·文献综述·

木犀草素在眼科疾病中的研究进展

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摘要

天然黄酮类化合物因其良好的生物安全性和多重药理活性而受到广泛关注。其中,木犀草素(luteolin)作为代表性成分,在多种眼科疾病模型中显示出显著的抗炎、抗氧化、抗血管生成及神经保护作用。其作用机制主要涉及NF-κB、PI3K/Akt、Nrf2/HO-1、AGE-RAGE等关键信号通路的调控。大量实验研究表明,木犀草素在角膜与眼表疾病、炎症性眼病、青光眼、白内障、糖尿病视网膜病变及年龄相关性黄斑变性等多种疾病的防治中具有潜在应用价值。然而,其临床研究仍有限。文章系统综述了近5 a来木犀草素在眼科疾病中的研究进展,分析其分子机制与治疗潜力,并探讨未来的研究方向,为其临床转化提供理论依据。

关键词:木犀草素;眼科疾病;抗氧化;抗炎
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Research progress of luteolin in ocular diseases

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Abstract

• Natural flavonoids have attracted considerable attention owing to their favorable biosafety profiles and multiple pharmacological properties in recent years. Luteolin, a representative flavonoid compound, exhibits anti-inflammatory, antioxidant, anti-angiogenic, and neuroprotective effects in multiple ocular disease models by modulating key signaling pathways, including NF-κB, PI3K/Akt, Nrf2/HO-1, and AGE-RAGE. Accumulating experimental evidence supports the potential application of luteolin in various ocular diseases, including corneal and ocular surface diseases, inflammatory eye diseases, glaucoma, cataract, diabetic retinopathy, and age-related macular degeneration. However, clinical evidence remains limited. This review systematically summarizes research progress on luteolin in ocular diseases over the past five years, analyzes its molecular mechanisms and therapeutic potential, and discusses future directions, so as toprovide a theoretical basis for clinical translation.

• KEYWORDS: luteolin; ocular diseases; antioxidation; anti-inflammation

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0 引言

眼部疾病是导致视觉功能损害和生活质量下降的主要原因之一,随着当今社会人口老龄化,电子屏幕暴露增加以及环境因素变化,眼病的发病率呈持续上升趋势,甚至还会增加全身性非眼科疾病的发病率和死亡风险[1]。因此,开发兼具多靶点活性的安全药物已逐渐成为研究重点。近年来,天然黄酮类化合物因其多重药理活性和良好的生物安全性,受到广泛关注[2]。其中,木犀草素(luteolin,3,4,5,7-四羟基黄酮)作为代表性成分,广泛存在于夏枯草、金银花、黄芩、野菊花等多种植物中,具有明确的抗氧化、抗炎、抗凋亡和抗血管新生等活性[3-4](图 1)。在眼科领域的研究表明木犀草素可通过调控多条关键信号通路在眼科疾病中发挥广泛的保护作用。其作用机制主要涉及核因子-κB(NF-κB)、磷脂酰肌醇-3-激酶/蛋白激酶 B(PI3K/Akt)存活信号通路等[5-7]。实验研究显示,木犀草素在干眼、葡萄膜炎、糖尿病视网膜病变及年龄相关性黄斑变性等多种眼科疾病模型中,均能显著减轻氧化应激与炎症反应,抑制细胞凋亡及新生血管生成,从而发挥抗炎、抗氧化和神经保护作用。本综述旨在系统梳理近 5 a 来木犀草素在各类眼部疾病中的实验研究进展,归纳其作用机制、干预方式与研究模型,分析当前研究的不足与未来的研究方向,为其在眼科治疗中的进一步应用和探索提供理论依据。

1 木犀草素在不同眼病中的研究进展

现有研究表明,木犀草素在眼科疾病领域的探索不断深入,已涉及角膜、睫状体、晶状体等多种眼部组织。为系统梳理相关研究进展,本文将按照眼部疾病的分类,依次探讨木犀草素的治疗应用与机制。

2 角膜与眼表疾病

角膜与眼表疾病包括干眼综合征、角膜上皮损伤及化学性烧伤等常见病变,常伴随眼表屏障功能障碍及慢性炎症反应,导致眼表稳态失衡,并引发干涩、异物感、烧灼感等典型临床症状[8]。Xie 等[5]构建了小鼠干眼模型,发现木犀草素可上调 Sirt1 表达并抑制 NF-κB 激活及 NLRP3 炎症小体组装,从而降低 IL-1β 和 IL-18 水平,缓解眼表炎症状态,改善泪液分泌不足与角膜上皮损伤。在碱烧角膜损伤模型[9]中,木犀草素同样通过抑制 NF-κB 通路,下调 TNF-α、IL-1β、VEGF 及 MMP-2/9 的表达,从而减轻前房炎症与角膜新生血管形成,并保护胶原结构。

