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植物雌激素改善结肠炎的研究进展

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摘　要

溃疡性结肠炎(Ulcerative Colitis, UC)是一种反复发作的慢性炎症性肠病，性别差异在UC的流行病学、症状表现以及治疗反应中起着重要作用。女性的激素水平波动，特别是妊娠期和月经周期等生理变化，在一定程度上改善该疾病的活动性。男性与女性的UC发病率无明显差异，但男性的疾病活动性和严重程度更高。植物雌激素是具有雌激素特性的小分子化合物，与人体雌激素受体亲和力高，在治疗乳腺癌、骨质疏松症、动脉粥样硬化、神经退行性疾病和自身免疫性疾病等疾病呈现良好的前景。植物雌激素具有抗结肠炎的效应，在抑制炎症反应、调节免疫应答、保护肠道屏障和维持肠道菌群健康等方面发挥重要作用。本文主要阐述植物雌激素的作用与机制，以及从炎症、免疫、肠道屏障和菌群的角度对植物雌激素改善实验性结肠炎的作用机制进行归纳总结，为该领域的研究提供参考。

关键词

植物雌激素，炎症，免疫，肠道屏障，肠道菌群

The Research Progress of Phytoestrogens in Improving Colitis

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Abstract

Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease, and gender differences play a significant role in the epidemiology, clinical manifestation, and therapeutic response of UC. Fluctuations in estrogen levels in females, particularly during pregnancy and the menstrual cycle,

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can partially improve the disease activity. The incidence of UC is similar between males and females; however, males tend to have more severe disease activity and greater severity. Phytoestrogens are small molecules with estrogen-like properties that exhibit a high affinity for human estrogen receptors. They show promising potential in the treatment of various diseases, such as breast cancer, osteoporosis, atherosclerosis, neurodegenerative diseases, and autoimmune diseases. Phytoestrogens have demonstrated anti-colitis effects, playing an important role in inhibiting inflammatory responses, regulating immune responses, protecting the intestinal barrier, and maintaining gut microbiota health. This paper primarily discusses the actions and mechanisms of phytoestrogens, summarizing their mechanisms in improving experimental colitis from the perspectives of inflammation, immunity, intestinal barrier, and microbiota, thus providing a reference for further research in this field.

Keywords

Phytoestrogens, Inflammation, Immunity, Gut Barrier, Gut Microbiota

1. 引言

溃疡性结肠炎(Ulcerative Colitis, UC)是一种影响结肠黏膜的慢性疾病，通常以腹泻和便血为特征，其严重程度分为轻度、中度和重度。随着生活方式的改变，我国 UC 的患病率和发病率逐年上升，且发病年龄趋于年轻化[1] [2]。UC 的主要临床表现为体重减轻、腹痛、血性腹泻等，严重影响患者的生活质量[3]。UC 的病因与免疫系统异常、环境因素和遗传易感性有关，而这些因素导致人体肠道免疫失调和肠道菌群紊乱，引发持续的肠道炎症[4]-[6]。目前，UC 的研究集中在炎症、免疫、肠道屏障和菌群，而抗炎是治疗 UC 的首要方式[7]。UC 的活动期(如腹泻和腹痛)会限制患者的日常活动和社会参与。此外，长期的治疗和潜在的并发症(如结肠癌风险增加)会给患者带来心理和经济负担[8]。

UC 的性别差异在流行病学、疾病表现、病程和并发症、依从性和精神疾病等方面都有所不同。根据流行病学调查，男性与女性的 UC 发病率无明显差异，但男性的疾病活动性和严重程度更高[9] [10]。人体的性激素在炎症和自身免疫性疾病中起着重要作用，如雌激素具有调节血管生成、抗氧化、抑制炎症反应、细胞增殖等多种生物功能[11] [12]。植物雌激素最初是 19 世纪末在植物中发现的具有雌激素特性的小分子化合物，与人体雌激素受体亲和力高[13]。已知植物雌激素存在于人类通常食用的水果、蔬菜、全谷物和药用植物，能治疗乳腺癌、骨质疏松症、动脉粥样硬化、神经退行性疾病和自身免疫性疾病等疾病[11] [14]。有研究表明植物雌激素具有抗结肠炎的效应，本文主要对植物雌激素改善实验性结肠炎的作用机制进行归纳总结，为该领域的研究提供参考。

