

木犀草素的现代研究进展

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摘要

木犀草素是一种广泛存在于中药中的天然化合物, 是许多药用植物的关键活性成分。体内外研究发现木犀草素具有显著的抗氧化、抗炎等生物活性, 且生物活性之间存在一定的相关性。基于现有研究进展, 本文综述了木犀草素的合成途径、药理活性以及对木犀草素的功能修饰, 以提高其生物利用度、溶解度和靶向性, 对其临床应用与开发提供参考价值。

关键词

木犀草素, 合成, 药理活性, 功能化修饰

A Comprehensive Review on Modern Research on Luteolin

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Abstract

Luteolin is a natural compound widely present in traditional Chinese medicine and is a key active ingredient in many medicinal plants. In vitro and in vivo studies have found that luteolin has significant antioxidant, anti-inflammatory and other biological activities, and there is a certain correlation among these biological activities. Based on the existing research progress, this article reviews the synthetic pathways, pharmacological activities and functional modifications of luteolin to enhance its bioavailability, solubility and targeting, providing reference value for its clinical application

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and development.

Keywords

Luteolin, Synthetic Pathway, Pharmacological Activities, Functional Modifications

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1. 引言

黄酮类化合物是中药中最常见的一类酚性化合物。木犀草素(3',4',5,7-四羟基黄酮)是黄酮类化合物中具有代表性的一种天然儿茶酚类黄酮化合物,其分子式为 $C_{15}H_{10}O_6$, 分子量为 286.23 [1]。木犀草素为黄色针状结晶,熔点 $328^{\circ}\text{C}\sim 330^{\circ}\text{C}$, 化学性质比较稳定,能溶于乙醇、乙醚,微溶于热水,难溶于冷水,有弱酸性,可溶于碱水,在自然界中少数以游离型存在,多数以糖苷型存在,且糖苷多为氧苷[2]。木犀草素广泛存在于中药中,如菊花、裸花紫珠等,且多为中药的特征性活性成分。木犀草素作为一种重要的生物活性物质,其药理作用受到了广泛关注。该化合物不仅具有抗肿瘤、神经保护、心血管及肝肾保护等多重生物学效应[3][4],还能通过尿苷二磷酸葡萄糖醛酸转移酶 UGTs 介导的葡萄糖醛酸化等途径在体内代谢[5]。目前,虽然通过生物合成与化学修饰已在一定程度上提升了其可溶性,并通过纳米载体等策略改善了其生物利用度,但其深层作用网络、临床转化证据缺乏以及剂型优化瓶颈等问题,仍制约着其从活性分子向临床治疗药物的跨越。因此,对木犀草素的合成、药理、修饰及转化研究进行系统梳理与前瞻分析,对推动该天然产物的现代化开发具有重要价值。

2. 木犀草素的合成途径

在植物体内,木犀草素的合成多以苯丙氨酸作为原料,依次经苯丙氨酸解氨酶(PAL)、肉桂酸 4-羟化酶(4CH)和 4-香豆酰 CoA 连接酶(4CL)三步催化得到 4-香豆酰-CoA。在查尔酮合成酶(CHS)催化聚合作用下,一分子 4-香豆酰-CoA 与三分子丙二酰-CoA 结合形成柚皮素查尔酮。硫酮异构酶(CHI)催化柚皮素查尔酮的杂环 C 闭合生成柚皮素和二碘醇,柚皮素继续经黄酮合成酶(FNS)、黄酮 3O-羟化酶(F3'H)催化生成木犀草素[6]。

木犀草素在食品与药品中发挥着重要作用,但从植物中直接获得的量非常有限,因此生物合成和化学合成是获得木犀草素的重要途径。Laura Marin 等[7]对白色链霉菌(*Streptomyces albus*)进行基因编辑,导入编码木犀草素合成酶(TAL, 4CL, CHS, CHI, FNS, and F3'H 六种木犀草素生成的关键酶)的基因,并将基因编辑后的白色链霉菌在 25 ml R5A 培养基中孵育 184 h,用乙酸乙酯提取培养基上清液和被破坏的菌丝颗粒,并进一步纯化得到木犀草素。

常用的木犀草素的化学合成方法多具有合成途径复杂、难以规模生产等缺点,后续研究逐步简化了木犀草素的合成途径[8]。Wang 等[9]介绍了两种新的木犀草素合成方法,在第一种路线中,3,5-二甲氧基苯酚被转化为 2-羟基-4,6-二甲氧基苯乙酮后,在室温下与 3,4-二甲氧基苯甲醛发生缩合反应,得到化合物 A,化合物 A 经碘催化反应和去甲基反应后转化为木犀草素。与第一种方法不同的是,在第二种路线中,3,5-二甲氧基苯酚,在 $\text{BF}_3\cdot\text{Et}_2\text{O}$ 中,与 3,4-二甲氧基肉桂酰氯聚合得到化合物 A。Kobayashi 等以柚皮苷为原料,经化学-酶促反应合成木犀草素,此路线经八步反应完成,反应过程中采用了双苷侧链保