总体而言,木犀草素在干眼和角膜烧伤等眼表疾病模型中显示出明确的治疗潜力,体现了其在眼表疾病中的应用价值。部分眼表病变(如病毒性角膜炎)伴随复杂的免疫炎症过程,其机制与系统性炎症相关,相关内容将在“炎症性眼病”一节进一步讨论。

3 炎症性眼病

炎症性眼病是一类以免疫炎症反应异常激活为共同病理基础的眼部疾病,可由感染性或非感染性因素诱发,累及角膜、虹膜、脉络膜及视网膜等多种组织结构,其共同病理特征为免疫细胞浸润、炎症因子释放及组织结构破坏,严重时可导致不可逆视功能损害[10]。前列腺素内过氧化物合酶-2(PTGS2/COX-2)作为炎症反应的关键诱导酶,其上调与多种眼部炎症相关。

在 HSV-1 诱导的单纯疱疹性角膜炎(HSK)小鼠模型中,Zhao[6]发现结膜下注射木犀草素可减轻角膜混浊与水肿并改善中央角膜厚度;机制研究表明,木犀草素通过抑制 PTGS2 表达并阻断 NF-κB 通路活化,下调 IL-1β、TNF-α和 IL-6 等炎症因子,其抗炎作用主要依赖于 PTGS2/NF-κB 炎症轴。Omran 等[11]构建了以木犀草素为活性成分的眼部给药体系,并在体内模型中验证了其抗炎效果。结果表明,该体系滴眼处理后可显著缓解虹膜充血、角膜混浊及结膜水肿等急性炎症表现,炎症评分自第 2 d 起明显下降,至第 5 d 基本恢复正常,提示其在非感染性眼部炎症中同样具有抗炎保护作用。

除角膜及前节炎症外,木犀草素在葡萄膜炎模型中亦表现出抗炎效应。葡萄膜炎是一类可由感染性或非感染性因素诱发、累及葡萄膜及邻近组织的常见致盲性眼病[12-13]。糖皮质激素(如泼尼松龙)为急性期常用的一线治疗药物,但其长期或高剂量应用存在不良反应风险,因此需要开发更安全的替代或辅助治疗策略。Zhang 等[14]通过网络药理学及分子对接分析指出,木犀草素可能是四逆散中发挥抗炎作用的关键活性成分,其作用可能涉及 PI3K-Akt、TNF 及 IL-17 等炎症相关通路。Kanai 等[15-16]在 LPS 诱导的 Lewis 大鼠急性前葡萄膜炎模型中进一步证实,腹腔注射木犀草素可降低临床炎症评分、房水炎性

