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异戊烯基黄酮在神经系统疾病中应用的研究进展

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摘　要

异戊烯基黄酮(Prenylated flavonoids)因其特殊的结构和广泛的生物活性受到关注，特别是其在神经保护方面的重要性已引起神经科学领域的重视。尽管目前其在炎症、肿瘤等方面有不少成功探索，但仍亟待解决异戊烯基对于神经功能机制方面的难题。本文旨在深入总结和探讨异戊烯基黄酮与神经系统疾病之间的联系。特别强调的是揭示了一些热门药物在神经系统疾病上的研究。

关键词

异戊烯基黄酮，神经系统疾病，抗炎，神经元保护

Research Progress on the Application of Prenylated Flavonoids in Nervous System Diseases

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Abstract

Prenylated flavonoids have attracted attention for their specific structure and wide range of biological activities, the importance of prenylated flavonoids in neuroprotection has attracted the attention of the field of neuroscience. Although it has been successfully explored in a number of areas such as inflammation, cancer, there is still urgent to solve the problem of its neurological mechanism. This article aims to summarize and explore the relationship between prenylated flavonoids and neurological diseases. Special emphasis is placed on revealing some popular drugs that have been studied in anti-neurological disease research.

Keywords

Prenylated Flavonoids, Neurodegenerative Disease, Anti-Inflammatory, Neuronal Protect

1. 引言

随着人口老龄化的加快，神经系统疾病的发病率和死亡率的持续上升，寻找和开发更有效的新型神经保护药物已经成为人类重点完成的任务之一。中药及天然药物具有悠久的临床应用历史，它们的化学成分一直是现代新药发现的重要来源。目前在天然药物的活性成分分析中，总结发现了一些具有特定结构的化合物，他们同时对于某类疾病具有一定程度的相似性。深入研究药物结构，筛选更合适的治疗药物，对于改善患者的生活质量、健康和功能有重大意义。异戊烯基黄酮(prenylated flavonoids)是中药中常见的一类活性部位，也是天然产物中的一类重要化学成分，被报道具有广泛的神经保护作用。本文总结异戊烯基黄酮类天然药物在神经保护方面的作用，为神经相关疾病的临床研究和治疗提供更多的理论依据。

2. 异戊烯基黄酮简介

异戊烯基黄酮(Prenylated flavonoids)是中药中常见的一类组成成分，也是天然产物中的一类重要化学成分，主要分布在豆科、桑科、小檗科、芸香科、藤黄科、萝藦科和大戟科等科的部分属的植物中，目前已有 37 个属的植物被报道含有异戊烯基黄酮类化合物，其中大多数为传统中药药材，以豆科和桑科种类最多[1]。在药用植物化学分类研究领域，以该类化合物为典型特征性成分的常见中药淫羊藿、甘草、苦参、补骨脂、啤酒花、桑白皮等都富含有异戊烯基黄酮结构化合物。

异戊烯基黄酮由黄酮骨架和 1~2 个异戊烯基侧链组成。狭义上讲，异戊烯基侧链是指含有 5C 的异戊烯基侧链，广义上还包括 10C 的香叶基侧链和 15C 的法尼基侧链。研究表明，异戊烯基侧链可以显著增加黄酮类化合物的亲脂性，降低了黄酮类化合物的清除率，其增强各种生物活性的能力获得了极大的关注[2]。目前，异戊烯基黄酮的药理活性已经获得了比较充分的研究，其具有广泛的生物活性，如抗癌、抗炎、神经保护、抗糖尿病、抗肥胖、心脏保护作用和抗骨关节炎活性[3]。尤其是在神经保护方面的研究发现，异戊烯基黄酮生物活性表现十分突出，展现出越来越多的药用价值，具有广阔的应用前景，本文通过对近年来异戊烯基黄酮在神经系统疾病中的应用进行综述。

