

中药在骨质疏松症治疗中的研究进展

孟庆贺*, 殷婉祺, 刘晓颖[#]

大连医科大学附属第一医院全科医学科, 辽宁 大连

收稿日期: 2024年12月7日; 录用日期: 2025年1月1日; 发布日期: 2025年1月9日

摘要

骨质疏松症是一种骨骼疾病, 目前临床上治疗该病的西药可能产生药物副作用, 长期使用可能存在某些弊端。近年来, 一些经典的骨特异性的天然中药被广泛关注, 它们似乎具有促进成骨细胞活性和抑制破骨细胞的作用, 能够在细胞水平改善骨代谢, 而且副作用较少, 具有独特优势。因此, 本文从中药治疗的角度出发, 综述了目前治疗该病的常见天然中药及其作用机理, 同时对其临床应用前景进行探索, 以期抗骨质疏松症治疗提供新策略。

关键词

骨质疏松症, 中药治疗, 药理作用, 综述

Research Progress of Traditional Chinese Medicine in the Treatment of Osteoporosis

Qinghe Meng*, Wanqi Yin, Xiaoying Liu[#]

Department of General Practice, First Affiliated Hospital of Dalian Medical University, Dalian Liaoning

Received: Dec. 7th, 2024; accepted: Jan. 1st, 2025; published: Jan. 9th, 2025

Abstract

Osteoporosis is a bone disease. The current western medicine for the treatment of the disease may have side effects, and long-term use may have some disadvantages. In recent years, some classical bone-specific natural traditional Chinese medicines have been widely focused. They seem to have the effect of promoting osteoblast activity and inhibiting osteoclasts, and can improve bone metabolism at the cellular level with few side effects, which has unique advantages. Therefore, from the perspective of traditional Chinese medicine treatment, this article reviews the common natural

*第一作者。

[#]通讯作者。

Chinese herbs for the treatment of osteoporosis and their mechanism of action, and explores their clinical application prospects, in order to provide new strategies for the treatment of osteoporosis.

Keywords

Osteoporosis, Traditional Chinese Medicine Treatment, Pharmacological Action, Review

Copyright © 2025 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

骨质疏松症是一种最为常见的代谢性骨病,主要表现为骨量减少、骨组织微结构破坏进而导致骨痛、骨脆性及骨折危险性增加[1]。随着我国人口老龄化的加快,该病的发病率呈现逐年升高的趋势。目前用于治疗骨质疏松症的药物包括双磷酸盐类、降钙素、绝经激素治疗、选择性雌激素受体调节剂、甲状旁腺激素类似物等。然而,这些药物长期应用可能产生某些弊端。如双磷酸盐会增加胃肠道不耐受、颌骨坏死、非典型股骨骨折和肾功能损伤的风险。降钙素具有潜在增加肿瘤风险的可能。绝经激素治疗会增加子宫内膜癌、乳腺癌、心血管疾病、血栓等风险。选择性雌激素受体调节剂会增加静脉栓塞的危险性。甲状旁腺激素类似物常见不良反应为恶心、眩晕等[2]。近年来,越来越多的人开始关注用传统中医药治疗骨质疏松症,与西药相比,中药长期服用不良反应较少,通常通过“多成分、多靶点、多途径”的模式发挥治疗作用,这与骨质疏松症的多因素性质相吻合[3]。因此,本文系统综述了目前常见的用于治疗骨质疏松症的中药及它们可能的作用机理,并评估了它们在治疗骨质疏松症方面的潜力。

2. 人参

人参皂苷是人参、西洋参和三七的主要活性物质,具有镇痛、抗炎、抗过敏、抗肿瘤等作用[4] [5]。人参皂苷通过上调细胞内成骨转录因子和成骨相关基因产物的表达,诱导成骨前体细胞成骨分化,刺激成骨细胞增殖,促进骨结节形成和基质矿化,进而显示出抗骨质疏松的作用[6]。

人参皂苷包括 Rb1、Rb2、Rb3、Rh2、Rd、Rc、Rg1、Rg2 和 Rg3 [4] [5] [7] [8]。一项动物实验证明,人参皂苷 Rb1 可促进成骨细胞分化,其机制与芳香烃受体(AHR)的上调有关。AHR 可通过与 PRELP (proline/arginine-rich end leucine-rich repeat protein)启动子区域结合促进 PRELP 转录,从而导致其上调。同时,PRELP 可抑制核转录因子 κ B (nuclear factor kappa-B, NF- κ B)通路的激活,这是 AHR 促进成骨分化的基础[9]。因此,人参皂苷 Rb1 可能是通过调节 AHR/PRELP/NF- κ B 轴来延缓骨质疏松症的进展,这为治疗骨质疏松症提供了理论依据。此外,人参皂苷复合物-k (CK)是人参皂苷 Rb1 的代谢产物之一,具有抗衰老、抗炎、抗癌、降脂等作用。一项动物实验结果表明,CK 通过抑制 NF- κ B p65 磷酸化和氧化应激,抑制核因子- κ B 受体激活剂配体(receptor activator of nuclear factor kappa B ligand, RANKL)介导的小鼠单核巨噬细胞白血病细胞的破骨细胞分化和活性氧,从而抑制骨髓源性巨噬细胞的骨吸收,即通过抑制破骨细胞的活性和减轻体内氧化应激减轻骨质流失[10]。