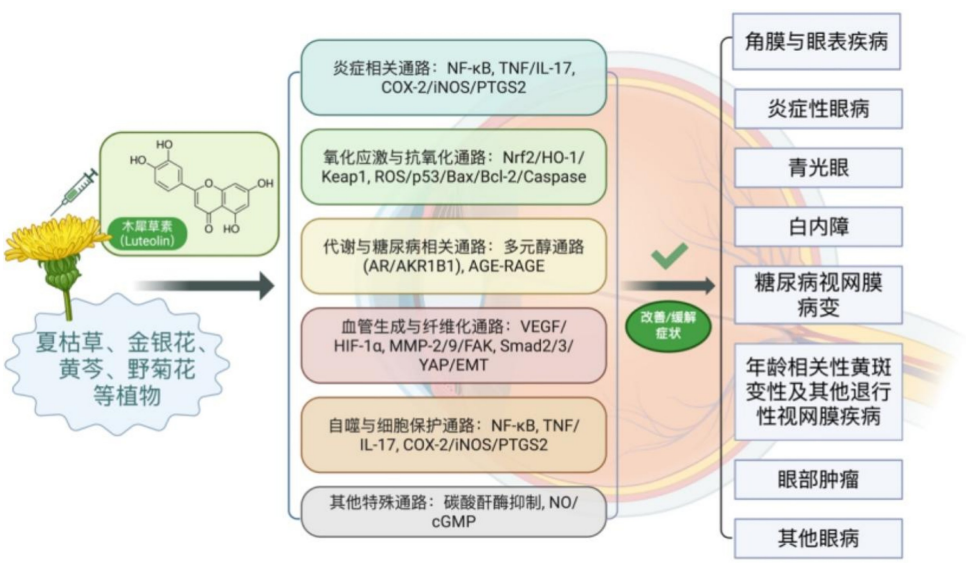

图 1　木犀草素在不同眼病中的研究进展示意图。

细胞数及蛋白浓度,并抑制 TNF-α、NO 和 PGE_2 释放,下调前列腺素合酶(COX-2)和一氧化氮合酶(iNOS)的表达,其整体抗炎效力与泼尼松龙相当,有望作为糖皮质激素的潜在替代或辅助用药[16]。

4 青光眼

青光眼是一种以视网膜神经节细胞进行性退行性变为特征的视神经疾病,表现为视神经盘凹陷及视力逐渐丧失[17]。目前临床治疗仍以降低眼压的局部用药为主,但长期用药带来的眼表疾病等问题,严重影响患者的治疗依从性和生活质量[18]。

在多种高眼压动物模型中,木犀草素通过不同递送策略显示出良好的降眼压及神经保护作用。Omran 等[11]在激素诱导的家兔高眼压模型中发现,壳聚糖偶联植物立方体递送木犀草素可显著延长其眼内滞留时间并提高稳定性、显著降低眼压,伴随视网膜及视神经中 TNF-α、IL-6 等炎症因子显著下调和氧化应激水平降低。在小鼠高眼压模型[19]中的进一步研究显示,木犀草素结合油菜孢子外壳植物立方体与卡拉胶修饰的递送系统,可增强角膜黏附性与持续释放能力,有效延长降眼压时间,并通过抗氧化途径发挥保护作用。Elsherbiny 等[20]采用牛初乳外泌体负载木犀草素并经微针阵列递送,在新西兰白兔中显著提升角巩膜渗透性与滞留时间,单次给药即可恢复并长期维持眼压稳定,同时抑制 TNF-α、IL-8、IL-1β 等多种炎症因子表达并增强抗氧化酶活性。提示其具备多靶点的神经保护作用。

在酶抑制与分子对接研究中,Aggul 等[21]发现木犀草素及其 7-O-葡萄糖苷可在低微摩尔浓度下抑制人碳酸酐酶Ⅰ和Ⅱ活性,其中 7-O-葡萄糖苷可与 Zn^{2+} 及关键氨基酸残基形成稳定结合,其抑制能力优于临床常用药物乙酰唑胺,为木犀草素类化合物作为潜在碳酸酐酶抑制剂提供了理论依据。Yu 等[22]通过网络药理学与 H_2O_2 诱导的 RGC-5 细胞模型证实,木犀草素可通过调节线粒体功能相关的 p53 依赖性凋亡通路,降低过量活性氧(ROS)水平并抑制 Caspase 级联反应,从而提高视网膜神经节细胞存活率。

5 白内障

白内障是全球致盲的主要原因之一,其发生发展与氧化应激密切相关。ROS 可诱导晶状体蛋白质聚集和细胞凋亡,导致晶状体混浊[23]。研究显示,木犀草素在体内外白内障模型中均具保护作用。体外 H_2O_2 诱导的兔晶状体上皮细胞实验表明,其可改善氧化应激指标(SOD、GSH-Px、MDA、·OH),并通过上调 Beclin-1、下调 P62 增强自噬流,从而减轻细胞损伤[24]。体内硒酸钠诱导的乳鼠白内障模型显示,木犀草素可以改善氧化应激,抑制炎症因子表达(TNF-α、IL-2、IL-6)并通过调控凋亡相关蛋白(上调 Bcl-2、p-PI3K、p-AKT,下调 Bax、Caspase-3)保护晶状体细胞;进一步网络药理学与分子对接分析提示,木犀草素可能通过 PI3K/AKT 信号通路协调抗氧化、抗炎及抗凋亡效应[7]。

6 糖尿病视网膜病变

糖尿病视网膜病变是糖尿病最常见且最严重的微血管并发症之一,其发生与多元醇通路异常激活、晚期糖基化终末产物(advanced glycation end products, AGEs)积聚及氧化应激密切相关[25]。研究表明,木犀草素可通过多靶点干预上述病理过程,发挥抗氧化和代谢保护作用。

