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异补骨脂二氢黄酮的生物活性研究进展

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摘 要

异补骨脂二氢黄酮(Isobavachin)是一种异戊二烯基化的二氢黄酮类化合物，主要存在于豆科植物补骨脂(*Psoralea corylifolia* Linn.)中，具有广泛的药理作用和生理活性，如治疗组织疏松、抗炎、抗高尿酸血症等。近年来，随着生物技术的进步，人们对天然产物异补骨脂二氢黄酮的生物活性进行了更为深入的研究。本文将梳理天然产物异补骨脂二氢黄酮生物活性的最新研究进展。

关键词

天然产物，异补骨脂二氢黄酮，生物活性

Research Progress on the Biological Activity of Isobavachin

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Abstract

Isobavachin is an isoprenylated dihydroflavonoid compound, which is mainly found in the leguminous plant *Psoralea corylifolia* Linn. It has a wide range of pharmacological and physiological activities, such as the treatment of tissue looseness, anti-inflammation, and anti-hyperuricemia. In recent years, with the advancement of biotechnology, people have conducted more in-depth research on the biological activity of the natural product Isobavachin. This article will review the latest research progress on the biological activity of the natural product Isobavachin.

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Keywords

Natural Product, Isobavachin, Biological Activity

1. 引言

补骨脂(豆科) (*Psoralea corylifolia* Linn.)是一种一年生草本植物，广泛分布于东南亚。并且是一种著名的传统中药，在东亚国家被广泛用于治疗支气管哮喘、白细胞减少症、白癜风和牛皮癣等各种疾病[1]-[4]。

研究表明，补骨脂主要代谢物是香豆素、黄酮类化合物和单萜酚类的杂萜类化合物。异补骨脂二氢黄酮(IBA)在植物界中广泛分布，尤其在补骨脂的种子与果实中含量丰富[5] [6]。IBA 是一种异戊二烯基化的黄酮类化合物，其结构式简单(见图 1)，为 C20H20O4。目前研究表明，IBA 具有多种活性作用，能显著刺激成骨细胞增殖和分化[7]。IBA 对代谢活性较低的 C6 胶质瘤细胞和代谢活性较高的 H4IIE 肝癌细胞有细胞毒作用[8]，此外，IBA 还具有抗菌、抗氧化作用[9]，正是由于这些显著的活性作用，IBA 受到了越来越多的关注[10] [11] (见表 1)。

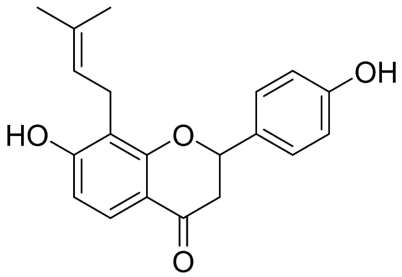

Figure 1. Isobavachin
图 1. 异补骨脂二氢黄酮

Table 1. Biological activities of Isobavachin
表 1. 异补骨脂二氢黄酮生物活性

	生物活性	作用机制	引用
异补骨脂二氢黄酮(IBA)	抗骨质疏松	抑制丝裂原活化蛋白激酶(MAPK)通路上调铁转运蛋白 1 (Fpn1)表达并促进 Fpn1 介导的细胞内铁外流	[7]
	抗炎	通过下调 MAPK 和 NF-κB 通路具有抗炎活性	[27]
	抗高尿酸血症	抑制人尿酸转运蛋白 1 (hURAT1)葡萄糖转运蛋白 9 (GLUT9)	[33]

2. 补骨脂二氢黄酮类天然产物的生物活性研究

2.1. 抗骨质疏松症

骨质疏松症的特征表现为骨密度降低及骨组织微结构的退化，进而引发骨脆性增高，易发生骨折[12]-

[14]。近期的临床研究揭示，骨质疏松症的病理机制主要为骨代谢紊乱，其中骨形成与骨吸收之间的失衡发挥着关键作用[15]。成骨细胞在新骨形成过程中起主导作用，而破骨细胞则主要负责骨吸收。因此，在正常的骨重塑过程中，促进成骨细胞的增殖或诱导其分化，均能有效促进骨形成[16]。