2. 植物雌激素的作用与机制

植物雌激素是指来源于植物的外源性雌激素，并非由内分泌系统产生，而是食用植物或加工食品摄入。它在结构和功能上与哺乳动物雌激素相似，已被证明对人类有各种健康益处[15]。植物雌激素对人体雌激素调节起到双重作用，当人体处于低雌激素状态时，它与受体结合发挥雌激素作用；当处于高雌激素状态时，它阻止体内雌激素分子与受体结合，起到抗雌激素的作用，故植物雌激素被认为是“选择性雌激素受体调节剂”[15] [16]。

雌激素受体有两种经典亚型雌激素受体 α (ERα)和雌激素受体 β (ERβ)，它们结构高度相似但组织分布不同，ERα 主要分布在乳腺、子宫、卵巢和骨骼等组织，对生殖系统发育、骨骼硬度、心血管保护有重要作用；ERβ 主要分布在大脑、前列腺、肺和结肠等组织中，对神经保护、免疫调节、抑制肿瘤生长有重要作用[17]。ERα 和 ERβ 属于核受体，在细胞核内发挥转录调控功能。当雌激素与其受体结合后，受体会发生构象变化，形成二聚体，并迁移至细胞核内。在细胞核中，雌激素受体与特定的 DNA 序列(称为雌激素反应元件)结合，调控目标基因的转录[18] [19]。G 蛋白偶联雌激素受体(G protein-Coupled Estrogen Receptor, GPER)是一种新型的雌激素膜受体，与经典的核雌激素受体不同，GPER 主要位于细胞膜上，通过非基因组信号途径介导雌激素的效应[20]。GPER 参与细胞增殖、凋亡以及骨代谢等多种生理和病理过程，并且与癌症、自身免疫性疾病等疾病密切相关[21]。

3. 植物雌激素对结肠炎的改善作用

植物雌激素根据化学结构不同可分为黄酮类、异黄酮类、木脂素类和二苯乙烯类等，主要存在于植物的根、茎、叶和种子[22]。现代药理研究发现，诸多中药、蔬菜、水果具有植物雌激素样作用，并且具有抗结肠炎效应。

3.1. 植物雌激素抑制炎症改善实验性结肠炎

UC 的主要特征是肠道黏膜的持续炎症，炎症是导致结肠炎症状和并发症的主要原因，抑制炎症可以减少肠道黏膜肿胀和出血，从而减轻腹痛、腹泻、便秘等不适症状[23]。抗炎是 UC 治疗的主要策略，常用的抗炎药物包括 5-氨基水杨酸、生物制剂(如抗 TNF-α 药物)和靶向炎症通路的小分子药物(如 JAK 抑制剂)等。抑制炎症是治疗结肠炎的关键，针对炎症和炎症过程中涉及的关键分子或信号通路的治疗剂可以有效预防和治疗 UC [24]。

毛蕊异黄酮(Calycosin)是从黄芪中提取的天然植物雌激素，属于异黄酮类化合物。毛蕊异黄酮与 ERα 受体结合，促进乳腺细胞增殖和子宫发育等，其与 ERβ 受体结合后，主要发挥抗炎和抗氧化等作用[25]。毛蕊异黄酮(25, 50 mg/kg)显示良好的抗结肠炎效应，其可能的机制是显著下调结肠组织 NF-κB 和 JNK 的磷酸化，从而抑制炎症因子的 mRNA 表达，减少肠道的氧化应激[26]。

染料木素(Genistein)是一种存在于多种植物中的天然异黄酮类化合物，在豆科植物如金雀花和广豆中含量丰富。它具有多种生物活性，包括雌激素样作用、抗氧化、诱导细胞凋亡等[27]。染料木素的纳米颗粒(GEN-NP2)抗结肠炎的效应显著强于染料木素，并能靶向递送至结肠组织。GEN-NP2 显著降低结肠组织中 H_2O_2、丙二醛(MDA)、TNF-α 和 IL-1β 的水平，显著缓解肠道氧化应激和炎症反应。体外研究显示，GEN-NP2 上调 HT-29 细胞 LC3II/LC3I 的比例，抑制 ASC 和 Caspase-1 蛋白的表达，提示抑制炎症的机制与增强结肠上皮细胞自噬和抑制炎症小体活化相关[28]。

甘草素(Liquiritigenin)是一种对 ERβ 高度选择性的配体，具有抗溃疡、抗炎等药理效应[29]。在 TNBS 诱导的小鼠结肠炎模型，甘草素能增加小鼠体重，抑制结肠缩短，改善结肠组织病变，其机制可能与抑制结肠组织 IKKβ、p65 和 IκB-α 磷酸化，下调促炎细胞因子表达相关[30]。