3. 异戊烯基黄酮对神经元细胞的保护作用

3.1. 抗炎作用

淫羊藿苷(Icariin)和淫羊藿次苷(Icariside II)均为8-异戊烯基黄酮糖苷类化合物，是传统中草药淫羊藿的主要活性成分。淫羊藿苷和淫羊藿次苷可显著抑制脂多糖(Lipopolysaccharides, LPS)诱导的肿瘤坏死因子(TNF-α)和白细胞介素-1β (IL-1β)的mRNA表达以及增加ERK1/2和AKT的磷酸化水平，并能通过IGF-1受体信号通路对星形胶质细胞产生调节作用[4]。也有报道淫羊藿次苷和淫羊藿苷可通过调节IKK/IκB/NF-κB/BACE1信号通路抑制脂多糖诱导的大鼠星形胶质细胞炎症和淀粉样蛋白的产生，从而发挥神经细胞的保护作用[5]。多种化合物都具有相同的异戊烯基侧链或相似的结构使得研究者猜测，在抗炎作用方面是因为异戊烯基侧链在发挥作用，但这并未排除化合物中其他基团的单独或协同抗炎作用，因此需要结合更多的证据及控制足够的变量进一步证明其抗炎性。而上述证据表明，淫羊藿次苷和淫羊藿苷几乎具有相同的作用通路，这为异戊烯基抗炎作用提供了很有价值的参考。

有学者对来自传统中药补骨脂中的异戊烯基黄酮进行分析，结果表明异补骨脂色烯查耳酮(4-hydroxylonchocarpin)和chromenoflavanone可以通过抑制活化小胶质细胞中的I-κB-α降解进而抑制一氧化氮合酶(iNOS)的表达，可以作为开发神经保护药物的先导化合物[6]。进一步证明了异戊烯基可利用相同的机制发挥抗炎作用，尤其在保护神经元方面。此外，补骨脂乙素(Isobavachalcone)、补骨脂色烯查耳酮(Bavachromene)、kanzonol B可通过调节激活的小胶质细胞中iNOS和环氧合酶-2 (COX-2)的表达而有益于神经炎性疾病的治疗[7]，而补骨脂异黄酮(Corylin)可能通过抑制LPS诱导的炎症反应并减弱小胶质细胞中NLRP3炎症小体的激活[8]。

通过对经典名方五子衍宗丸的组成成分分析，发现朝藿定A (Epimedin A)、朝藿定B (Epimedin B)、朝藿定C (Epimedin C)能抑制LPS诱导的BV2细胞p-p38的表达发挥抗神经炎活性[9]。同类药性混合物中往往存在多种具有相似特性的异戊烯基结构化合物，并且证明其具有一定的安全性，这也为研究化合物疗效差别提供了更多的支持，分析其结构特性，筛选出更强大的抗炎药物为药物研发提供前期支持。此外还有报道，从槐树中分离出的一种新的紫檀型抗炎化合物sophotokin剂量依赖性地抑制脂多糖刺激的小胶质细胞中NO、TNF-α和IL-1β的产生，这种抗神经炎症作用与sophotokin阻断LPS诱导的炎症介质iNOS和COX-2的产生有关[10]。

3.2. 氧化应激

啤酒花也是异戊烯基黄酮的重要来源，来自啤酒花的异戊烯基黄酮黄腐酚C(Xanthohumol C)促进神经元分化并促进神经突生长[11]，黄腐酚(Xanthohumol)可通过上调主要内源性抗氧化剂Nrf2及其下游信号通路来减轻氧化/亚硝化应激，同时通过抑制NF-κB通路来减轻急性外周和中枢炎症反应[12]。此外，从桑树果实中分离得到的morachalcone A和来自槐花的薰衣草酰黄烷酮(2S)-2'-methoxykurarinone和sophoraflavanone G都可令HT22细胞免受谷氨酸诱导的神经毒性[13] [14]。淫羊藿苷可以通过特异性靶向Bax来减轻AGE诱导的PC12神经细胞的氧化应激和线粒体凋亡，是一种具有显著抗氧化作用的神经保护剂[15]。