研究显示，通过 MTT 法评估了 IBA 对大鼠颅骨成骨细胞增殖活性的影响，淫羊藿苷(Icariin)作为阳性对照。结果表明，与淫羊藿苷相比，IBA 在相同浓度下展现出显著的细胞增殖活性，并且在 48 小时治疗后呈现剂量依赖性[7]。

骨骼作为一种动态代谢组织，在骨形成与骨吸收的持续重塑与维持中保持平衡[17]。骨骼重塑失衡导致的骨质流失是牙周炎和骨质疏松症等溶骨性疾病的主要特征[18] [19]。牙周炎以牙槽骨过度吸收为特征，是全球第六大常见疾病，对全球健康和经济造成了重大负担[20] [21]。过度的骨吸收与破骨细胞数量及活性的增加密切相关[22]。因此，破骨细胞被视为治疗骨质流失性疾病的关键靶点。

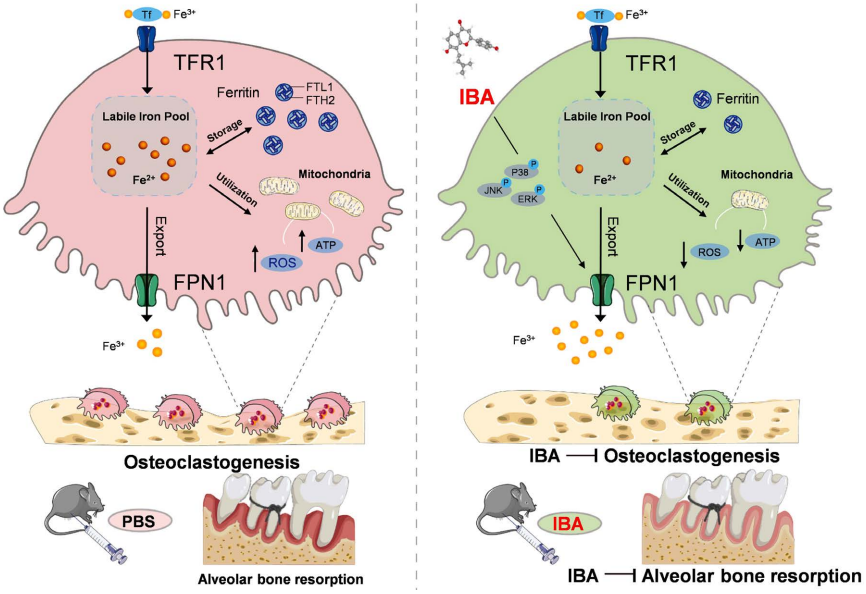

Figure 2. Mechanism of action of Isobavachin
图 2. 异补骨脂二氢黄酮的作用机理

研究发现，IBA 能够抑制 BMM 和 RAW264.7 细胞中 RANKL 诱导的破骨细胞生成，并且能够抑制破骨细胞介导的体外骨吸收。转录组分析揭示，IBA 处理后，差异表达基因在铁稳态和活性氧(ROS)代谢过程中富集。IBA 通过抑制破骨细胞中的铁积累发挥其抗破骨细胞生成作用。机制上，IBA 通过抑制丝裂原活化蛋白激酶(MAPK)通路，上调铁转运蛋白 1 (Fpn1)的表达并促进 Fpn1 介导的细胞内铁外流，从而减弱了 RANKL 诱导的破骨细胞中的铁积累(见图 2)。

总体而言，这些研究结果表明 IBA 可作为一种有前景的治疗策略，用于以破骨细胞骨吸收为特征的骨病[23]。

2.2. 抗炎活性

炎症是人体对刺激物、损伤和感染的防御机制，可激活免疫系统[24]。巨噬细胞在炎症期间通过释放细胞因子和生长因子发挥关键作用，并参与抗原呈递、吞噬作用和免疫调节[25]。当脂多糖(LPS)与巨噬细胞 Toll 样受体(TLR)结合时，它会触发细胞内信号通路，如 NF-κB 和 MAPK，从而产生炎症介质和促炎细胞因子[26]。虽然这些物质可以激活免疫力、对抗病原体，但过量分泌会损害组织、导致基因突变和