柚皮苷(Naringin)是天然的类黄酮化合物，主要存在于柑橘类水果(如柚子、橙子等)的果皮和果肉中。有研究表明柚皮苷具有雌激素样的作用，它激活 ERα 增强骨损伤小鼠的骨愈合率和硬度[31]。柚皮苷对 DSS 诱导小鼠结肠炎具有保护作用，其可能的机制是激活结肠上皮细胞 PPARγ，抑制 NF-κB 和炎症小体活化[32]。另一研究表明，枳实的主要成分柚皮苷抑制 DSS 诱导小鼠结肠炎中活性氧(ROS)介导的结肠上皮细胞坏死性死亡，缓解结肠炎小鼠的焦虑和抑郁行为，抑制海马体的神经炎症[33]。

丹参酮(Tanshinone)是从丹参中提取的一种主要活性成分，属于萜类化合物。丹参酮具有雌激素样作

用，能够缓解更年期的症状、治疗心血管疾病和抑制乳腺癌生长等[34]。在 DSS 诱导的小鼠结肠炎模型，丹参酮显示良好的抗结肠炎效应，其可能机制是丹参酮直接结合 RIPK2，抑制 RIPK2 磷酸化，遏制 NF-κB 和 MAPK 信号通路，RIPK2 的 KD 结构域内 LEU153 和 VAL32 是丹参酮结合的关键氨基酸残基[35]。

3.2. 植物雌激素调节免疫应答改善实验性结肠炎

肠道是人体最大的免疫器官之一，其中包含大量的免疫细胞和微生物群。正常情况下，免疫系统能够识别并清除病原体，同时维持肠道对微生物和食物的耐受性。然而，在结肠炎患者，这种平衡被打破，导致免疫系统对肠道组织产生过度反应，引发慢性炎症。在结肠炎状态下，Th1 和 Th17 细胞被异常激活，这些细胞可产生炎症介质，如 IFN-γ 和 IL-17，导致肠道黏膜的炎症和损伤[36] [37]。巨噬细胞在结肠炎的病程中具有双重作用，巨噬细胞功能失调可能导致炎症的过度激活或抑制不足，从而加剧疾病进展。

牛蒡子苷元(Arctigenin)属于木脂素类化合物，能够选择性激活 ERβ，具有植物雌激素样作用。牛蒡子苷元在改善妇科疾病(宫颈癌和卵巢癌)中展现出多方面的潜力，包括抑制肿瘤生长和转移、促进癌细胞凋亡以及低细胞毒性[38]。牛蒡子苷元(25, 50 mg/kg)在抗结肠炎显示良好的效应，主要表现为抑制结肠缩短，增加小鼠体重和降低 MPO 的活力，其可能的机制与干预 ERβ-raptor/m-TOR 复合物形成、抑制 mTORC1 激活和 Th1/Th17 细胞应答有关[39]。

薯蓣皂苷(Diosgenin)是一种具有植物雌激素样作用的天然化合物，主要来源于薯蓣类植物。它在调节雌激素水平、缓解更年期症状、提高女性生育等方面具有潜力[40]。薯蓣皂苷能调节巨噬细胞向 M1 或向 M2 极化，恢复肠道免疫平衡，发挥抗结肠炎作用。其可能的机制是抑制 mTORC1/HIF-1α 信号通路，阻遏 M1 型巨噬细胞极化，并且激活 mTORC2/PPAR-γ 信号通路，促进 M2 型巨噬细胞极化[41]。

淫羊藿苷(Icariin)是从淫羊藿中提取的主要活性成分之一，属于黄酮类化合物。淫羊藿苷可以升高体内雌激素水平，尤其在更年期女性和一些激素水平低下的人群。淫羊藿传统上被用作强肾补阳的草药，有助于改善性功能和治疗骨质疏松[42]。淫羊藿对 DSS 诱导小鼠结肠炎具有保护作用，下调结肠组织 STAT1 和 STAT3 的磷酸化水平，抑制 Th1 和 Th17 细胞分化，减轻肠道免疫应答[43]。

五味子素(Schisandrin)属于木脂素类化合物，是五味子中最主要的活性成分之一。五味子素能与体内的 ERα 结合，发挥类似雌激素样效应[44]。五味子素改善慢性小鼠结肠炎、急性小鼠结肠炎和 CD4+细胞高表达小鼠诱导的结肠炎，其可能的机制是遏制 STAT3 信号，抑制 Th17 细胞分化，减少 IL-17 的分泌[45]。