3.3. 抑制神经元凋亡

Hak Ju Lee等在桑科植物桑白皮的醇提取物中，分离纯化出10个具有异戊烯基结构的黄酮化合物，其中6个双异戊烯基黄酮环桑素(cyclomulberrin)、neocyclomorusin、桑根酮I (sanggenon I)、桑辛素(morusin)、kuwanon U、kuwanon E能够剂量依赖性的抑制硝普纳刺激引起的神经母细胞瘤SH-SY5Y细胞凋亡，且其神经细胞保护作用显著强于4个单异戊烯基黄酮甘草黄酮C (licoflavone C)，moracin P，

moracin O 和 mulberrofuran Q [16]。此外，淫羊藿苷通过调控细胞周期基因和蛋白的表达促进细胞周期进程发挥对神经干细胞的生长和增殖的增强作用[17]。

3.4. 其他

有研究证实了 8-异戊烯基柚皮素、6-异戊烯基柚皮素在体外分化诱导的潜力，发现其可诱导神经前体细胞分化[18]。另一项研究也表明 8-异戊烯基柚皮素在神经发生和神经分化中的积极作用[19]。来自槐树根的天然异戊烯基黄酮苦参黄素(kurarinone)可通过靶向 BACE1 激活 P13K-AKT 信号，发挥对皮质酮诱导的大鼠海马神经元细胞的保护作用[20]。

Cudraflavone B 和柘树二氢黄酮 B (cudraflavanone B)是从桑科植物拓树根的根皮中分离得到的异戊烯基黄酮，cudraflavone B 可通过 Nrf2 和 PI3K/Akt 信号通路对谷氨酸诱导的小鼠海马 HT22 细胞损伤提供神经保护[21]。此外在桑科属橙桑的果实中提取到的橙桑黄酮(pomiferin)可通过激活 Akt/Nrf2 通路和抑制 NF-κB 通路发挥抗神经炎症作用[22]。除了一般通路外，黄腐酚还可通过调节肠道菌群产生神经保护作用[23]。

4. 异戊烯基黄酮对神经退行性疾病的保护

神经退行性疾病是神经元结构或功能逐渐丧失甚至死亡而导致功能障碍的一类疾病，包括肌萎缩侧索硬化症、PD、AD、亨廷顿氏病以及脊髓性肌萎缩症等，目前这类疾病病因尚不明确也无法治愈，严重威胁着人类健康与日常生活。

4.1. 阿尔兹海默病

阿尔茨海默病是一种与年龄相关的神经退行性疾病，它的发病机制涉及许多生物靶点，病理特征是 Aβ 和 tau 蛋白的异常沉积[24]。研究发现从补骨脂科果实中鉴定出的补骨脂乙素(Isobavachalcone)和补骨脂二氢黄酮甲醚(Bavachinin)可以显著改善 AD 小鼠的焦虑，记忆和识别缺陷，减弱 Aβ 寡聚化和成纤维化，减少 tau 蛋白的过度磷酸化，并阻止 tau 蛋白聚集从而发挥 AD 的治疗作用[25]。此外多篇文献表明淫羊藿苷能保护神经功能，其可以抑制大脑皮层铁超载，改善 AD 小鼠的空间学习和记忆障碍[26]。淫羊藿苷也可以降低铁死亡水平并增强对氧化应激的抵抗力，从而改善 AD 小鼠的神经行为、记忆和运动能力[27]。还可通过减轻 3 × TgAD 小鼠髓鞘损伤改善 AD 病理，减少了海马体中 Aβ 沉积和 tau 蛋白磷酸化[28]。

此外，来自中药当归根的查尔酮黄色当归醇(Xanthoangelol)具有通过减轻东莨菪碱诱导的神经炎症和神经退行性变来改善 AD 症状的能力，在 HT-22 细胞中产生神经保护作用并改善了小鼠的空间记忆缺陷[29]。从蔷薇目豆科植物千斤拔根部提取的 philippinone B 通过抑制 Aβ1-42 聚集体的形成发挥治疗 AD 的作用[30]；桑科橙桑属植物中提取的 osajin 和橙桑黄酮对皮层神经元也具有保护作用，并以浓度依赖性方式抑制花生四烯酸诱导的 tau 纤维化而发挥神经保护作用[31]。从豆科槐属植物苦参中筛选出的 5 种异戊烯基黄酮 sophoraflavanone G、苦参黄素、leachianone A、苦参醇 A (kushenol A)、(2S)-2'-Methoxykurarinone 都可通过抑制 BACE1 从而限制 β 淀粉样蛋白的产生，进而延缓或预防 AD [32]。另外，从大麻中提取的 cannflavin A 在低浓度下对 Aβ1-42 诱导的神经毒性具有显著的神经保护和抗聚集作用，在高浓度时产生毒性[33]。因此，从天然草本植物中筛选出合适的异戊烯基黄酮化合物对于 AD 的保护是非常有意义的，发掘更多有药用价值的化合物，仍需进一步研究。