神经损伤，因此需要调节 NF-κB 和 MAPK [5]。

例如 Chung Y C 等人在 2023 年研究了使用斑马鱼炎症模型评估了 IBC (异补骨脂二氢黄酮)在巨噬细胞中的抗炎作用。RAW264.7 细胞处于 IBC (3.75-30 μM)和 LPS (脂多糖) (100 ng/mL) 21 小时后，对细胞活力没有显著影响。后续实验集中于 3.75、7.5、15 和 30 μM 的 IBC 浓度(见图 3(A))。仅用 LPS 处理时，NO 和 PGE2 水平增加，用 IBC 处理(3.75-30 μM)时，NO 和 PGE2 水平以剂量依赖性方式显著降低(见图 3(B))。qRT-PCR 和 Western blot 结果显示，负责 NO 和 PGE2 产生的 INOS 和 COX-2 被 IBC 下调(见图 3(C))。IBC (7.5-30 μM)有效减少了促炎细胞因子的释放。值得注意的是，30 μM 的 IBC 处理分别抑制了 LPS 诱导的 TNF-α、IL-6 和 IL-1β 分泌 36.7%、74.6%和 38.1% (见图 3(D))。该研究表明，IBC 通过下调 MAPK 和 NF-κB 通路具有抗炎活性[27]。

综上所述，异补骨脂二氢黄酮(IBC)在斑马鱼炎症模型中能有效降低炎症介质 NO 和 PGE2 水平，并减少促炎细胞因子的释放，表明 IBC 具有抗炎作用。由于其简单的结构，可以进一步衍生化，作为药物的良好前体。