Hwang 等[26]发现,木犀草素可显著抑制醇脱氢酶(aldose reductase, AR)活性,减少山梨醇积聚并阻断 AGEs 生成,同时增强自由基清除能力。此外,木犀草素通过下调 NF-κB、PI3K-AKT、HIF-1 及 TNF 等信号通路,调控 AKT1、VEGFA 等炎症与血管生成相关靶点,从而抑制炎症反应和新生血管形成,改善视网膜结构与血流灌注[27-29]。同时,其可与 TNF 结合并下调其表达,进一步减轻炎症反应[30]。在细胞层面,木犀草素通过抑制 NLRP1、NOX4、TXNIP 及 NLRP3 蛋白表达,调控线粒体自噬相关通路 SQSTM1/BNIP3L,降低 ROS 水平并恢复 SIRT1 活性,抑制 p53 乙酰化及 Caspase 级联反应,从而减少凋亡与炎症损伤,改善视网膜结构与功能[31-33]。

7 年龄相关性黄斑变性及其他退行性视网膜疾病

7.1 年龄相关性黄斑变性 年龄相关性黄斑变性(age-related macular degeneration, ARMD)是老年人视力丧失的主要原因之一,可分为干性(萎缩型)和湿性(渗出型)两种类型。干性 ARMD 以视网膜色素上皮(RPE)及光感受器退变为特征,湿性 ARMD 则主要由脉络膜新生血管生成及渗漏引起。

在 RPE 氧化损伤模型中,木犀草素能显著降低 IL-6、IL-8、MCP-1 等炎症因子,抑制 MAPK 家族成员(p38、JNK、ERK1/2)及转录因子 CREB 的活化,改善细胞炎症和氧化损伤[34-37]。此外,Huang 等[38]报道,木犀草素可促进 AKT 磷酸化、抑制 NF-κB 核转位及 MAPK 通路活化,上调抗氧化基因 HO-1 表达,减少炎症介质释放和免疫细胞黏附,显著提高 RPE 细胞存活率并减轻凋亡。

在纤维化相关研究中,Chen 等[39]报道,木犀草素可激活 Nrf2/AKT-GSK-3β 通路,逆转氧化损伤诱导的上皮-间质转化(epithelial-mesenchymal transition, EMT),维持上皮黏附蛋白 E-cadherin 与紧密连接蛋白 ZO-1 的表达,从而保持细胞连接完整性;Zhang 等[40]在激光诱导的 CNV/SF 模型中进一步证实,木犀草素通过抑制 Smad2/3 磷酸化及增强 YAP 磷酸化(分别为 TGF-β 和 Hippo 通路关键因子),减少脉络膜新生血管及纤维组织沉积,改善视网膜结构。

7.2 其他 视网膜退行性疾病光损伤等因素导致的视网膜色素变性(retinitis pigmentosa, RP)等疾病亦与氧化应激密切相关。蓝光或高强度光照可诱导 RPE 细胞产生 ROS,导致脂褐素沉积与光感受器凋亡[41]。Hayakawa 等[42]发现,木犀草素通过激活 Keap1/Nrf2 通路,上调 HO-1和 ALDH1a1 表达,减少蓝光诱导的脂褐素形成并延缓 RPE 退化。Cao 等[43]进一步指出,其与枸杞子多糖协同作用,可抑制 Müller 细胞凋亡并改善干性 ARMD 相关视网膜萎缩。

此外,木犀草素在高渗应激 RPE 模型中能下调成纤维细胞生长因子(bFGF)、肝细胞表皮生长因子(HB-EGF)及血管内皮生长因子(VEGF)的表达,减轻促血管生成反应[44];在 RP 模型中,其可通过调控多种凋亡与抗氧化靶点,改善光感受器变性[45]。网络药理学研究亦表明,木犀草素可通过 HIF-1、EGFR、IL-6 和 VEGFA 等靶点参与炎症反应、血管生成及铁死亡相关过程的调控[46]。

8 眼部肿瘤

眼部肿瘤是指发生在眼球及其附属结构的良恶性肿瘤,其中以恶性眼内肿瘤如脉络膜黑色素瘤和视网膜母细胞瘤最为常见[47]。尽管总体发病率较低,但部分肿瘤侵

袭性强且易转移,具有潜在致盲性和威胁生命的风险。现有治疗手段包括手术、放疗、化疗及局部消融等,但在视功能保留、远处转移控制及治疗相关并发症等方面仍存在局限,治疗策略有待完善。在脉络膜黑色素瘤研究中,Shi 等[48]发现,木犀草素可降低细胞上清液中 VEGF 水平,同时下调 Bcl-2、上调 Bax,诱导细胞周期阻滞并抑制血管生成。进一步研究发现,木犀草素可抑制肿瘤细胞的黏附、迁移与侵袭,伴随 MMP-2、MMP-9 及 FAK 表达减少。