4.2. 帕金森病

来自于小檗科植物心叶淫羊藿地上部分朝藿定 B，是淫羊藿黄酮类化合物中除淫羊藿苷外活性最高的成分，朝藿定 B 治疗可改善 MPTP 诱导的 PD 小鼠运动功能障碍。此外，朝藿定 B 治疗可显著抑制

MPTP 诱导的凋亡相关蛋白 Bcl-2 和 Bax 以及内质网应激相关蛋白葡萄糖调节蛋白 78 (GRP78)和 C/EBP 同源蛋白(CHOP)的变化，表明朝藿定 B 可通过抑制线粒体功能障碍和氧化应激保护 PD 小鼠[34]。这提示可能具有相同异戊烯基结构的淫羊藿黄酮类化合物在药物活性、改善运动功能障碍、氧化应激等方面存在不小差异。中来自豆科槐属植物苦参中的苦参黄素通过增加神经递质和 TH 阳性细胞的表达来缓解 MPTP 诱导帕金森病步态障碍和多巴胺能神经毒性，可溶性环氧化物水解酶(sEH)酶是苦参黄素治疗 PD 的一个潜在的靶点[35]。来自甘草属植物光果甘草的光甘草定通过抑制 ERK 信号通路、抗氧化、减轻炎症等发挥对 MPTP 致 PD 小鼠学习记忆能力的保护作用[36]。Mulberrin (桑黄酮)以剂量依赖性方式缓解 MPTP 诱导的运动协调障碍，并抑制神经元损伤[37]。天然植物中存在多种异戊烯基黄酮并以多种形式发挥抗病作用，使得其可获得性和经济性方面存在更多价值。

4.3. 其他

淫羊藿苷通过调节 GluR2/ERK I/II 通路，防止缺氧诱导的新生癫痫大鼠模型的神经元损伤并改善认知功能[38]，通过调节 miR-144-3p/ATP1B2/mTOR 信号通路缓解精神分裂症样症状的作用[39]。淫羊藿苷还在多发性硬化症小鼠复发缓解模型中，通过下调主要炎症信号通路改善实验性自身免疫性脑脊髓炎的进展[40]，另外，在多发性硬化症模型中，改善神经功能缺损并通过抑制小胶质细胞 NLRP3 炎症小体激活改善神经炎症[41]。淫羊藿苷还能减轻成年 BTBR 小鼠的自闭症样行为、海马炎症和 vGlut1 表达[42]。淫羊藿次苷可通过抑制 T 型钙通道和 USP5Cav3.2 相互作用减轻炎症和神经性疼痛[43]。sophoraflavanone G 通过 mTOR 介导的 BDNF/Trkb 信号通路缓解慢性应激小鼠的抑郁样症状[44]。

5. 异戊烯基黄酮对认知功能的保护

综合目前报道，淫羊藿苷对衰老、各种神经精神疾病和辐射引起的认知功能障碍具有显著的神经保护作用[45]。淫羊藿苷通过增强海马的乙酰化改善创伤性脑损伤后的认知障碍[46]，还可显著减轻抑郁症大鼠模型的海马损伤、学习和记忆障碍、海马神经发生功能障碍和齿状回神经元死亡[47]，抑制海马神经炎症减轻老年大鼠手术创伤所致的认知功能障碍[48]，改善秋水仙素诱导大鼠模型中的神经元形态学损伤、β 淀粉样蛋白沉积和认知功能障碍[49]，抑制内质网应激改善 APP/PS1 小鼠的认知功能[50]，还通过上调 PI3K/AKT 通路和下调 JNK/cJUN 信号级联，发挥减轻血管性痴呆小鼠的认知缺陷的作用[51]。此外还通过抗淀粉样变性作用对大鼠慢性脑灌注不足引起的认知缺陷具有保护作用[52]。在 SAMP8 小鼠早期 AD 模型中，淫羊藿苷通过减少 β-淀粉样肽沉积和抑制神经元凋亡来改善认知缺陷[53]，还通过抑制自噬延缓脑老化[54]。