护 C-7 羟基的方法。

3. 木犀草素的药理活性

木犀草素作为一种来源广泛的天然植物提取物, 主要生物活性是抗氧化、抗炎、抗肿瘤等。木犀草素的 1,4 吡咯烷酮结构能有效地清除自由基发挥抗氧化作用, B 环中的邻二羟基结构和 2, 3-双键与 C 环的 4-氧功能结合, 提供了木犀草素良好的抗氧化能力[10]。木犀草素抑制花生四烯酸合成和清除过氧化氢的反应活性与其 B 环上邻二羟基基团的存在和 A 环 C-5 位置上的羟基有关[11]。木犀草素的生物学效应可能在功能上相互关联。例如, 木犀草素通过抗炎, 诱导细胞凋亡, 抑制细胞增殖、转移以及抑制血管生成诱导人结肠癌细胞凋亡[12]。本文基于木犀草素的生物学效应以及生物学效应之间的相互关联, 综述了木犀草素的抗癌、抗病毒作用和对肝、肾、心血管系统、神经系统等的保护作用。

3.1. 抗癌作用

癌症是指具有侵袭潜能的异常细胞生长引起的一组疾病[13]。氧化应激在不同类型癌症的病理学中起着至关重要的作用[14]。因此, 具有显著抗氧化活性的木犀草素有潜在的抗癌作用。研究表明木犀草素可以通过抑制肿瘤细胞增殖、阻滞细胞周期来抑制肿瘤细胞的体外和体内生长, 也可通过作用不同的信号通路诱导肿瘤细胞凋亡。

研究表明, 木犀草素可通过上调 miR-203 的表达, 阻碍 TGF- β 1 诱导的 EMT (上皮-间质转化), 抑制 Ras/Raf/MEK/ERK 信号通路, 显著降低 MDA-MB-453 和 MCF-7 细胞活力并加速其凋亡[15]。还可通过改变细胞形态特征、下调上皮细胞标记、上调间充质标记、抑制 EMT 相关转录因子, 逆转上皮间质转化来抑制三阴性乳腺癌细胞的侵袭和转移[16]。在人乳腺癌细胞异种移植裸鼠模型中, 木犀草素可抑制孕激素依赖性血管生成、干细胞样特征和人乳腺癌异种移植的生长[17]。木犀草素具有较强的抑制肺癌的能力。Zhang [18]等人发现木犀草素在体外显著抑制 A549 细胞的增殖和迁移, 同时诱导细胞凋亡, 还可下调 p-Akt (Ser473)、MDM2、Bcl-2 的表达, 上调 p53、Bax 的表达, 具有良好的抗 nsclc 作用, 其诱导凋亡作用可能与 Akt/MDM2/p53 信号通路有关。此外, 木犀草素对胰腺癌、肝癌等也具有预防或治疗作用, 其机制一般为诱导细胞凋亡, 阻滞细胞周期, 抑制血管生成等[19] [20]。

3.2. 神经保护作用

神经退行性疾病, 是一种年龄相关疾病, 主要导致老年人认知或运动障碍, 包括阿尔兹海默症、帕金森病等[21]。迄今为止, 神经退行性疾病的原因尚未完全阐明, 大量研究发现神经组织容易受到氧化损伤, 神经炎症和氧化应激反应是神经变性的重要原因[22]。比如, 在 AD 患者大脑中, 氧化应激和炎症增加[23]; 活性氧(ROS)的清除缺陷是导致帕金森病的潜在原因[24]。植物化学物质在作为神经保护剂在体内和体外实验中均表现出较高的疗效和较低的副作用, 具有氧化自由基清道夫作用的化合物具有减轻神经元损伤的作用[25]。而木犀草素作为具有较强氧化活性的天然生物活性成分, 具有显著的神经保护作用。

木犀草素在体内和体外模型中都表现出减轻阿尔兹海默症症状的作用, 可通过抑制星形胶质细胞(GFAP)的过度激活和炎症细胞因子(TNF- α 、IL-1 β 、IL-6、NO、COX-2 和 iNOS 蛋白)的过度释放, 降低脑组织内质网应激标志物 GRP78 和 IRE1 α 的表达, 从而改善 AD 小鼠的记忆缺陷和神经炎症[26]。进一步研究发现木犀草素可通过直接与过氧化物酶体增殖物激活受体 γ (PPAR γ)结合, 抑制 A β 生成、修复线粒体损伤和减少神经元凋亡, 进而发挥神经保护作用[27]。在帕金森病的体内模型中, 木犀草素与棕榈酰乙醇酰胺联合使用可减弱 A β 诱导的星形胶质细胞的激活, 对胶质细胞具有明显的保护作用[28], 还可调节帕金森的神经炎症过程和自噬反应[29]。此外, 木犀草素对癫痫、外伤性脑损伤和糖尿病相关认知功能下降等其他神经性疾病有潜在治疗作用, 其主要机制为减轻氧化应激反应和神经炎症[30]。

3.3. 心血管系统的保护作用

心血管疾病(CVD)是心脏或血管的功能异常,包括动脉粥样硬化、缺血性心脏病、外周血管疾病、冠状动脉血管壁缺血损伤后再狭窄等[31]。心血管疾病已成为世界范围内非传染性疾病死亡的主要原因[32]。木犀草素通过复杂的信号转导途径和靶效应物,发挥显著的心血管保护作用。

在 LPS 诱导的大鼠心肌细胞肥大和自噬模型中,木犀草素能有效抑制 LPS 介导的自噬和 Wnt 信号通路相关基因的 mRNA 和蛋白表达水平,提高心肌细胞的细胞活力,降低心肌肥厚相关标志物(ANP 和 BNP)的表达,有效抑制大鼠心肌细胞肥大和自噬[33]。在高脂肪饮食(HFD)小鼠模型中,木犀草素通过调节 SIRT1/CXCR4 信号通路,促进自噬,抑制血管钙化,有效地预防 HFD 致胖小鼠心脏代谢功能和血管功能障碍[34]。在 LDL 受体缺陷小鼠模型中,木犀草素通过诱导氧化低密度脂蛋白,抑制巨噬细胞中 AMPK-SIRT1 信号,降低总胆固醇水平和 THP-1 来源巨噬细胞的趋化因子和炎症因子的表达,以发挥阻止腹腔主动脉斑块的形成和脂质的积累的功效[35]。木犀草素还可以通过激活 STAT3 信号通路部分抑制 I/R 诱导的 SERCA2a 活性下降、减少心肌梗死面积、乳酸脱氢酶的释放和 I/R 损伤时的细胞凋亡[36]。