3.3. 植物雌激素保护肠道屏障改善实验性结肠炎

肠道屏障由机械屏障(如紧密连接蛋白)、黏液屏障(由杯状细胞分泌的黏液)和免疫屏障组成，其主要功能是防止有害物质(如细菌、毒素和未消化的食物颗粒)进入血液循环，同时允许营养物质和水分通过。其还可以限制肠道抗原的暴露，减少免疫系统的过度激活，从而降低自身免疫反应的风险。当肠道屏障受损时，会导致“肠漏”现象，细菌抗原易位增加，进而引发肠道黏膜炎症[46] [47]。

葛根素(Puerarin)是一种从葛根中提取的主要单体成分之一，属于异黄酮类植物雌激素，具有抗炎、抗氧化、抗凋亡和抗肿瘤等药理活性[48]。在 DSS 诱导小鼠结肠炎模型，结肠黏液厚度显著降低，隐窝和黏液层中 Muc2 蛋白表达减少。葛根素显著促进杯状细胞分化，上调 Muc2 和 Muc4 表达水平，从而改善黏液屏障功能。其尚能促进紧密连接蛋白 Claudin-1 和 ZO-1 表达，保护肠道屏障功能[49]。

白藜芦醇(Resveratrol)广泛存在于葡萄、花生和一些浆果中，是一种多酚二苯乙烯化合物，在结构上与人体内雌激素相似，已被归类为植物雌激素[50]。白藜芦醇具有改善结肠炎的作用，能上调结肠组织 LC3II/LC3I 的比例和 Beclin-1 蛋白表达水平，并且促进紧密连接蛋白 ZO-1 和 Occludin 的表达，可能机

制与增强肠道结肠上皮细胞自噬，恢复肠黏膜屏障损伤有关[51]。

3.4. 植物雌激素回调肠道菌群失衡改善实验性结肠炎

肠道菌群失衡，是指肠道内微生物的种类和数量发生改变，导致有益菌减少，有害菌增多。有害菌的增多可以导致炎症介质的产生增加，如 TNF-α、IL-1 和 IL-6，这些促炎细胞因子可以加剧肠道黏膜的炎症反应[52]。肠道菌群在结肠炎中具有重要作用，其组成和功能可以影响肠道的生理和病理状态。临床研究表明补充益生菌，可以改善 UC 的症状[53]。

山奈酚(Kaempferol)是一种植物来源的异黄酮类化合物，主要来源于葡萄、西兰花和黄色水果。山奈酚在抗癌、抗炎以及调节雌激素相关疾病(如三阴性乳腺癌、更年期症状等)方面展现出一定的潜力[54]。在 DSS 诱导小鼠结肠炎模型，有益菌(拟杆菌门和厚壁菌门)的丰度显著降低，而致病菌(变形杆菌门、γ-变形杆菌属和肠杆菌科)的丰度显著增加。山奈酚显著逆转结肠炎小鼠中有益菌和致病菌的失衡，保护肠道菌群的健康[55]。

4. 结语

植物雌激素的药理作用广泛，其临床疗效包括保护神经系统、治疗心血管疾病、抗骨质疏松、抗癌、辅助治疗代谢综合征等[56] [57]。近年来的研究表明，植物雌激素在改善结肠炎症状展现积极的潜力，在抑制炎症反应、调节免疫应答、保护肠道屏障和维持肠道菌群健康等方面发挥重要作用。尽管临床前研究结果令人鼓舞，但植物雌激素在结肠炎治疗中的临床研究仍处于初步阶段。大豆异黄酮和白藜芦醇等植物雌激素能够改善 UC 患者的症状和生活质量，并且没有明显的副作用，值得深入研究[58]。未来不仅需要开展临床试验评估不同植物雌激素的疗效和安全性，还需进一步阐明植物雌激素激活受体和其他信号通路发挥作用的分子机制，为结肠炎患者提供更完善的治疗方案。

参考文献

[1] Bruner, L.P., White, A.M. and Proksell, S. (2023) Inflammatory Bowel Disease. *Primary Care*: *Clinics in Office Practice*, **50**, 411-427. https://doi.org/10.1016/j.pop.2023.03.009

[2] Kaplan, G.G. (2015) The Global Burden of IBD: From 2015 to 2025. *Nature Reviews Gastroenterology & Hepatology*, **12**, 720-727. https://doi.org/10.1038/nrgastro.2015.150

[3] Kobayashi, T., Siegmund, B., Le Berre, C., Wei, S.C., Ferrante, M., Shen, B., *et al*. (2020) Ulcerative Colitis. *Nature Reviews Disease Primers*, **6**, Article No. 74. https://doi.org/10.1038/s41572-020-0205-x