人参皂苷 Rb2 是人参中含量最多的皂苷,它能提高碱性磷酸酶活性,促进钙矿化和成骨 mRNA 表达,发挥抗骨质疏松的作用。一项关于人参皂苷 Rb2 对生酮饮食所致骨质量恶化的实验研究表明,人参皂苷 Rb2 可有效改善生酮饮食所致骨质疏松症的骨质流失并维持其生物力学表现。潜在机制可能是人参

皂苷 Rb2 抑制骨吸收过程并诱导成骨分化, 这为人参皂苷作为治疗生酮饮食所致骨质疏松症的替代方案提供了证据[6]。

人参皂苷 Rc 与 Rb1、Rb2 化学结构相似。一项动物实验表明, 人参皂苷 Rc 可增强骨小梁的微观结构, 促进骨形成相关基因的表达, 通过激活 β -catenin 和成骨基因 Runt 相关转录因子 2 (Runt-related transcription factor 2, RUNX2) 典型 Wnt 通路促进成骨细胞分化和基质矿化, 进而上调骨标志物的表达增加骨形成[4]。因此有望成为预防和治疗骨质疏松症的天然替代品。

人参皂苷 Rg1 是人参皂苷中最有效的成分之一, 它可以调节细胞增殖、分化和再生, 具有抗炎、抗凋亡等药理活性。人参皂苷 Rg1 能够干预葡萄糖的运输和储存, 通过改变胰岛素分泌以及与受体的结合控制血糖, 通过调节骨形态发生蛋白 2 (bone morphogenetic protein 2, BMP2)/SMAD 信号通路促进大鼠骨髓间充质干细胞的成骨分化[5], 还可通过介导磷脂酰肌醇 3 激酶(Phosphatidylinositol 3 kinase, PI3K)/丝氨酸/苏氨酸蛋白激酶(RAC- α serine/threonine-protein kinase, Akt)通路中的 G 蛋白偶联雌激素受体表达, 调节 Akt 磷酸化, 进而调控成骨[11]。一项体外实验还发现, Rg1 可增加骨祖细胞的数量, 减轻高糖诱导的骨祖细胞凋亡, 促进骨祖细胞分泌血管内皮生长因子(vascular endothelial growth factor, VEGF)以及成骨和血管的耦联。Rg1 还可促进高糖培养的人脐静脉内皮细胞增殖, 增强内皮细胞的血管生成能力, 并激活 Notch 通路, 促进内皮细胞分泌成骨相关因子 Noggin 来调节成骨, 进一步促进血管生成和骨形成。体内实验也证实 Rg1 促进 VEGF 分泌, 激活 Noggin/Notch 通路, 增加 H 型血管与成骨的耦联水平, 进而改善骨质疏松症大鼠的骨结构, 在糖尿病性骨质疏松症中发挥积极作用。因此, Rg1 作为一种潜在的生物活性分子, 是治疗糖尿病性骨质疏松症有希望的候选药物[5]。

人参皂苷 Rg2 是人参根、茎、叶中主要的活性成分之一, 在抗细胞凋亡、抗糖尿病、心血管保护以及调控炎症因子等方面发挥作用。一项实验结果表明, 人参皂苷 Rg2 的治疗作用与 c-Fos 和活化 T 细胞胞质核因子 1 (nuclear factor of activated T cell cytoplasmic 1, NFATc1) 表达降低以及与细胞外调节蛋白激酶(extracellular regulated protein kinase, ERK)、c-Jun-N 端激酶(c-Jun-N-terminal kinase, JNK)和 p38 磷酸化有关, 从而导致抗酒石酸酸性磷酸酶和破骨细胞相关受体的表达降低, 故人参皂苷 Rg2 可能成为预防和治療骨质疏松症的草药[7]。