3.4. 保肝作用

肝脏是具有解毒、代谢、蛋白质合成等其他多种功能的脏器,在各种生理过程的调节中起着至关重要的作用,是内源性代谢废物或外源性有毒化合物代谢的主要场所,这也导致了肝脏易受到毒性成分或被代谢后产生的毒性成分的损伤[37]。迄今为止,还没有药物能完全恢复肝脏功能或促进肝细胞的再生。许多被人类食用的植物显示出了保肝作用,其中膳食植物化学成分与人体相容性好、副作用低,已成为筛选肝脏保护药的重要来源[38]。

在四氯化碳(CCl_4)诱导大鼠肝损伤模型中, CCl_4 严重损伤大鼠肝组织,造成肝严重肿胀、坏死,肝小叶结构紊乱,木犀草素可以减轻上述病理状态,其机制可能为作用于溶质载体家族 7a 成员 11 (SLC7A11)抑制铁死亡,减轻 CCl_4 诱导的肝损伤[39]。在急性-慢性酒精性肝损伤中,木犀草素通过恢复 NRF2 的稳定性,从而阻止 ACS2 和组蛋白 H3 乙酰化的核积累,减少肝脏脂肪的生成,并最终改善酒精性肝损伤[40]。高脂饮食会引起代谢功能障碍相关脂肪性肝病(MAFLD),木犀草素能减轻肝脂肪变性,提高血浆脂联素水平,并上调肝脏脂联素受体 1 (AdipoR1)、amp 活化蛋白激酶(AMPK)和过氧化物酶体增殖物活化受体 γ (PPAR- γ)蛋白的表达($p < 0.05$) [41]。

3.5. 肾保护作用

木犀草素通过靶向 Nr4a1-Slc7a11-GPX4 通路抑制铁死亡,减轻草酸钙(CaOx)晶体沉积所致的肾损伤和肾纤维化,改善肾功能[42]。木犀草素通过调节 Nrf2/HO-1,逆转大鼠肾脏缺血再灌注损伤引起的肾功能障碍、组织损伤、中性粒细胞积聚、和内质网应激等,显著减少凋亡细胞,恢复受损肾组织的细胞活力[43]。在双酚 A 诱导的大鼠肾损伤模型中,大鼠肾容量下降,肌酐清除率降低,肾小球过滤功能减弱。木犀草素可通过抑制氧化应激、上调 Nrf2/ARE/HO-1 途径减轻大鼠上述病理损伤[44]。肾性贫血是慢性肾脏疾病(CKD)的重要并发症,木犀草素处理后小鼠血红蛋白和红细胞压积显著升高,血尿素氮和肌酐显著降低,肾间质损伤和纤维化程度显著减轻,通过 SIRT1/FOXO3 途径减轻肾纤维化引起的肾贫血[45]。

3.6. 骨关节保护作用

骨关节炎是一种以炎症和软骨退化为特征的关节疾病[46]。在 IL-1 β 刺激软骨细胞的体外骨关节炎模型,木犀草素治疗后能显著抑制 IL-1 β 诱导的 II 型胶原的降解,并增强 II 型胶原的表达,防止大鼠软骨破坏[47]。木犀草素还可通过激活 PI3K/AKT 轴,改善线粒体功能障碍,有效减少卵巢切除术引起的全身

骨质流失和氧化应激, 可用于绝经后骨质疏松症的预防和治疗[48]。体外实验表明, 木犀草素能抑制 IL-1 β 诱导的基质金属蛋白酶(MMP), 有降解胶原蛋白, 破坏关节软骨的作用的基因表达, 并抑制 MMP 的分泌与活性[49]。

3.7. 抗病毒作用

木犀草素可以通过调控 Caspase-8 介导的外源性途径和 Caspase-9 介导的线粒体通路途径的凋亡相关基因表达, 从而抑制流感病毒感染诱导的细胞凋亡[50]。木犀草素能在甲型流感病毒感染的早期干扰病毒的复制, 并能通过干扰病毒外壳蛋白 I 的表达, 抑制病毒的进入和内吞途径[51]。木犀草素能抑制宿主蛋白转化酶弗林蛋白酶的活性, 抑制虫媒病毒成熟后在高尔基体中的转运, 对登革热病毒的四种血清型均有抑制作用, 但选择性较弱。能非竞争性抑制抑制登革热病毒重组 NS2B/NS3 蛋白酶, 可减少 Huh-7 细胞中感染性病毒颗粒的形成[52]。

3.8. 其他药理作用

除上述药理作用外, 木犀草素可通过抑制 IPEC-J2 细胞中 NF- κ B 和 ERK 信号通路的激活, 降低 IL-6 和 IL-1 β 的表达, 从而抑制伏马菌素 B1 (FB1) 诱导的肠道炎症损伤[53]。木犀草素能靶向作用于 hly mRNA 编码区, 抑制了李斯特菌素 O 的翻译过程, 能有效抑制单核细胞增多性李斯特氏菌介导的感染[54]。木犀草素可通过激活核受体 DAF-16/FOXO 和 NHR-49/PPAR- α 抑制秀丽隐杆线虫脂肪积累、延长寿命, 是一种潜在的减肥和抗衰老分子[55]。