[4] Singh, N. and Bernstein, C.N. (2022) Environmental Risk Factors for Inflammatory Bowel Disease. *United European Gastroenterology Journal*, **10**, 1047-1053. https://doi.org/10.1002/ueg2.12319

[5] Du, L. and Ha, C. (2020) Epidemiology and Pathogenesis of Ulcerative Colitis. *Gastroenterology Clinics of North America*, **49**, 643-654. https://doi.org/10.1016/j.gtc.2020.07.005

[6] Guo, M. and Wang, X. (2023) Pathological Mechanism and Targeted Drugs of Ulcerative Colitis: A Review. *Medicine*, **102**, e35020. https://doi.org/10.1097/md.0000000000035020

[7] Liang, Y., Li, Y., Lee, C., Yu, Z., Chen, C. and Liang, C. (2024) Ulcerative Colitis: Molecular Insights and Intervention Therapy. *Molecular Biomedicine*, **5**, Article No. 42. https://doi.org/10.1186/s43556-024-00207-w

[8] Ge, L., Liu, S., Li, S., Yang, J., Hu, G., Xu, C., *et al*. (2022) Psychological Stress in Inflammatory Bowel Disease: Psychoneuroimmunological Insights into Bidirectional Gut-Brain Communications. *Frontiers in Immunology*, **13**, Article ID: 1016578. https://doi.org/10.3389/fimmu.2022.1016578

[9] Lungaro, L., Costanzini, A., Manza, F., Barbalinardo, M., Gentili, D., Guarino, M., *et al*. (2023) Impact of Female Gender in Inflammatory Bowel Diseases: A Narrative Review. *Journal of Personalized Medicine*, **13**, Article No. 165. https://doi.org/10.3390/jpm13020165

[10] Rustgi, S.D., Kayal, M. and Shah, S.C. (2020) Sex-Based Differences in Inflammatory Bowel Diseases: A Review. *Therapeutic Advances in Gastroenterology*, **13**, 1-11. https://doi.org/10.1177/1756284820915043

[11] Chavda, V.P., Chaudhari, A.Z., Balar, P.C., Gholap, A. and Vora, L.K. (2024) Phytoestrogens: Chemistry, Potential

Health Benefits, and Their Medicinal Importance. *Phytotherapy Research*, **38**, 3060-3079. https://doi.org/10.1002/ptr.8196

[12] Sirotkin, A.V. and Harrath, A.H. (2014) Phytoestrogens and Their Effects. *European Journal of Pharmacology*, **741**, 230-236. https://doi.org/10.1016/j.ejphar.2014.07.057

[13] Canivenc-Lavier, M. and Bennetau-Pelissero, C. (2023) Phytoestrogens and Health Effects. *Nutrients*, **15**, Article No. 317. https://doi.org/10.3390/nu15020317

[14] Dixon, R.A. (2004) Phytoestrogens. *Annual Review of Plant Biology*, **55**, 225-261. https://doi.org/10.1146/annurev.arplant.55.031903.141729

[15] Patra, S., Gorai, S., Pal, S., Ghosh, K., Pradhan, S. and Chakrabarti, S. (2023) A Review on Phytoestrogens: Current Status and Future Direction. *Phytotherapy Research*, **37**, 3097-3120. https://doi.org/10.1002/ptr.7861

[16] Domínguez-López, I., Yago-Aragón, M., Salas-Huetos, A., Tresserra-Rimbau, A. and Hurtado-Barroso, S. (2020) Effects of Dietary Phytoestrogens on Hormones throughout a Human Lifespan: A Review. *Nutrients*, **12**, Article No. 2456. https://doi.org/10.3390/nu12082456

[17] Garcia-Villatoro, E.L. and Allred, C.D. (2021) Estrogen Receptor Actions in Colitis. *Essays in Biochemistry*, **65**, 1003-1013. https://doi.org/10.1042/ebc20210010

[18] Arao, Y. and Korach, K.S. (2021) The Physiological Role of Estrogen Receptor Functional Domains. *Essays in Biochemistry*, **65**, 867-875. https://doi.org/10.1042/ebc20200167

[19] Jia, M., Dahlman-Wright, K. and Gustafsson, J. (2015) Estrogen Receptor Alpha and Beta in Health and Disease. *Best Practice & Research Clinical Endocrinology & Metabolism*, **29**, 557-568. https://doi.org/10.1016/j.beem.2015.04.008

[20] Arterburn, J.B. and Prossnitz, E.R. (2023) G Protein-Coupled Estrogen Receptor GPER: Molecular Pharmacology and Therapeutic Applications. *Annual Review of Pharmacology and Toxicology*, **63**, 295-320. https://doi.org/10.1146/annurev-pharmtox-031122-121944