同样, 有研究发现, 人参皂苷 Rg3 可能通过腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)/雷帕霉素蛋白(mammalian target of rapamycin, mTOR)信号通路减轻卵巢切除术诱导的骨质疏松症[8], 还能有效缓解氯化铝诱导[12]以及糖皮质激素引发的骨质疏松症, 这可能源于其具有促进骨形成和抑制骨吸收的作用, 通过调节骨形态发生蛋白-2 信号通路减轻糖皮质激素的效应, 是治疗糖皮质激素诱导的骨质疏松症的潜在候选药物[13]。

3. 丹参

丹参因其抗氧化特性, 被广泛用于治疗外伤、骨折和活血化瘀等。丹参的主要化合物有丹酚酸 A、丹酚酸 B、丹参酮 IIA、丹参醇等, 它们通过增加成骨相关基因和蛋白的表达促进骨形成, 并通过抑制活性氧减少破骨细胞生成, 发挥抗骨质疏松的作用[14]。有 36 项临床试验将丹参与其他草药和成分结合使用, 用于治疗绝经后、老年性和继发性骨质疏松症, 发现这些治疗方案具有疗效高、毒性低的特点[15]。

隐丹参酮可由天然中药丹参中提取, 一项体内和体外实验的证据表明, 隐丹参酮通过抑制破骨细胞分化的激活, 继而抑制破骨细胞前体中组织蛋白酶 K (Cathepsin K, CTSK)、c-Fos 和 NFATc1 的表达, 从而发挥抗破骨细胞生成的作用, 并对肾脏损伤具有保护作用, 这凸显了其在临床应用中的优势[16]。

丹参酮是丹参根中发现的一类亲脂性菲类化合物, 具有抗炎、抗氧化活性。一项荟萃分析显示, 丹参酮通过阻断 RANKL 诱导的 NF- κ B、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、蛋

白激酶 B (protein kinase B, PKB)和巨噬细胞集落刺激因子(macrophage colony-stimulating factor, M-CSF)、c-Src 信号的激活,发挥抗破骨细胞生成的作用,还可抑制成骨细胞凋亡,并通过改善氧化应激和炎症反应促进成骨细胞生成。动物实验研究表明,丹参酮可减缓雌激素缺乏、糖尿病以及炎症诱发的骨质疏松症模型的骨骼退化,还能防止聚乙烯诱导的骨溶解,改善骨折愈合[17]。

丹参醇是从丹参中提取的一种脂溶性成分,一项关于系统评价丹参醇治疗骨质疏松动物模型的荟萃分析显示,丹参醇可显著增加骨密度、改善骨微结构和生物力学指标以及促进血清骨钙素在大鼠中的表达,因此具有治疗骨质疏松症的潜力[18]。

4. 巴戟天

巴戟天是茜草科、巴戟属植物,主要分布在热带和亚热带地区[19]。巴戟天自古以来就被广泛用于补肾阳,是中国著名的“四大南药”之一,可治疗骨质疏松症、风湿性关节炎、不孕不育、老年痴呆等。研究发现,巴戟天治疗骨质疏松症的有效成分主要是巴戟天多糖,其具有广泛的药理作用,包括抗氧化、抗疲劳、免疫调节、抗骨质疏松等[20]。从海巴戟中提取的有效成分海巴戟多糖具有一定的生物活性和药用潜力,在预防和治疗骨质疏松症方面具有广阔的前景[21][22]。

巴戟天多糖可增强卵巢切除术后大鼠股骨远端的骨密度、单位骨小梁体积、骨小梁数量和骨小梁厚度,降低骨小梁分离度,提高血清中铜、铁和镁的水平以及超氧化物歧化酶、谷胱甘肽和谷胱甘肽过氧化物酶的含量,降低丙二醛的含量,并通过抑制过氧化物酶体增殖激活受体 γ 共激活因子 1α (peroxisome proliferator-activated receptor γ coactivator 1α , PGC- 1α)/核受体过氧化物酶体增殖激活受体 γ (peroxisome proliferators-activated receptor γ , PPAR γ)通路改善卵巢切除术后大鼠的骨质疏松症[19]。另一项动物实验研究还表明,巴戟天多糖通过上调微小 RNA-21 (microRNA-21, miR-21)、激活 PI3K/Akt 通路调控大鼠骨间充质干细胞的成骨分化和成脂分化,miR-21 过表达可促进大鼠骨间充质干细胞的成骨分化,抑制成脂分化[23]。一项使用巴戟天多糖治疗人间充质干细胞的实验研究表明,巴戟天多糖可能通过 miR-210-3p/A 类清道夫受体 3 蛋白(Scavenger receptor class A member 3, Scara3)轴促进间充质干细胞的成骨分化和抑制成脂分化[24]。上述均说明巴戟天多糖具有促进成骨、改善骨质疏松的作用。