4. 木犀草素的功能化修饰

木犀草素具有多靶点、水溶性差等特点, 对其进行功能化修饰, 能提高木犀草素的生物利用度、靶向性等, 并增加其药理活性, 更好地发挥木犀草素的药理作用。

4.1. 木犀草素的靶向性修饰

以木犀草素为原料, 将高水溶性和生物相容性的超支化聚酯作为载体, 制成的木犀草素水溶性共聚物, 能将木犀草素靶向传递到人类乳腺癌细胞(MCF-7), 且系统稳定, 载药量高[56]。Wang 等[57]制备的木犀草素乳糜微粒超分子纳米乳, 能明显改善在胃肠道中的通透性和稳定性, 可经淋巴运输进入血液循环, 有效降低血清尿酸水平, 减轻高尿酸血症所致肾损伤。以木犀草素作为原料和以可降解蛋白的玉米醇溶蛋白和酪蛋白酸钠作为纳米载体制备得到木犀草素包封纳米颗粒, 其清除自由基的能力增强、生物利用度增高[58]。

4.2. 增加木犀草素的生物利用度

Wang 等[59]采用液体反溶剂沉淀法和真空冷冻干燥法制备得到的高水溶性木犀草素纳米颗粒, 显著增加了木犀草素的水溶性和生物利用度, 更有效地抑制大鼠肝脏微粒体的过氧化反应。Xu 等[60]以酪蛋白酸钠为静电稳定剂, 制备了木犀草素负载玉米蛋白纳米颗粒(Lut-ZNP), 木犀草素在 Lut-ZNP 中的溶解度、稳定性和释放度均有较大提高。Lu [61]以木犀草素和合成 RA-SS-mPEG 聚合物材料制备聚合物胶束(L-RSPMs), 发现与游离木犀草素相比, L-RSPMs 的相对生物利用度提高了 28%, 通过促进抗氧化作用和调节细胞因子释放来改善 tnbs 诱导的结肠炎症。Mao [62]等采用溶剂蒸发法合成木犀草素磷脂复合物(Lut-pc)提高木犀草素的溶解度和生物活性, 结果表明 Lut-pc 能有效降低尿酸, 对肾的保护作用强于 Lut。

5. 木犀草素的临床应用

验证木犀草素在人体中的生物学相关性是其临床应用的关键步骤。临床研究在将医学科学转化为实

际应用方面发挥着至关重要的作用, 为医疗实践提供了科学依据。目前, 现有文献表明木犀草素的临床试验数据较为有限。仅有一项于 2017 年开展的临床试验, 主要研究木犀草素及其纳米颗粒对舌鳞状癌细胞系的治疗效果[3], 但该试验并未完成或公开发表。由于临床试验数据的缺乏, 以及细胞和动物模型实验的结果无法完全代表在人体中的实际作用, 给木犀草素的临床应用带来了挑战。为弥补这一空白, 后续研究可借助现代技术手段, 结合现有研究成果, 对木犀草素在人体内展开全面的药理学研究。这一方法旨在提升研究的深度与广度, 从而阐明木犀草素的临床应用及其潜在益处。

6. 小结与展望

木犀草素作为一种广泛存在于食品与常用中药中的天然化合物, 对人体有较好的可接受性。本综述系统梳理了其合成、药理、修饰及临床转化现状, 揭示出该分子兼具显著的多靶点生物活性与亟待突破的应用瓶颈。

当前研究已明确, 木犀草素的核心价值源于其儿茶酚及吡喃酮结构赋予的强抗氧化与抗炎活性。以此为基础, 通过调控 Akt/p53、NF- κ B、Nrf2、PI3K/AKT 等关键信号通路, 在肿瘤、神经退行性疾病、心血管及代谢性器官损伤等模型中展现出广谱的保护潜力。为克服其固有的水溶性差、生物利用度低等理化缺陷, 纳米递药系统(如聚合物胶束、纳米乳)及磷脂复合物等新型制剂策略已取得积极进展, 初步证明了通过改善剂型优化其成药性的可行性。然而, 尽管临床前研究数据丰富且充满前景, 但木犀草素向临床应用的转化却严重滞后, 高质量的临床试验证据几乎空白。

因此, 木犀草素的深入研究亟需实现从基础活性阐释到临床价值验证的关键跨越。未来应致力于运用化学蛋白质组学等手段精准解析其多靶点作用网络, 并开发智能响应型递送系统以克服其药学缺陷。当前首要任务是完成系统的临床前评价, 并优先在机制明确的适应症领域开展严谨的临床试验。通过多学科协同整合, 系统性解决天然产物在靶点确证、制剂优化与临床转化中的共性难题, 方能将这一传统活性分子转化为具临床价值的现代医学成果。

综上所述, 木犀草素的未来研究是一项涉及多学科深度整合的系统工程。其终极意义不仅在于开发出一个潜在的药物分子, 更在于以它为范式, 探索并解决天然产物在靶点确证、制剂创新与临床验证全链条中的共性科学问题, 从而真正架起连接传统医药智慧与现代医学实践的桥梁。