[21] Prossnitz, E.R. and Barton, M. (2011) The G-Protein-Coupled Estrogen Receptor GPER in Health and Disease. *Nature Reviews Endocrinology*, **7**, 715-726. https://doi.org/10.1038/nrendo.2011.122

[22] Kiyama, R. (2017) Estrogenic Potentials of Traditional Chinese Medicine. *The American Journal of Chinese Medicine*, **45**, 1365-1399. https://doi.org/10.1142/s0192415x17500756

[23] Wang, T., Huang, Y., Jiang, P., Yuan, X., Long, Q., Yan, X., *et al*. (2025) Research Progress on Anti-Inflammatory Drugs for Preventing Colitis-Associated Colorectal Cancer. *International Immunopharmacology*, **144**, Article ID: 113583. https://doi.org/10.1016/j.intimp.2024.113583

[24] Honap, S., Jairath, V., Sands, B.E., Dulai, P.S., Danese, S. and Peyrin-Biroulet, L. (2024) Acute Severe Ulcerative Colitis Trials: The Past, the Present and the Future. *Gut*, **73**, 1763-1773. https://doi.org/10.1136/gutjnl-2024-332489

[25] Deng, M., Chen, H., Long, J., Song, J., Xie, L. and Li, X. (2020) Calycosin: A Review of Its Pharmacological Effects and Application Prospects. *Expert Review of Anti-infective Therapy*, **19**, 911-925. https://doi.org/10.1080/14787210.2021.1863145

[26] Chao, L., Zheng, P., Xia, L., *et al*. (2017) Calycosin Attenuates Dextran Sulfate Sodium-Induced Experimental Colitis. *Iranian Journal of Basic Medical Sciences*, **20**, 1056-1062.

[27] Yu, L., Rios, E., Castro, L., Liu, J., Yan, Y. and Dixon, D. (2021) Genistein: Dual Role in Women's Health. *Nutrients*, **13**, Article No. 3048. https://doi.org/10.3390/nu13093048

[28] Fan, W., Zhang, S., Wu, Y., Lu, T., Liu, J., Cao, X., *et al*. (2021) Genistein-Derived Ros-Responsive Nanoparticles Relieve Colitis by Regulating Mucosal Homeostasis. *ACS Applied Materials & Interfaces*, **13**, 40249-40266. https://doi.org/10.1021/acsami.1c09215

[29] Liu, J., Viswanadhapalli, S., Garcia, L., Zhou, M., Nair, B.C., Kost, E., *et al*. (2017) Therapeutic Utility of Natural Estrogen Receptor Beta Agonists on Ovarian Cancer. *Oncotarget*, **8**, 50002-50014. https://doi.org/10.18632/oncotarget.18442

[30] Min, J.K., Lee, C.H., Jang, S., Park, J., Lim, S., Kim, D., *et al*. (2015) Amelioration of Trinitrobenzene Sulfonic Acid-induced Colitis in Mice by Liquiritigenin. *Journal of Gastroenterology and Hepatology*, **30**, 858-865. https://doi.org/10.1111/jgh.12812

[31] Zhao, Q., Feng, J., Liu, F., Liang, Q., Xie, M., Dong, J., *et al*. (2024) Rhizoma Drynariae-Derived Nanovesicles Reverse Osteoporosis by Potentiating Osteogenic Differentiation of Human Bone Marrow Mesenchymal Stem Cells via Targeting Erα Signaling. *Acta Pharmaceutica Sinica B*, **14**, 2210-2227. https://doi.org/10.1016/j.apsb.2024.02.005

[32] Cao, H., Liu, J., Shen, P., Cai, J., Han, Y., Zhu, K., *et al*. (2018) Protective Effect of Naringin on DSS-Induced Ulcerative Colitis in Mice. *Journal of Agricultural and Food Chemistry*, **66**, 13133-13140. https://doi.org/10.1021/acs.jafc.8b03942

[33] Lee, K., Kim, M., Yuk, H.J., Jo, Y., Kim, H.J., Kim, J., *et al*. (2024) Alleviating Depressive-Like Behavior in DSS-Induced Colitis Mice: Exploring Naringin and Poncirin from Poncirus Trifoliata Extracts. *Biomedicine & Pharmacotherapy*,

175, Article ID: 116770. https://doi.org/10.1016/j.biopha.2024.116770

[34] Zhang, Y., Pan, H., Yu, C., Liu, R., Xing, B., Jia, B., *et al*. (2023) Phytoestrogen-Derived Multifunctional Ligands for Targeted Therapy of Breast Cancer. *Asian Journal of Pharmaceutical Sciences*, **18**, Article ID: 100827. https://doi.org/10.1016/j.ajps.2023.100827