从巴戟天中提取分离出的粗多糖 MO50 以及由它分离出来的菊粉型果聚糖 MOW50-1,也被证实可能在预防和治疗骨质疏松症方面有重要作用[25]。此外,成骨活性实验结果表明,通过分离纯化得到的两种精制多糖(MOP70-1 和 MOP70-2)能显著促进小鼠胚胎成骨细胞前体细胞的增殖、分化和矿化。MOP70-2 还可上调 RUNX2、成骨相关转录因子(Osterix, OSX)、骨钙素、骨桥蛋白、骨唾液酸蛋白和骨保护蛋白的基因表达。这意味着 MOP70-2 通过上调成骨分化相关标记基因刺激成骨细胞分化[26]。另有研究发现,从巴戟天中提取的粗多糖 MO90 能显著提高卵巢切除术后大鼠整个股骨、股骨远端和股骨近端的骨密度,还能降低骨转换标志物的水平,防止骨小梁微结构的恶化。此外,从 MO90 中分离出的新型菊粉型果聚糖 MOW90-1 也可通过上调 RUNX2、OSX、骨钙素和骨桥蛋白的表达促进小鼠胚胎成骨细胞前体细胞的增殖、分化和矿化。这为未来将这种新颖的巴戟天多糖果聚糖用于临床治疗提供了支持性证据[27]。

5. 骨碎补

骨碎补具有补肾、活血、促进组织再生的功效,常用于治疗骨科肌肉骨骼创伤性疾病[28]。骨碎补总黄酮是从骨碎补干燥根茎中提取的有效成分,具有抗骨质疏松的作用。柚皮苷是骨碎补药材中的二氢黄酮类成分,众多研究表明,以柚皮苷为主的总黄酮成分在抗炎、抗骨质疏松、促进骨折愈合、促进牙齿生长等多个方面起到重要作用[29]。陈玄等发现骨碎补-续断药对具有促进成骨代谢,抑制破骨代谢的作用,而低氧诱导因子 1α (hypoxia-inducible factor 1α , HIF 1α)可能是骨碎补-续断药对的一个重要作用靶点

[30]。上官文姬等发现柚皮苷可以调节骨代谢,改善骨密度,其作用机制可能是通过调节 HIF1 α /VEGF 信号通路、促进 H 型血管形成来实现的[31]。另有研究表明,柚皮苷通过激活 PI3K/AKT/mTOR 信号通路对糖皮质激素诱导的骨质疏松症发挥保护作用,这可能与自噬诱导和成骨细胞增殖增强有关[32]。此外,骨碎补总黄酮具有抗骨质疏松的作用还可能与多种信号通路有关,如 Wnt3a/ β -catenin [33]、BMP-Smad [34]、血小板源性生长因子 BB (platelet-derived growth factor BB, PDGF-BB)/VEGF/RUNX2/OSX 信号轴 [35]、PI3K/AKT [36]等。

骨碎补总黄酮已被开发上市成为一种中药,名为强骨胶囊。一项研究表明,与常规干预相比,单用强骨胶囊或强骨胶囊加碳酸钙片对原发性骨质疏松症患者改善骨密度有益[37]。另有荟萃分析结果显示,联合疗法和单用骨碎补总黄酮在改善骨矿物质密度、提高治疗效果方面分别优于常规疗法[38]。此外,一项动物实验研究表明,使用外源性骨碎补总黄酮和碳酸钙治疗可显著提高骨质疏松症大鼠的抗氧化防御能力、增加骨密度并减少骨矿物质流失,从而预防或改善骨质疏松症[39]。

6. 淫羊藿

淫羊藿常用于治疗哮喘、心脑血管疾病、月经不调、更年期综合征以及调节免疫功能等[40][41]。淫羊藿苷是淫羊藿中最丰富的成分,它不仅是一种经酶水解的生物活性化合物,也是淫羊藿八种主要黄酮类化合物的肠道代谢产物[42]。多糖是淫羊藿物质基础的主要成分之一,淫羊藿多糖不仅能增强免疫、抗氧化,还能促进机体激素分泌、增强核酸和蛋白质代谢及血小板凝聚作用[43]。淫羊藿苷可抑制破骨细胞活性,刺激骨髓基质祖细胞和成骨细胞的成骨分化和成熟,调节两种转录因子 RUNX2 和 PPAR γ 的活性,促进间充质干细胞向成骨细胞分化,增加骨保护素的 mRNA 表达,抑制 RANKL 的 mRNA 表达。目前,淫羊藿苷正在进行用于治疗骨质疏松症的 1 期临床试验,是一种很有前途的新型药物[42]。Zheng 等人研究发现,淫羊藿多糖预处理完全逆转了地塞米松诱导的原代成骨细胞凋亡模型中裂解的 Caspase-3 和促凋亡蛋白 Bax 表达的增加、抗凋亡蛋白 Bcl-2 表达的减少以及 PI3K、Akt 和 mTOR 蛋白的磷酸化,并显著上调低密度脂蛋白相关蛋白-5 (low density lipoprotein receptor related-protein, LRP-5)、 β -catenin、RUNX2 和 OSX 的蛋白表达[44]。这些结果表明,淫羊藿多糖预处理可能是糖皮质激素诱导的骨质疏松症患者的潜在治疗药物。Wang 等人通过 37 项临床试验发现将淫羊藿与其他中草药合方作为抗骨质疏松药物,用于治疗绝经后和老年性骨质疏松症,其总体疗效在 73%至 100%之间[45]。此外,荟萃分析表明,淫羊藿作为辅助药物或替代药物口服可能对骨质疏松症患者的骨密度、有效率和视觉模拟量表有积极影响[46]。因此,淫羊藿作为治疗骨质疏松症的新选择值得期待。