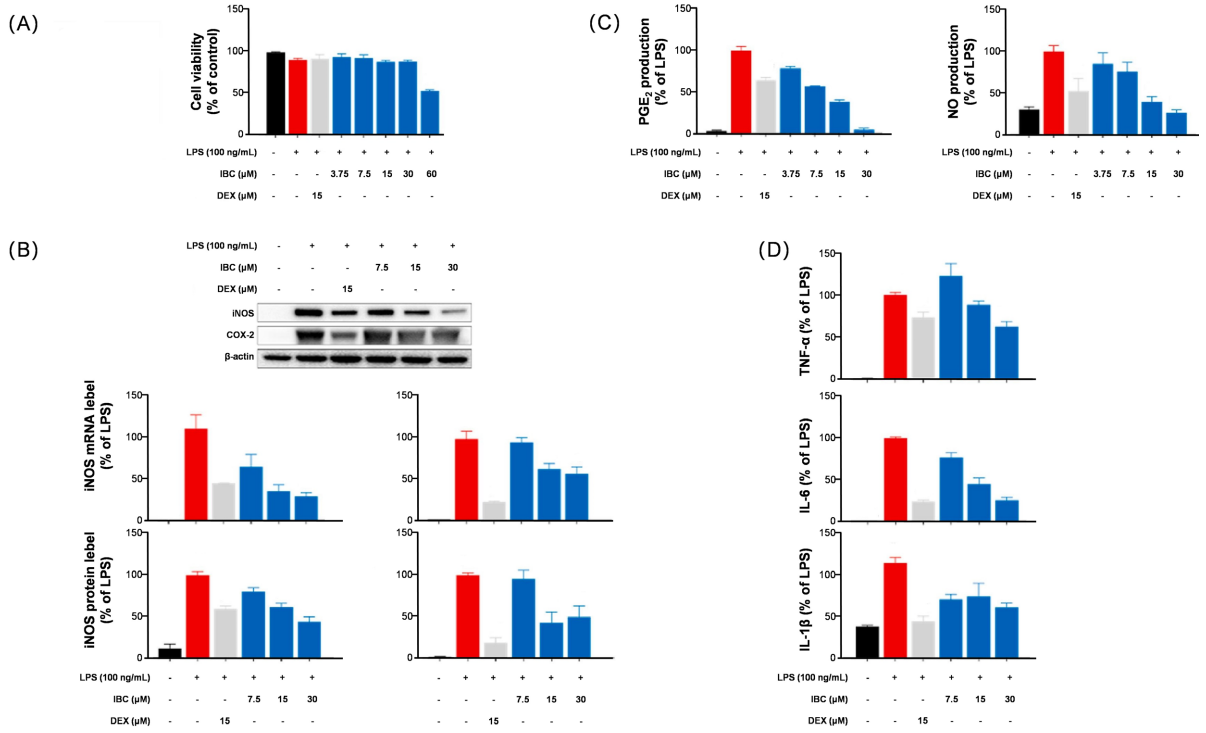

Figure 3. Regulatory effects of isopsoralen flavonoids (IBC) on LPS-induced inflammatory responses *in vivo* and *in vitro*. (A) Chemical structure of isopsoralen flavonoids and its activity against LPS-treated RAW264.7 cells. (B) Production of nitric oxide (NO) and prostaglandin E2 (PGE2). (C) Expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (cox-2) mRNA and protein in RAW264.7 cells. (D) Expression levels of proinflammatory cytokines

图 3. 异补骨脂二氢黄酮(IBC)对 LPS 诱导的体内外炎症反应的调节作用。(A) 异补骨脂二氢黄酮对 LPS 处理过的 RAW264.7 细胞活性。(B) 一氧化氮(NO)和前列腺素 E2 (PGE 2)的产生。(C) RAW264.7 细胞中诱导型一氧化氮合酶(iNOS)和环氧合酶-2 (cox-2) mRNA 和蛋白的表达。(D) 促炎性细胞因子的表达水平

2.3. 抗高尿酸血症

近年来，高尿酸血症(HUA)已成为亟待解决的公共卫生问题[28]。尿酸(UA 或尿酸盐)是嘌呤核苷酸代谢的最终产物，UA 异常升高导致高尿酸血症的发生[29]。

超过 90%的滤过尿酸被重吸收入血液，而这种重吸收过程受到肾脏近端小管上皮细胞多种转运蛋白

的影响，主要有肾小管上皮细胞端腔膜上的人尿酸转运蛋白1 (hURAT1)、有机阴离子转运蛋白4/10 (OAT4和OAT10)、基底外侧膜上的葡萄糖转运蛋白9 (GLUT9)和基底外侧刷状缘膜上的ATP结合盒G亚家族成员2 (ABCG2)等。其中，hURAT1作为尿酸重吸收的第一步，由于hURAT1的底物特异性和药用特性，是治疗HUA和痛风最重要的靶点之一[30]。

2021年Zhao Z通过结构建模和构象研究，从天然产物数据库中筛选出了针对hURAT1靶标的IBA [31]。之后采用14C标记尿酸摄取试验测定了IBA的hURAT1体外抑制活性。以商用hURAT1抑制剂(Lesinurad)为阳性对照药物。结果表明对hURAT1的IC50值，Lesinurad为7.18 μM，而IBA为0.24 μM。IBA的活性远高于lesinurad。此外，GLUT9以电压依赖的方式转运尿酸[32]，采用电生理技术检测IBA对GLUT9的抑制作用。在HEK293-GLUT9细胞中，1mM尿酸诱发相对电流，IBA在10 μM时显著抑制尿酸诱导电流，抑制率为84.5%。IBA表现出较强的GLUT9抑制作用，IC50值为1.12 ± 0.26 μM。综上IBA具有强效的hURAT1和GLUT9双靶点抑制作用，强于现有的所有降尿酸药物[33]。随后在2024年，该课题组进一步研究了IBA的细胞毒性，从用IBA治疗的小鼠身上取下肾脏进行病理检查。对肾脏进行HE染色。与对照组相比，模型组肾组织表现出明显的肾小管扩张、肾小球缺血和萎缩。IBA缓解了这些症状，表明IBA可以缓解高尿酸血症引起的肾损伤。

3. 结论

本文全面综述了异补骨脂二氢黄酮(Isobavachin)生物活性的研究进展。通过对近年来相关研究的分析，得出以下结论：

异补骨脂二氢黄酮具有广泛的生物活性，在抗高尿血酸症方面有显著抑制效果，对于其他方面也有较为不错的活性。因其化学结构简单，可作为各种治疗药物的前体化合物对其进行进一步衍生化。

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