参考文献

- [1] 姜亚玲, 李文渊, 冯爽, 等. 木犀草素的结构修饰及其生物活性研究进展[J]. 中草药, 2023, 54(20): 6889-6902.
- [2] 王晶晶, 倪睿, 李紫薇, 等. 负载木犀草素纳米粒的壳聚糖/海藻酸钠水凝胶伤口敷料研究[J]. 中国药学杂志, 2025, 60(8): 856-865.
- [3] Zhu, M., Sun, Y., Su, Y., Guan, W., Wang, Y., Han, J., et al. (2024) Luteolin: A Promising Multifunctional Natural Flavonoid for Human Diseases. *Phytotherapy Research*, **38**, 3417-3443. <https://doi.org/10.1002/ptr.8217>
- [4] Deniz, O.G., Soytürk, H., Him, A., Sağır, D. and Annaç, E. (2025) Luteolin Mitigates Hippocampal Damage in a Rat Model of Streptozotocin-Induced Diabetes. *Biomolecules and Biomedicine*, **25**, 2364-2377. <https://doi.org/10.17305/bb.2025.12305>
- [5] 智婷, 赵一伍, 冉志芳, 等. 木犀草苷生物合成相关的尿苷二磷酸依赖的糖基转移酶研究进展[J]. 中药材, 2025(10): 2666-2673.
- [6] Falcone Ferreyra, M.L., Rius, S.P. and Casati, P. (2012) Flavonoids: Biosynthesis, Biological Functions, and Biotechnological Applications. *Frontiers in Plant Science*, **3**, Article ID: 222. <https://doi.org/10.3389/fpls.2012.00222>
- [7] Marín, L., Gutiérrez-del-Río, I., Yagüe, P., Manteca, Á., Villar, C.J. and Lombó, F. (2017) De Novo Biosynthesis of Apigenin, Luteolin, and Eriodictyol in the Actinomycete *Streptomyces Albus* and Production Improvement by Feeding and Spore Conditioning. *Frontiers in Microbiology*, **8**, Article ID: 921. <https://doi.org/10.3389/fmicb.2017.00921>
- [8] Kong, L., Wu, W., Li, C., Ma, L., Ma, J., Pan, M., et al. (2025) Structure Modification of Luteolin and the Influence of Its Derivatives on Biological Activities. *Frontiers in Nutrition*, **12**, Article ID: 1546932.