7. 小结

综上所述,人参、丹参、巴戟天、骨碎补、淫羊藿等天然中药,是经典的骨特异性药物,大多具有中医补阳的功能,它们对骨骼发育和新陈代谢有改善作用。本文综述了上述天然中药在骨质疏松症治疗中的重要药理作用及其作用机制,并深层次地挖掘其理论基础及实验依据,从中药作用的不同靶点和信号通路,包括 RANKL、MAPK、Wnt、Smad、HIF-1 α 等,到体内和体外实验研究证明天然中药成分可有效改善骨质疏松症。然而,天然中药治疗骨质疏松症的作用机制仍需要进一步研究,我们将致力于探索经典中药及其有效活性成分在骨质疏松症治疗中的应用前景,努力将中药治疗骨质疏松症的潜力极致发挥。同时,也要关注其副作用,开展更多高质量的临床研究,为其更安全的抗骨质疏松治疗提供更多的证据。

参考文献

- [1] 王永炫,李梅,章振林,等.《原发性骨质疏松症诊疗指南(2022)》要点解读[J].协和医学杂志,2023,14(6):1203-

1207.

- [2] Lin, J., Zhu, J., Wang, Y., Zhang, N., Gober, H., Qiu, X., *et al.* (2017) Chinese Single Herbs and Active Ingredients for Postmenopausal Osteoporosis: From Preclinical Evidence to Action Mechanism. *BioScience Trends*, **11**, 496-506. <https://doi.org/10.5582/bst.2017.01216>
- [3] Zhuo, Y., Li, M., Jiang, Q., Ke, H., Liang, Q., Zeng, L., *et al.* (2022) Evolving Roles of Natural Terpenoids from Traditional Chinese Medicine in the Treatment of Osteoporosis. *Frontiers in Endocrinology*, **13**, Article 901545. <https://doi.org/10.3389/fendo.2022.901545>
- [4] Yang, N., Zhang, X., Li, L., Xu, T., Li, M., Zhao, Q., *et al.* (2022) Ginsenoside RC Promotes Bone Formation in Ovariectomy-Induced Osteoporosis *in Vivo* and Osteogenic Differentiation *in Vitro*. *International Journal of Molecular Sciences*, **23**, Article 6187. <https://doi.org/10.3390/ijms23116187>
- [5] Chen, W., Jin, X., Wang, T., Bai, R., Shi, J., Jiang, Y., *et al.* (2022) Ginsenoside Rg1 Interferes with the Progression of Diabetic Osteoporosis by Promoting Type H Angiogenesis Modulating Vasculogenic and Osteogenic Coupling. *Frontiers in Pharmacology*, **13**, Article 1010937. <https://doi.org/10.3389/fphar.2022.1010937>
- [6] Liu, Q., Zhou, J., Yang, Z., Xie, C., Huang, Y., Ling, L., *et al.* (2021) The Ginsenoside Exhibits Antiosteoporosis Effects in Ketogenic-Diet-Induced Osteoporosis via Rebalancing Bone Turnover. *Frontiers in Pharmacology*, **11**, Article 593820. <https://doi.org/10.3389/fphar.2020.593820>
- [7] Lee, S., Park, S., Kim, J.H., Kim, N. and Lee, J. (2023) Ginsenoside Rg2 Inhibits Osteoclastogenesis by Downregulating the NFATC1, C-Fos, and MAPK Pathways. *BMB Reports*, **56**, 551-556. <https://doi.org/10.5483/bmbrep.2023-0100>
- [8] Zhang, X., Huang, F., Chen, X., Wu, X. and Zhu, J. (2020) Ginsenoside Rg3 Attenuates Ovariectomy-Induced Osteoporosis via AMPK/mTOR Signaling Pathway. *Drug Development Research*, **81**, 875-884. <https://doi.org/10.1002/ddr.21705>
- [9] Zhang, D., Du, J., Yu, M. and Suo, L. (2022) Ginsenoside RB1 Prevents Osteoporosis via the AHR/PRELP/NF- κ B Signaling Axis. *Phytomedicine*, **104**, Article 154205. <https://doi.org/10.1016/j.phymed.2022.154205>
- [10] Ding, L., Gao, Z., Wu, S., Chen, C., Liu, Y., Wang, M., *et al.* (2023) Ginsenoside Compound-K Attenuates OVX-Induced Osteoporosis via the Suppression of Rankl-Induced Osteoclastogenesis and Oxidative Stress. *Natural Products and Bioprospecting*, **13**, Article No. 49. <https://doi.org/10.1007/s13659-023-00405-z>