在葡萄膜黑色素瘤中,木犀草素同样展现出抗肿瘤和抗血管生成活性。体外实验显示,其可抑制多种血管生成模式并削弱肿瘤细胞与内皮细胞相互作用,该效应与 PI3K/Akt 信号通路抑制相关[49]。Yu 等[50]在三维球体培养模型中进一步证实,在更接近体内微环境的条件下,木犀草素的抑制效应仍然存在。

9 小结

综上所述,木犀草素通过抗炎、抗氧化及细胞保护作用,在多种眼科疾病模型中显示出良好的干预效果和多靶点干预潜力(表 1),为眼部疾病的防治提供了新的思路。但现有研究仍主要集中于临床前阶段,尚缺乏系统的药效学-药代动力学研究及高质量临床证据。未来研究可在完善眼部递药系统的基础上,结合机制研究与规范化临床试验,为其在眼科领域的实际应用提供新策略。

表 1 木犀草素在眼部疾病治疗中的研究进展

疾病模型	机制(靶点/方向)	作用效果
干眼/角膜烧伤	Sirt1↑→NF-κB/NLRP3↓→IL-1β、IL-18、TNF-α↓	抗炎、抗氧化、促进修复
	VEGF↓	抑制角膜新生血管
	MMP-2/9↓	抑制基质降解与血管浸润
单纯疱疹性角膜炎/葡萄膜炎	PTGS2↓→NF-κB↓→TNF-α、IL-6、IL-1β↓	免疫调控、抗炎
	PI3K-Akt 调控	免疫调控、抗炎
	IL-17 信号抑制	抗炎、抑制免疫过度反应
	COX-2↓	减少炎性介质生成
	iNOS↓	减少 NO 介导炎症
青光眼(高眼压/RGC 损伤)	碳酸酐酶抑制	房水生成减少、降眼压
	ROS↓→p53 抑制	抗氧化、神经保护
	Bax↓、Bcl-2↑	抗凋亡、神经保护
	Caspase-3/9↓	抗凋亡、神经保护
	PI3K-Akt 激活	细胞存活率↑、神经保护
	TNF-α↓	抗炎、神经保护
	IL-6↓	抗炎、神经保护
白内障(氧化应激/糖尿病相关)	PI3K-Akt 激活	抗凋亡、抗氧化
	Bcl-2↑、Bax↓	抗凋亡
	Caspase-3↓	抗凋亡
	Beclin-1↑、P62↓→自噬增强	调控自噬、延缓晶状体损伤
糖尿病视网膜病变	AR/AKR1B1↓→山梨醇减少	缓解渗透压损伤、抗氧化
	AGE-RAGE↓→HIF-1、TNF↓	抗炎、抗血管生成
	PI3K-Akt 调控	细胞存活/血管稳态调控
	TNF↓	抗炎
	HIF-1↓	抗血管生成、减少渗漏
	NLRP1/3、NOX4、TXNIP↓	抗炎、减少 ROS
	SIRT1↑/p53↓	抗凋亡、抗氧化
	SQSTM1/BNIP3L↑→线粒体自噬↑	增强自噬、减少 ROS
ARMD/其他视网膜退行性病变	NF-κB↓	抗炎
	MAPK(p38/JNK/ERK)↓	抗炎、减轻应激反应
	CREB↓	抗炎
	Nrf2/HO-1↑(Keap1 受抑)	抗氧化、保护 RPE
	AKT/GSK-3β↑	抗氧化、细胞存活↑
	Smad2/3↓	抗纤维化
	YAP↓	抑制 EMT/纤维化
	HIF-1 调控	抑制血管生成
	补体通路调控	减轻补体介导损伤
眼部肿瘤(脉络膜/葡萄膜黑色素瘤)	VEGF↓	抗血管生成、减少渗漏
	MMP-2/9↓	抑制迁移与侵袭
	FAK↓	抑制黏附/迁移信号
	Bax↑、Bcl-2↓	促凋亡
	PI3K-Akt 调控	抑制增殖

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