- <https://doi.org/10.3389/fnut.2025.1546932>
- [9] O'Keefe, B.M., Simmons, N. and Martin, S.F. (2011) Facile Access to Sterically Hindered Aryl Ketones via Carbonylative Cross-Coupling: Application to the Total Synthesis of Luteolin. *Tetrahedron*, **67**, 4344-4351. <https://doi.org/10.1016/j.tet.2011.03.074>
 - [10] Wang, Q., Zhang, J., Liu, M., Yang, J., Zhang, X., Zhou, L., *et al.* (2015) Modified Syntheses of the Dietary Flavonoid Luteolin. *Journal of Chemical Research*, **39**, 550-552. <https://doi.org/10.3184/174751915x14404221529907>
 - [11] Isika, D.K., Özkömeç, F.N., Çeşme, M. and Sadik, O.A. (2022) Synthesis, Biological and Computational Studies of Flavonoid Acetamide Derivatives. *RSC Advances*, **12**, 10037-10050. <https://doi.org/10.1039/d2ra01375d>
 - [12] Hung, W., Ho, C. and Hwang, L.S. (2011) Inhibitory Activity of Natural Occurring Antioxidants on Thiyl Radical-Induced *Trans*-Arachidonic Acid Formation. *Journal of Agricultural and Food Chemistry*, **59**, 1968-1973. <https://doi.org/10.1021/jf1036307>
 - [13] Devi, K.P., Rajavel, T., Nabavi, S.F., Setzer, W.N., Ahmadi, A., Mansouri, K., *et al.* (2015) Hesperidin: A Promising Anticancer Agent from Nature. *Industrial Crops and Products*, **76**, 582-589. <https://doi.org/10.1016/j.indcrop.2015.07.051>
 - [14] Bailly, C. (2020) Regulation of PD-L1 Expression on Cancer Cells with Ros-Modulating Drugs. *Life Sciences*, **246**, Article 117403. <https://doi.org/10.1016/j.lfs.2020.117403>
 - [15] Gao, G., Ge, R., Li, Y. and Liu, S. (2019) Luteolin Exhibits Anti-Breast Cancer Property through Up-Regulating Mir-203. *Artificial Cells, Nanomedicine, and Biotechnology*, **47**, 3265-3271. <https://doi.org/10.1080/21691401.2019.1646749>
 - [16] Wu, H., Lin, J., Liu, Y., Chen, H., Hsu, K., Lin, S., *et al.* (2021) Luteolin Suppresses Androgen Receptor-Positive Triple-Negative Breast Cancer Cell Proliferation and Metastasis by Epigenetic Regulation of MMP9 Expression via the AKT/mTOR Signaling Pathway. *Phytomedicine*, **81**, Article 153437. <https://doi.org/10.1016/j.phymed.2020.153437>
 - [17] Zhang, L., Liu, Q., Huang, L., Yang, F., Liu, A. and Zhang, J. (2020) Combination of Lapatinib and Luteolin Enhances the Therapeutic Efficacy of Lapatinib on Human Breast Cancer through the Foxo3a/nqo1 Pathway. *Biochemical and Biophysical Research Communications*, **531**, 364-371. <https://doi.org/10.1016/j.bbrc.2020.07.049>
 - [18] Zhang, J., Li, C., Li, W., Shi, Z., Liu, Z., Zhou, J., *et al.* (2024) Mechanism of Luteolin against Non-Small-Cell Lung Cancer: A Study Based on Network Pharmacology, Molecular Docking, Molecular Dynamics Simulation, and in Vitro Experiments. *Frontiers in Oncology*, **14**, Article ID: 1471109. <https://doi.org/10.3389/fonc.2024.1471109>
 - [19] Kato, H., Sato, M., Naiki-Ito, A., Inaguma, S., Sano, M., Komura, M., *et al.* (2024) The Role of DPYD and the Effects of DPYD Suppressor Luteolin Combined with 5-Fu in Pancreatic Cancer. *Cancer Medicine*, **13**, e70124. <https://doi.org/10.1002/cam4.70124>
 - [20] Rath, P., Chauhan, A., Ranjan, A., Aggarwal, D., Rani, I., Choudhary, R., *et al.* (2024) Luteolin: A Promising Modulator of Apoptosis and Survival Signaling in Liver Cancer. *Pathology-Research and Practice*, **260**, Article 155430. <https://doi.org/10.1016/j.prp.2024.155430>
 - [21] Bhat, M.A. and Dhaneshwar, S. (2024) Neurodegenerative Diseases: New Hopes and Perspectives. *Current Molecular Medicine*, **24**, 1004-1032. <https://doi.org/10.2174/1566524023666230907093451>
 - [22] Jiang, Q., Liu, J., Huang, S., Wang, X., Chen, X., Liu, G., *et al.* (2025) Antiageing Strategy for Neurodegenerative Diseases: From Mechanisms to Clinical Advances. *Signal Transduction and Targeted Therapy*, **10**, Article No. 76. <https://doi.org/10.1038/s41392-025-02145-7>
 - [23] Liu, Y., Dong, Y., Cao, Z., Ji, Y., Cheng, X. and Zheng, X. (2025) The Multi-Dimensional Action Map of Resveratrol against Alzheimer's Disease: Mechanism Integration and Treatment Strategy Optimization. *Nutrients*, **17**, Article 3451. <https://doi.org/10.3390/nu17213451>
 - [24] Moaket, O.S., Obaid, S.E., Obaid, F.E., Shakeeb, Y.A., Elsharief, S.M., Tania, A., *et al.* (2025) GLP-1 and the Degen-erating Brain: Exploring Mechanistic Insights and Therapeutic Potential. *International Journal of Molecular Sciences*, **26**, Article 10743. <https://doi.org/10.3390/ijms262110743>
 - [25] Alkhamash, A., Alotaibi, G., Algethami, A. and Alqarni, M. (2025) Decoding Apoptosis-Associated Pathways in In-flammatory and Neurodegenerative Diseases: A Network Pharmacology Based Drug Discovery Approach. *European Journal of Pharmacology*, **1007**, Article 178231. <https://doi.org/10.1016/j.ejphar.2025.178231>
 - [26] Kou, J., Shi, J., He, Y., Hao, J., Zhang, H., Luo, D., *et al.* (2022) Luteolin Alleviates Cognitive Impairment in Alzheimer's Disease Mouse Model via Inhibiting Endoplasmic Reticulum Stress-Dependent Neuroinflammation. *Acta Pharmacolog-ica Sinica*, **43**, 840-849. <https://doi.org/10.1038/s41401-021-00702-8>
 - [27] He, Z., Li, X., Wang, Z., Cao, Y., Han, S., Li, N., *et al.* (2023) Protective Effects of Luteolin against Amyloid Beta-Induced Oxidative Stress and Mitochondrial Impairments through Peroxisome Proliferator-Activated Receptor Γ -De-pendent Mechanism in Alzheimer's Disease. *Redox Biology*, **66**, Article 102848. <https://doi.org/10.1016/j.redox.2023.102848>