- [11] Jiang, Z., Deng, L., Li, M., Alonge, E., Wang, Y. and Wang, Y. (2024) Ginsenoside Rg1 Modulates PI3K/AKT Pathway for Enhanced Osteogenesis via GPER. *Phytomedicine*, **124**, Article 155284. <https://doi.org/10.1016/j.phymed.2023.155284>
- [12] Song, M., Jia, F., Cao, Z., Zhang, H., Liu, M. and Gao, L. (2020) Ginsenoside Rg3 Attenuates Aluminum-Induced Osteoporosis through Regulation of Oxidative Stress and Bone Metabolism in Rats. *Biological Trace Element Research*, **198**, 557-566. <https://doi.org/10.1007/s12011-020-02089-9>
- [13] Zhang, X., Chen, K., Wei, B., Liu, X., Lei, Z. and Bai, X. (2016) Ginsenosides Rg3 Attenuates Glucocorticoid-Induced Osteoporosis through Regulating BMP-2/BMPRII/Runx2 Signaling Pathway. *Chemico-Biological Interactions*, **256**, 188-197. <https://doi.org/10.1016/j.cbi.2016.07.003>
- [14] He, J., Li, X., Wang, Z., Bennett, S., Chen, K., Xiao, Z., *et al.* (2019) Therapeutic Anabolic and Anticatabolic Benefits of Natural Chinese Medicines for the Treatment of Osteoporosis. *Frontiers in Pharmacology*, **10**, Article 1344. <https://doi.org/10.3389/fphar.2019.01344>
- [15] Guo, Y., Li, Y., Xue, L., Severino, R.P., Gao, S., Niu, J., *et al.* (2014) Salvia Miltiorrhiza: An Ancient Chinese Herbal Medicine as a Source for Anti-Osteoporotic Drugs. *Journal of Ethnopharmacology*, **155**, 1401-1416. <https://doi.org/10.1016/j.jep.2014.07.058>
- [16] Yang, W., Han, J., Gong, S., Zhao, J., Yu, T. and Ma, J. (2022) Cryptotanshinone Suppressed Postmenopausal Osteoporosis by Preventing Rankl-Mediated Osteoclastogenesis against Kidney Injury. *Evidence-Based Complementary and Alternative Medicine*, **2022**, 1-8. <https://doi.org/10.1155/2022/2821984>
- [17] Ekeuku, S.O., Pang, K. and Chin, K. (2021) The Skeletal Effects of Tanshinones: A Review. *Molecules*, **26**, Article 2319. <https://doi.org/10.3390/molecules26082319>
- [18] Wang, S., Yuan, Y., Lin, Q., Zhou, H., Tang, B., Liu, Y., *et al.* (2022) Antiosteoporosis Effect of Tanshinol in Osteoporosis Animal Models: A Systematic Review and Meta-Analysis. *Frontiers in Pharmacology*, **13**, Article 937538. <https://doi.org/10.3389/fphar.2022.937538>
- [19] Rong, K., Chen, P., Lang, Y., Zhang, Y., Wang, Z., Wen, F., *et al.* (2022) Morinda Officinalis Polysaccharide Attenuates Osteoporosis in Rats Underwent Bilateral Ovariectomy by Suppressing the PGC-1 α /PPAR γ Pathway. *Journal of Orthopaedic Surgery*, **30**, Article 10225536221130824. <https://doi.org/10.1177/10225536221130824>
- [20] Liu, M., Wang, C., Zhang, H., Guo, H., Kang, L., Li, H., *et al.* (2024) A Systematic Review on Polysaccharides from Morinda Officinalis How: Advances in the Preparation, Structural Characterization and Pharmacological Activities. *Journal of Ethnopharmacology*, **328**, Article 118090. <https://doi.org/10.1016/j.jep.2024.118090>

