而为 RA 的治疗提供了可行的药理学依据。

5 黄酮类小分子化合物治疗痛风性关节炎及机制

痛风性关节炎(gouty arthritis, GA)是常见的炎症性关节病,其核心特征为高尿酸血症和单钠尿酸盐单晶(monosodium urate, MSU)在滑膜及关节周围组织的沉积,急性发作时表现为突发性剧烈疼痛、关节肿胀、红热等症状[47]。该病可能常反复发作,并可在关节内形成痛风石,导致结构性损伤和功能障碍[48]。其发病机制与 NOD 样受体热蛋白结构域相关蛋白 3(NOD-like receptor-associated protein 3, NLRP3)炎症小体的活化[49]和 ROS 信号网络密切相关,ROS 作为关键上游因子,与 MAPK 信号、中性粒细胞胞外诱捕器(neutrophil extracellular traps, NETs)、自噬通量及铁死亡等下游通路密切耦合。可以有效抑制 GA 关节组织中的炎症、氧化应激、细胞坏死和病理症状[50]。

既往研究表明[51-52],异补骨脂二氢黄酮(Isoba-

vachin)在体外可显著抑制肾近曲小管的关键尿酸盐转动体1(urate transporter 1, URAT1)和葡萄糖转运蛋白9(glucose transporter 9, GLUT9)的功能,此外,ZHAO等[51]进一步发现,在高尿酸血症动物模型中,Isobavachin(10~20mg·Kg^{-1})可能通过与黄嘌呤氧化酶(xanthine oxidase,XOD)的Mo-Pt催化中心相互作用,显著抑制XOD活性,从而减少尿酸生成。基于天然产物的新型骨架的发现,为高尿酸血症药物研发提供了巨大前景的方向。在慢性高尿酸血症小鼠模型中,CEN等报道[53],Isobavachin可在成骨细胞中激活G蛋白偶联受体35-NOD样受体热蛋白结构域相关蛋白3(G protein-coupled receptor 35-NOD-like receptor-associated protein 3, GPR35-NLRP3)通路,进而负向调控高浓度可溶性尿酸诱导的NLRP3过度活化,维持成骨分化能力并减轻骨丢失。异补骨脂二氢黄酮兼具调控体内尿酸稳态与抑制炎症小体活化的双重潜力,有望成为治疗高尿酸血症介导骨丢失的新型治疗策略。

6 结语

骨关节疾病是全球范围内高发且致残率较高的一类慢性疾病,其致病机制复杂,涉及炎症、免疫、氧化应激、骨重塑失衡等多重病理过程,严重影响患者生活质量并加重公共卫生负担。补骨脂来源黄酮类小分子化合物具有多靶点、多环节的调控优势,可同时作用于成骨促进、破骨抑制、抗炎抗氧化以及尿酸代谢调节等关键环节。现有研究已在骨质疏松、骨关节炎、类风湿关节炎及痛风性关节炎等多种实验模型中验证其显著的骨保护与关节保护作用,并明确其参与Wnt/β-catenin、RANKL/RANK、PI3K/Akt/GSK3β、Nrf2/HO-1、NFκB、MAPK、JAK/STAT等关键信号通路,为天然产物在骨关节疾病防治中的深入应用提供了重要理论依据和实验支持。

然而,当前研究仍存在一定局限性:① 多数证据来自细胞及动物模型,缺乏高质量的多中心随机对照临床试验验证,其在临床人群中的长期安全性和有效性尚未明确;② 分子机制研究深度不足,现有工作多聚焦于单一通路或单一成分,缺乏基于网络药理学、多组学及系统生物学的"多组分-核心靶点-多通路"交叉研究,对各组成分与各通路的协同/拮抗效应及核心药效靶点尚未清晰界定;③ 多数黄酮类化合物存在生物利用度低、代谢稳定性不足等药代动力学瓶颈,限制其由基础研究向临床转化的进程[54];④ 体内毒理学证据仍显不足,例如有研究提示Bavachinin可能诱发小鼠肝毒性[55],提示需进一步系统评估药物安全范围与风险控制。

基于上述局限,未来研究可重点围绕以下方向推进:① 基于先前的基础实验证据,设计并开展科学严谨的多中心随机对照临床试验,为其纳入骨关节疾病诊疗指南提供高质量循证证据;② 深化机制研究,结合单细胞测序、蛋白组学、代谢组学等技术,构建补骨脂黄酮类化合物作用于骨关节微环境的"多组分-核心靶点-多通路"信号网络图谱,明确不同疾病阶段、不同细胞类型的关键靶点与通路交互关系;③ 通过药物化学修饰优化理化性质与药代动力学特征,联用纳米递药、靶向载体与缓释体系,提高药物在病灶组织的有效浓度与作用持续性,增强临床可用性;④ 系统开展体内毒理学评估,明确剂量-暴露-毒性关系,探索基于分子分型与病理的精准用药策略,提升安全性与治疗针对性。

综上,补骨脂黄酮类小分子化合物作为具有多靶点综合干预优势的天然药物资源,在骨关节疾病防治领域展现出重要的应用潜力和发展价值。随着机制研究的深入与转化应用的推进,其有望为骨关节疾病的综合防治提供安全、有效且可持续的新型治疗选择。

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