- [28] Elmazoglu, Z., Yar Saglam, A.S., Sonmez, C. and Karasu, C. (2020) Luteolin Protects Microglia against Rotenone-Induced Toxicity in a Hormetic Manner through Targeting Oxidative Stress Response, Genes Associated with Parkinson's Disease and Inflammatory Pathways. *Drug and Chemical Toxicology*, **43**, 96-103. <https://doi.org/10.1080/01480545.2018.1504961>
- [29] Cordaro, M., Cuzzocrea, S. and Crupi, R. (2020) An Update of Palmitoylethanolamide and Luteolin Effects in Preclinical and Clinical Studies of Neuroinflammatory Events. *Antioxidants*, **9**, Article 216. <https://doi.org/10.3390/antiox9030216>
- [30] Grabarczyk, M., Justyńska, W., Czapkowska, J., Smolińska, E., Bielenin, A., Glabinski, A., *et al.* (2024) Role of Plant Phytochemicals: Resveratrol, Curcumin, Luteolin and Quercetin in Demyelination, Neurodegeneration, and Epilepsy. *Antioxidants*, **13**, Article 1364. <https://doi.org/10.3390/antiox13111364>
- [31] Guida, G., Attanasio, A., Disabato, G., Paglione, G. and Piepoli, M. (2024) Editorial Comments: Focus on Cardiovascular Diseases. *European Journal of Preventive Cardiology*, **31**, 501-503. <https://doi.org/10.1093/eurjpc/zwae085>
- [32] Lavie, C.J. (2022) Progress in Cardiovascular Diseases Statistics 2022. *Progress in Cardiovascular Diseases*, **73**, 94-95. <https://doi.org/10.1016/j.pcad.2022.08.005>
- [33] Gentile, D., Fornai, M., Pellegrini, C., Colucci, R., Benvenuti, L., Duranti, E., *et al.* (2018) Luteolin Prevents Cardiometabolic Alterations and Vascular Dysfunction in Mice with HFD-Induced Obesity. *Frontiers in Pharmacology*, **9**, Article ID: 1094. <https://doi.org/10.3389/fphar.2018.01094>
- [34] Yu, X., Xu, L., Su, C., Wang, C., Wang, Z., Wang, Y., *et al.* (2024) Luteolin Protects against Vascular Calcification by Modulating SIRT1/CXCR4 Signaling Pathway and Promoting Autophagy. *The AAPS Journal*, **26**, Article No. 111. <https://doi.org/10.1208/s12248-024-00982-y>
- [35] Yang, J., Qian, L., Zhang, F., Wang, J., Ai, H., Tang, L., *et al.* (2015) Cardioprotective Effects of Luteolin on Ischemia/Reperfusion Injury in Diabetic Rats Are Modulated by Enos and the Mitochondrial Permeability Transition Pathway. *Journal of Cardiovascular Pharmacology*, **65**, 349-356. <https://doi.org/10.1097/fjc.0000000000000202>
- [36] Liu, D., Luo, H. and Qiao, C. (2022) SHP-1/STAT3 Interaction Is Related to Luteolin-Induced Myocardial Ischemia Protection. *Inflammation*, **45**, 88-99. <https://doi.org/10.1007/s10753-021-01530-y>
- [37] Wang, H., Zhao, Z., Song, M., Zhang, W., Liu, C. and Chen, S. (2024) Luteolin Detoxifies DEHP and Prevents Liver injury by Degrading Urocl Protein in Mice. *EMBO Molecular Medicine*, **16**, 2699-2724. <https://doi.org/10.1038/S44321-024-00160-9>
- [38] Singh, D., Khan, M.A. and Siddique, H.R. (2024) Unveiling the Therapeutic Promise of Natural Products in Alleviating Drug-Induced Liver Injury: Present Advancements and Future Prospects. *Phytotherapy Research*, **38**, 22-41. <https://doi.org/10.1002/ptr.8022>
- [39] Han, Z., Batudeligen, Chen, H., Narisu, Anda, Xu, Y., *et al.* (2024) Luteolin Attenuates Ccl4-Induced Hepatic Injury by Inhibiting Ferroptosis via SLC7A11. *BMC Complementary Medicine and Therapies*, **24**, Article No. 193. <https://doi.org/10.1186/s12906-024-04486-2>
- [40] Cao, L., Lei, Q., Dong, Y., Meng, C., Qi, Q., Li, L., *et al.* (2025) Luteolin Protects against Alcoholic Liver Injury by Restoring NRF2 Stability to Suppress ACS2 Nuclear Accumulation. *npj Science of Food*, **9**, Article No. 234. <https://doi.org/10.1038/s41538-025-00600-x>
- [41] Taweessap, P., Potue, P., Khamsekaew, J., Iampanichakul, M., Jan-O, B., Pakdeechote, P., *et al.* (2025) Luteolin Relieves Metabolic Dysfunction-Associated Fatty Liver Disease Caused by a High-Fat Diet in Rats through Modulating the AdipoR1/AMPK/PPAR γ Signaling Pathway. *International Journal of Molecular Sciences*, **26**, Article 3804. <https://doi.org/10.3390/ijms26083804>
- [42] Ye, Z., Yang, S., Chen, L., Yu, W., Xia, Y., Li, B., *et al.* (2025) Luteolin Alleviated Calcium Oxalate Crystal Induced Kidney Injury by Inhibiting NR4A1-Mediated Ferroptosis. *Phytomedicine*, **136**, Article 156302. <https://doi.org/10.1016/j.phymed.2024.156302>
- [43] Wei, J., Zhao, B., Jiang, Z., Wang, P., Xu, Y., Ding, N., *et al.* (2025) Luteolin Mitigates Renal Ischemia-Reperfusion Injury via Anti-Inflammatory, Anti-Apoptotic, and NRF2/HO-1-Mediated Antioxidant Effects. *European Journal of Pharmacology*, **999**, Article 177676. <https://doi.org/10.1016/j.ejphar.2025.177676>
- [44] Xin, S., Yan, H., Ma, J., Sun, Q. and Shen, L. (2016) Protective Effects of Luteolin on Lipopolysaccharide-Induced Acute Renal Injury in Mice. *Medical Science Monitor*, **22**, 5173-5180. <https://doi.org/10.12659/msm.898177>
- [45] Li, F., Wei, R., Huang, M., Chen, J., Li, P., Ma, Y., *et al.* (2022) Luteolin Can Ameliorate Renal Interstitial Fibrosis-Induced Renal Anaemia through the SIRT1/FOXO3 Pathway. *Food & Function*, **13**, 11896-11914. <https://doi.org/10.1039/d2fo02477b>
- [46] Xu, Z., Su, P., Zhou, X., Zheng, Z., Zhu, Y. and Wang, Q. (2024) Exploring the Mechanism of Action of Modified Simiao Powder in the Treatment of Osteoarthritis: An In-Silico Study. *Frontiers in Medicine*, **11**, Article ID: 1422306. <https://doi.org/10.3389/fmed.2024.1422306>
- [47] Li, Y., Liu, F., Li, S., Huang, W., Zhou, S., Han, Y., *et al.* (2024) Luteolin Regulating Synthesis and Catabolism of