[35] Hu, C., Chen, Y., Jin, T., Wang, Z., Jin, B., Liao, J., *et al*. (2024) A Derivative of Tanshinone IIA and Salviadione, 15a, Inhibits Inflammation and Alleviates DSS-Induced Colitis in Mice by Direct Binding and Inhibition of RIPK2. *Acta Pharmacologica Sinica*, **46**, 672-686. https://doi.org/10.1038/s41401-024-01399-1

[36] Saez, A., Herrero-Fernandez, B., Gomez-Bris, R., Sánchez-Martinez, H. and Gonzalez-Granado, J.M. (2023) Pathophysiology of Inflammatory Bowel Disease: Innate Immune System. *International Journal of Molecular Sciences*, **24**, Article No. 1526. https://doi.org/10.3390/ijms24021526

[37] Giesler, S., Riemer, R., Lowinus, T. and Zeiser, R. (2025) Immune-Mediated Colitis after Immune Checkpoint Inhibitor Therapy. *Trends in Molecular Medicine*, **31**, 265-280. https://doi.org/10.1016/j.molmed.2024.09.009

[38] Liao, D., Liu, Y., Li, C., He, B., Zhou, G., Cui, Y., *et al*. (2023) Arctigenin Hinders the Invasion and Metastasis of Cervical Cancer Cells via the Fak/paxillin Pathway. *Heliyon*, **9**, e16683. https://doi.org/10.1016/j.heliyon.2023.e16683

[39] Wu, X., Dou, Y., Yang, Y., Bian, D., Luo, J., Tong, B., *et al*. (2015) Arctigenin Exerts Anti-Colitis Efficacy through Inhibiting the Differentiation of Th1 and Th17 Cells via an Mtorc1-Dependent Pathway. *Biochemical Pharmacology*, **96**, 323-336. https://doi.org/10.1016/j.bcp.2015.06.008

[40] Khushboo, M., Sanjeev, S., Murthy, M.K., Sunitadevi, M., Dinata, R., Bhanushree, B., *et al*. (2023) Dietary Phytoestrogen Diosgenin Interrupts Metabolism, Physiology, and Reproduction of Swiss Albino Mice: Possible Mode of Action as an Emerging Environmental Contaminant, Endocrine Disruptor and Reproductive Toxicant. *Food and Chemical Toxicology*, **176**, Article ID: 113798. https://doi.org/10.1016/j.fct.2023.113798

[41] Wu, M., Wang, Q., Huang, B., Mai, C., Wang, C., Wang, T., *et al*. (2021) Dioscin Ameliorates Murine Ulcerative Colitis by Regulating Macrophage Polarization. *Pharmacological Research*, **172**, Article ID: 105796. https://doi.org/10.1016/j.phrs.2021.105796

[42] Wong, K., Kong, T., Poon, C.C., Yu, W., Zhou, L. and Wong, M. (2023) Icariin, a Phytoestrogen, Exerts Rapid Estrogenic Actions through Crosstalk of Estrogen Receptors in Osteoblasts. *Phytotherapy Research*, **37**, 4706-4721. https://doi.org/10.1002/ptr.7939

[43] Tao, F., Qian, C., Guo, W., Luo, Q., Xu, Q. and Sun, Y. (2013) Inhibition of Th1/Th17 Responses via Suppression of STAT1 and STAT3 Activation Contributes to the Amelioration of Murine Experimental Colitis by a Natural Flavonoid Glucoside Icariin. *Biochemical Pharmacology*, **85**, 798-807. https://doi.org/10.1016/j.bcp.2012.12.002

[44] Lee, D., Kim, Y., Chin, Y. and Kang, K.S. (2021) Schisandrol a Exhibits Estrogenic Activity via Estrogen Receptor A-Dependent Signaling Pathway in Estrogen Receptor-Positive Breast Cancer Cells. *Pharmaceutics*, **13**, Article No. 1082. https://doi.org/10.3390/pharmaceutics13071082

[45] Ma, Z., Xu, G., Shen, Y., Hu, S., Lin, X., Zhou, J., *et al*. (2021) Schisandrin B-Mediated Th17 Cell Differentiation Attenuates Bowel Inflammation. *Pharmacological Research*, **166**, Article ID: 105459. https://doi.org/10.1016/j.phrs.2021.105459