- [21] Huang, S., Cao, Q., Cao, Y., Yang, Y., Xu, T., Yue, K., *et al.* (2021) Morinda Officinalis Polysaccharides Improve Meat Quality by Reducing Oxidative Damage in Chickens Suffering from Tibial Dyschondroplasia. *Food Chemistry*, **344**, Article 128688. <https://doi.org/10.1016/j.foodchem.2020.128688>
- [22] Zhang, D., Fan, L., Yang, N., Li, Z., Sun, Z., Jiang, S., *et al.* (2022) Discovering the Main “Reinforce Kidney to Strengthening Yang” Active Components of Salt Morinda Officinalis Based on the Spectrum-Effect Relationship Combined with Chemometric Methods. *Journal of Pharmaceutical and Biomedical Analysis*, **207**, Article 114422. <https://doi.org/10.1016/j.jpba.2021.114422>
- [23] Wu, P., Chen, W., Huang, H., Tang, W. and Liang, J. (2022) Morinda Officinalis Polysaccharide Regulates Rat Bone Mesenchymal Stem Cell Osteogenic-Adipogenic Differentiation in Osteoporosis by Upregulating miR-21 and Activating the PI3K/AKT Pathway. *The Kaohsiung Journal of Medical Sciences*, **38**, 675-685. <https://doi.org/10.1002/kjm2.12544>
- [24] Wu, Y., Chen, D. and Li, L. (2024) Morinda Officinalis Polysaccharide Promotes the Osteogenic Differentiation of Human Bone Marrow-Derived Mesenchymal Stem Cells via Microrna-210-3p/scavenger Receptor Class a Member 3. *Journal of Investigative Medicine*, **72**, 370-382. <https://doi.org/10.1177/10815589241229693>
- [25] Zhang, D., Zhang, S., Jiang, K., Li, T. and Yan, C. (2020) Bioassay-Guided Isolation and Evaluation of Anti-Osteoporotic Polysaccharides from Morinda Officinalis. *Journal of Ethnopharmacology*, **261**, Article 113113. <https://doi.org/10.1016/j.jep.2020.113113>
- [26] Jiang, K., Huang, D., Zhang, D., Wang, X., Cao, H., Zhang, Q., *et al.* (2018) Investigation of Inulins from the Roots of Morinda Officinalis for Potential Therapeutic Application as Anti-Osteoporosis Agent. *International Journal of Biological Macromolecules*, **120**, 170-179. <https://doi.org/10.1016/j.ijbiomac.2018.08.082>
- [27] Yan, C., Huang, D., Shen, X., Qin, N., Jiang, K., Zhang, D., *et al.* (2019) Identification and Characterization of a Polysaccharide from the Roots of Morinda Officinalis, as an Inducer of Bone Formation by Up-Regulation of Target Gene Expression. *International Journal of Biological Macromolecules*, **133**, 446-456. <https://doi.org/10.1016/j.ijbiomac.2019.04.084>
- [28] Fang, X.H., Zhou, G.E. and Lin, N. (2023) Total Flavonoids from Rhizoma Drynariae (Gusuibu) Alleviates Diabetic Osteoporosis by Activating BMP2/Smad Signaling Pathway. *Combinatorial Chemistry & High Throughput Screening*, **26**, 2401-2409. <https://doi.org/10.2174/1386207326666230223165730>
- [29] 谌顺清, 梁伟, 张雪妹, 等. 骨碎补化学成分和药理作用研究进展[J]. 中国中药杂志, 2021, 46(11): 2737-2745.
- [30] 陈玄, 陈娟, 谢丽华, 等. 骨碎补-续断药对对成骨/破骨代谢的双向调控作用及其对 Hif1 α 基因的影响[J]. 中国骨质疏松杂志, 2023, 29(1): 64-69.
- [31] 上官文姬, 张跃辉, 岳江, 等. 柚皮苷通过 HIF-1 α /VEGF 信号促进 H 型血管抗骨质疏松的研究[J]. 中国骨质疏松杂志, 2022, 28(12): 1755-1759.
- [32] Ge, X. and Zhou, G. (2021) Protective Effects of Naringin on Glucocorticoid-Induced Osteoporosis through Regulating the PI3K/AKT/mTOR Signaling Pathway. *American Journal of Translational Research*, **13**, 6330-6341.
- [33] Hu, Y., Mu, P., Ma, X., Shi, J., Zhong, Z. and Huang, L. (2021) Rhizoma Drynariae Total Flavonoids Combined with Calcium Carbonate Ameliorates Bone Loss in Experimentally Induced Osteoporosis in Rats via the Regulation of Wnt3 α / β -Catenin Pathway. *Journal of Orthopaedic Surgery and Research*, **16**, Article No. 702. <https://doi.org/10.1186/s13018-021-02842-3>
- [34] Sun, W., Li, M., Zhang, Y., Huang, Y., Zhan, Q., Ren, Y., *et al.* (2021) Total Flavonoids of Rhizoma Drynariae Ameliorates Bone Formation and Mineralization in Bmp-Smad Signaling Pathway Induced Large Tibial Defect Rats. *Bio-medicine & Pharmacotherapy*, **138**, 111480. <https://doi.org/10.1016/j.biopha.2021.111480>
- [35] Shen, Z., Dong, W., Chen, Z., Chen, G., Zhang, Y., Li, Z., *et al.* (2022) Total Flavonoids of Rhizoma Drynariae Enhances Cd31hiemcnhi Vessel Formation and Subsequent Bone Regeneration in Rat Models of Distraction Osteogenesis by Activating PDGF-BB/VEGF/RUNX2/OSX Signaling Axis. *International Journal of Molecular Medicine*, **50**, Article No. 112. <https://doi.org/10.3892/ijmm.2022.5167>
- [36] Lv, W., Yu, M., Kong, P. and Yan, B. (2021) Total Flavonoids of rhizoma Drynariae Ameliorate Steroid-induced Avascular Necrosis of the Femoral Head via the PI3K/AKT Pathway. *Molecular Medicine Reports*, **23**, Article No. 345. <https://doi.org/10.3892/mmr.2021.11984>
- [37] Wei, X., Xu, A., Shen, H. and Xie, Y. (2017) Qianggu Capsule for the Treatment of Primary Osteoporosis: Evidence from a Chinese Patent Medicine. *BMC Complementary and Alternative Medicine*, **17**, Article No. 108. <https://doi.org/10.1186/s12906-017-1617-3>
- [38] Zhang, Y., Jiang, J., Shen, H., Chai, Y., Wei, X. and Xie, Y. (2017) Total Flavonoids from Rhizoma Drynariae (Gusuibu) for Treating Osteoporotic Fractures: Implication in Clinical Practice. *Drug Design, Development and Therapy*, **11**, 1881-1890. <https://doi.org/10.2147/dddt.s139804>
- [39] Mu, P., Hu, Y., Ma, X., Shi, J., Zhong, Z. and Huang, L. (2021) Total Flavonoids of Rhizoma Drynariae Combined with