取自桑科植物根皮的桑辛素能够恢复及其保护三氯化铝诱导大鼠的记忆障碍，减少了脑 AChE 活性和脑氧化应激水平的升高[55]。淫羊藿次苷通过调节 MAPK 通路改善伊博替酸诱导的大鼠认知障碍和凋亡反应[56]。光甘草定是甘草的主要类黄酮，可以改善了东莨菪碱诱导的遗忘症，值得探索在 AD 患者中的治疗潜力[57]。而从甘草中分离的 dehydroglyasperin C 可能通过增加 MKP-1 表达并作为有效的抗神经退行性药物来抑制小胶质细胞的过度激活[58]。黄腐酚通过靶向肝脑轴减轻肥胖引起的代谢和神经认知障碍[59]，还能治疗改善高脂肪饮食(HFD)诱导的空间学习和记忆缺陷[60]。比较特别的是，黄腐酚可提高幼龄动物的认知灵活性，但在调节老年人神经元蛋白的棕榈酰化状态方面无效[61]。

6. 异戊烯基黄酮对脑血管相关疾病的保护

淫羊藿苷可抑制实验性缺血性脑卒中 NF-κB 的活化，增强亚低温诱导的神经保护作用[62]，还通过激活 ERα 和 ERβ 通路促进缺血缺氧性脑病新生小鼠的自噬，进而抑制细胞凋亡，起到神经保护作用[63]。

Icaritin 是淫羊藿苷的代谢产物，在大脑中动脉闭塞(MCAO)小鼠模型中，可显著减少急性缺血性卒中小鼠的神经损伤、梗死体积和组织病理学变化[64]。淫羊藿次苷通过靶向 Nrf2 和 OXPHOS/NF-κB/铁死亡通路，诱导对缺血性卒中的强大神经保护[65]，以及促进海马神经元轴突再生，改善慢性脑低灌注大鼠模型的学习和记忆[66]。淫羊藿次苷还通过抑制炎症反应、细胞凋亡和介导血小板活化，改善神经行为[67]。另外苦参根提取物含两种主要异戊烯基黄酮类化合物苦参黄素(45.5%)和 sophorafavone G (14.7%)对局灶性脑缺血具有神经保护作用，可能是其单独或部分发挥神经保护作用的原因[68]。光甘草定还能调节大鼠大脑中动脉闭塞(MCAO)诱导的脑损伤和星形孢素诱导的培养大鼠皮质神经元损伤[69]。

7. 展望

异戊烯基黄酮是天然植物中一类具有广泛抗炎、抗氧化的化合物；在各种疾病模型中，可以看到较显著的积极作用，尤其是在神经元结构和功能逐渐丧失的神经退行性疾病中。而目前在退行性疾病的治疗中，临床上往往只能缓解疾病进展，尚无彻底治愈的方法，深入研究疾病的机制，筛选具有良好效果的药物，特别是深入研究一些带有特殊基团并具有相同性质的药物是非常有前景的方向。

随着研究的深入，愈加发现带有异戊烯基结构的黄酮类化合物，其生物活性更强。可见在未来，神经退行性疾病患者使用异戊烯基黄酮类可成为一种替代药物治疗方式，而筛选出更有效改善神经症状的药物是医学工作者的重要任务。目前基于神经退行性疾病的发病机制和进展研究还在深入，筛选更优的药物进程仍在持续，需要探索的环节还有很多。但大量的实验表明，基于异戊烯基结构的新策略具有非常大的吸引力，但依旧需要进一步明确其在神经相关改变中的作用。

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