[46] Iacucci, M., Santacroce, G., Majumder, S., Morael, J., Zammarchi, I., Maeda, Y., *et al*. (2024) Opening the Doors of Precision Medicine: Novel Tools to Assess Intestinal Barrier in Inflammatory Bowel Disease and Colitis-Associated Neoplasia. *Gut*, **73**, 1749-1762. https://doi.org/10.1136/gutjnl-2023-331579

[47] Qiao, Y., He, C., Xia, Y., Ocansey, D.K.W. and Mao, F. (2025) Intestinal Mucus Barrier: A Potential Therapeutic Target for IBD. *Autoimmunity Reviews*, **24**, Article ID: 103717. https://doi.org/10.1016/j.autrev.2024.103717

[48] Yang, Y., Chen, D., Li, Y., Zou, J., Han, R., Li, H., *et al*. (2022) Effect of Puerarin on Osteogenic Differentiation *in Vitro* and on New Bone Formation *in Vivo*. *Drug Design, Development and Therapy*, **16**, 2885-2900. https://doi.org/10.2147/dddt.s379794

[49] Wu, Y., Li, Y., Ruan, Z., Li, J., Zhang, L., Lu, H., *et al*. (2020) Puerarin Rebuilding the Mucus Layer and Regulating Mucin-Utilizing Bacteria to Relieve Ulcerative Colitis. *Journal of Agricultural and Food Chemistry*, **68**, 11402-11411. https://doi.org/10.1021/acs.jafc.0c04119

[50] Novakovic, R., Rajkovic, J., Gostimirovic, M., Gojkovic-Bukarica, L. and Radunovic, N. (2022) Resveratrol and Reproductive Health. *Life*, **12**, Article No. 294. https://doi.org/10.3390/life12020294

[51] Pan, H., Zhou, X., Ma, Y., Pan, W., Zhao, F., Yu, M., *et al*. (2020) Resveratrol Alleviates Intestinal Mucosal Barrier Dysfunction in Dextran Sulfate Sodium-Induced Colitis Mice by Enhancing Autophagy. *World Journal of Gastroenterology*, **26**, 4945-4959. https://doi.org/10.3748/wjg.v26.i33.4945

[52] Wang, X., Peng, J., Cai, P., Xia, Y., Yi, C., Shang, A., *et al*. (2024) The Emerging Role of the Gut Microbiota and Its Application in Inflammatory Bowel Disease. *Biomedicine & Pharmacotherapy*, **179**, Article ID: 117302. https://doi.org/10.1016/j.biopha.2024.117302

[53] Bethlehem, L., Estevinho, M.M., Grinspan, A., Magro, F., Faith, J.J. and Colombel, J. (2024) Microbiota Therapeutics for Inflammatory Bowel Disease: The Way Forward. *The Lancet Gastroenterology & Hepatology*, **9**, 476-486. https://doi.org/10.1016/s2468-1253(23)00441-7

[54] Oh, S.M., Kim, Y.P. and Chung, K.H. (2006) Biphasic Effects of Kaempferol on the Estrogenicity in Human Breast Cancer Cells. *Archives of Pharmacal Research*, **29**, 354-362. https://doi.org/10.1007/bf02968584

[55] Qu, Y., Li, X., Xu, F., Zhao, S., Wu, X., Wang, Y., *et al*. (2021) Kaempferol Alleviates Murine Experimental Colitis by Restoring Gut Microbiota and Inhibiting the LPS-TLR4-NF-*κ*B Axis. *Frontiers in Immunology*, **12**, Article ID: 679897. https://doi.org/10.3389/fimmu.2021.679897

[56] Al-Shami, A.S., Essawy, A.E. and Elkader, H.A.E.A. (2023) Molecular Mechanisms Underlying the Potential Neuroprotective Effects of *Trifolium pratense* and Its Phytoestrogen-Isoflavones in Neurodegenerative Disorders. *Phytotherapy Research*, **37**, 2693-2737. https://doi.org/10.1002/ptr.7870

[57] Ceccarelli, I., Bioletti, L., Peparini, S., Solomita, E., Ricci, C., Casini, I., *et al*. (2022) Estrogens and Phytoestrogens in Body Functions. *Neuroscience & Biobehavioral Reviews*, **132**, 648-663. https://doi.org/10.1016/j.neubiorev.2021.12.007

[58] Xue, J., Yuan, S., Meng, H., Hou, X., Li, J., Zhang, H., *et al*. (2023) The Role and Mechanism of Flavonoid Herbal Natural Products in Ulcerative Colitis. *Biomedicine & Pharmacotherapy*, **158**, Article ID: 114086. https://doi.org/10.1016/j.biopha.2022.114086