- Calcium Attenuate Osteoporosis by Reducing Reactive Oxygen Species Generation. *Experimental and Therapeutic Medicine*, **21**, Article No. 618. <https://doi.org/10.3892/etm.2021.10050>
- [40] Dietz, B.M., Hajirahimkhan, A., Dunlap, T.L. and Bolton, J.L. (2016) Botanicals and Their Bioactive Phytochemicals for Women's Health. *Pharmacological Reviews*, **68**, 1026-1073. <https://doi.org/10.1124/pr.115.010843>
- [41] Ma, H., He, X., Yang, Y., Li, M., Hao, D. and Jia, Z. (2011) The Genus Epimedium: An Ethnopharmacological and Phytochemical Review. *Journal of Ethnopharmacology*, **134**, 519-541. <https://doi.org/10.1016/j.jep.2011.01.001>
- [42] Gao, L. and Zhang, S. (2022) Antiosteoporosis Effects, Pharmacokinetics, and Drug Delivery Systems of Icaritin: Advances and Prospects. *Pharmaceuticals*, **15**, Article 397. <https://doi.org/10.3390/ph15040397>
- [43] 李莉, 王嘉瑞, 王晶, 等. 淫羊藿的主要化学成分、药理作用研究进展及质量标志物的预测分析[J]. 中华中医药学刊, 2023, 41(11): 143-151.
- [44] Zheng, H., He, B., Wu, T., Cai, J. and Wei, J. (2020) Extraction, Purification and Anti-Osteoporotic Activity of a Polysaccharide from Epimedium Brevicornum Maxim. *in Vitro. International Journal of Biological Macromolecules*, **156**, 1135-1145. <https://doi.org/10.1016/j.ijbiomac.2019.11.145>
- [45] Wang, L., Li, Y., Guo, Y., Ma, R., Fu, M., Niu, J., *et al.* (2015) Herba Epimedii: An Ancient Chinese Herbal Medicine in the Prevention and Treatment of Osteoporosis. *Current Pharmaceutical Design*, **22**, 328-349. <https://doi.org/10.2174/1381612822666151112145907>
- [46] Shi, S., Wang, F., Huang, Y., Chen, B., Pei, C., Huang, D., *et al.* (2022) Epimedium for Osteoporosis Based on Western and Eastern Medicine: An Updated Systematic Review and Meta-Analysis. *Frontiers in Pharmacology*, **13**, Article 782096. <https://doi.org/10.3389/fphar.2022.782096>