- Osteoarthritis Chondrocytes via Activating Autophagy. *Heliyon*, **10**, e31028. <https://doi.org/10.1016/j.heliyon.2024.e31028>
- [48] Chai, S., Yang, Y., Wei, L., Cao, Y., Ma, J., Zheng, X., *et al.* (2024) Luteolin Rescues Postmenopausal Osteoporosis Elicited by OVX through Alleviating Osteoblast Pyroptosis via Activating PI3K-AKT Signaling. *Phytomedicine*, **128**, Article 155516. <https://doi.org/10.1016/j.phymed.2024.155516>
- [49] Shivnath, N., Siddiqui, S., Rawat, V., Khan, M.S. and Arshad, M. (2021) Solanum Xanthocarpum Fruit Extract Promotes Chondrocyte Proliferation in Vitro and Protects Cartilage Damage in Collagenase Induced Osteoarthritic Rats (Article Reference Number: JEP 114028). *Journal of Ethnopharmacology*, **274**, Article 114028. <https://doi.org/10.1016/j.jep.2021.114028>
- [50] Morimoto, R., Hanada, A., Matsubara, C., Horio, Y., Sumitani, H., Ogata, T., *et al.* (2023) Anti-Influenza A Virus Activity of Flavonoids *in Vitro*: A Structure-Activity Relationship. *Journal of Natural Medicines*, **77**, 219-227. <https://doi.org/10.1007/s11418-022-01660-z>
- [51] Zima, V., Radilová, K., Kožíšek, M., Albiñana, C.B., Karlukova, E., Brynda, J., *et al.* (2020) Unraveling the Anti-Influenza Effect of Flavonoids: Experimental Validation of Luteolin and Its Congeners as Potent Influenza Endonuclease Inhibitors. *European Journal of Medicinal Chemistry*, **208**, Article 112754. <https://doi.org/10.1016/j.ejmech.2020.112754>
- [52] Peng, M., Watanabe, S., Chan, K.W.K., He, Q., Zhao, Y., Zhang, Z., *et al.* (2017) Luteolin Restricts Dengue Virus Replication through Inhibition of the Proprotein Convertase Furin. *Antiviral Research*, **143**, 176-185. <https://doi.org/10.1016/j.antiviral.2017.03.026>
- [53] Wen, D., Han, W., Chen, Q., Qi, G., Gao, M., Guo, P., *et al.* (2024) Integrating Network Pharmacology and Experimental Validation to Explore the Mechanisms of Luteolin in Alleviating Fumonisin B1-Induced Intestinal Inflammatory Injury. *Toxicon*, **237**, Article 107531. <https://doi.org/10.1016/j.toxicon.2023.107531>
- [54] Lin, Y., Yang, N., Bao, B., Wang, L., Chen, J. and Liu, J. (2020) Luteolin Reduces Fat Storage in *Caenorhabditis elegans* by Promoting the Central Serotonin Pathway. *Food & Function*, **11**, 730-740. <https://doi.org/10.1039/c9fo02095k>
- [55] Liu, F., Hong, C., Gong, S., Fan, Z., Xiao, X. and Xiao, Y. (2025) Luteolin Decreases Fat Accumulation and Extends Lifespan in *Caenorhabditis elegans* via DAF-16/FOXO and NHR-49/PPAR- α . *Journal of Agricultural and Food Chemistry*, **73**, 30749-30760. <https://doi.org/10.1021/acs.jafc.5c08997>
- [56] Mahin, M., Ali, A., Elahe, K., *et al.* (2019) Synthesis of a Copolymer Carrier for Anticancer Drug Luteolin for Targeting Human Breast Cancer Cells. *Journal of Traditional Chinese Medicine*, **39**, 474-481.
- [57] Wang, M., Zhao, L., Liu, Y., *et al.* (2025) Chylomicron-Mimicking Supramolecular Nanoemulsion for Oral Luteolin Delivery against Hyperuricemia. *Pharmaceutical Development and Technology*, **30**, 1543-1556.
- [58] Shinde, P., Agrawal, H., Singh, A., Yadav, U.C.S. and Kumar, U. (2019) Synthesis of Luteolin Loaded Zein Nanoparticles for Targeted Cancer Therapy Improving Bioavailability and Efficacy. *Journal of Drug Delivery Science and Technology*, **52**, 369-378. <https://doi.org/10.1016/j.jddst.2019.04.044>
- [59] Sinha, A. and Suresh, P.K. (2019) Enhanced Induction of Apoptosis in HaCat Cells by Luteolin Encapsulated in Pegylated Liposomes—Role of Caspase-3/Caspase-14. *Applied Biochemistry and Biotechnology*, **188**, 147-164. <https://doi.org/10.1007/s12010-018-2907-z>
- [60] Xu, Q., Zhang, W., Xu, H. and Zhang, Q. (2023) Fabrication of Luteolin Loaded Zein-Caseinate Nanoparticles and Its Bioavailability Enhancement in Rats. *Journal of Pharmaceutical Sciences*, **112**, 3056-3066. <https://doi.org/10.1016/j.xphs.2023.06.010>
- [61] Lu, Z., Liu, J., Zhao, L., Wang, C., Shi, F., Li, Z., *et al.* (2023) Enhancement of Oral Bioavailability and Anti-Colitis Effect of Luteolin-Loaded Polymer Micelles with RA (Rosmarinic Acid)-Ss-Mpeg as Carrier. *Drug Development and Industrial Pharmacy*, **49**, 17-29. <https://doi.org/10.1080/03639045.2023.2175850>
- [62] Mao, J., Gao, T., Wang, L., Lv, X. and Zhao, X. (2025) Luteolin Phospholipid Complexes Improves the Bioavailability of Luteolin and Exhibits Potent Protection and High Safety in Mice with Gouty Nephropathy. *Natural Product Research*, 1-5. <https://doi.org/10.1080/14786419.2025.2534681>