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柚皮素调控脂质代谢的信号通路与靶点

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摘 要: 脂质过度积累是危害人类及动物健康的关键因素, 会导致肥胖、非酒精性脂肪肝等一系列代谢性疾病, 在畜牧业中还会导致饲料转化效率降低、畜禽产品品质下降, 制约行业可持续发展。随着健康养殖理念的深入和抗生素限制使用的全球趋势, 开发能够有效调控脂质代谢的天然饲料添加剂日益迫切。柚皮素(Naringenin, Nar)作为一种天然黄酮类化合物, 具有抗炎、抗氧化及免疫调节功能, 在调节脂质代谢、缓解脂类代谢异常相关疾病中展现潜在活性。虽其难以被消化道直接吸收, 但可通过调节肠道菌群结构, 改善肠道屏障功能、影响短链脂肪酸等菌群代谢产物生成, 实现系统性调控。同时, 柚皮素还能直接作用于 AMPK、Nrf2/HO-1 等关键信号通路, 抑制肝脏脂质合成、诱导白色脂肪“棕色化”, 并拮抗炎症因子释放以缓解代谢紊乱。为通过营养干预精准调控人类及动物脂质代谢提供重要的理论依据, 文章系统综述了柚皮素调控脂质代谢的作用机制, 重点探讨了其通过肠道和脂肪组织间的交叉对话发挥作用的分子途径, 并对其的应用前景进行了展望。

关键词: 柚皮素; 脂肪组织; 脂质代谢; 肠道菌群

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Signaling Pathways and Targets of Naringenin in the Regulation of Lipid Metabolism

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Abstract: Excessive lipid accumulation is a critical metabolic factor endangering the health of humans and animals. It not only leads to a series of metabolic diseases such as obesity and non-alcoholic fatty liver disease but also causes issues in the livestock industry, including reduced feed conversion efficiency and decreased quality of livestock and poultry products, which restricts the sustainable development of the industry. With the in-depth advancement of healthy breeding concepts and the global trend of restricting antibiotic use, the development of strategies for natural feed additives capable of effectively regulating lipid metabolism has become increasingly urgent. Naringenin(Nar), a natural flavonoid compound, possesses anti-inflammatory, antioxidant, and immunomodulatory functions, and has demonstrated potential activity in regulating lipid metabolism and alleviating diseases associated with abnormal lipid metabolism. Although it is difficult to be directly absorbed by the digestive tract, naringenin can achieve systemic regulation by modifying the structure of the gut microbiota, improving intestinal barrier function, and influencing the production of microbial metabolites such as short-chain fatty acids. Meanwhile, naringenin can also act directly on key signaling pathways including AMPK and Nrf2/HO-1 to inhibit hepatic lipid synthesis, induce the "browning" of white adipose tissue, and counteract the release of pro-inflammatory factors, thereby alleviating metabolic disorders. In this article, the mechanisms by which naringenin regulates lipid metabolism was systematically reviewed, with a focus on exploring the molecular pathways through which it exerts its effects via crosstalk between the intestine and adipose

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tissue, also, its application prospects were also discussed, aiming to provide an important theoretical basis for the precise regulation of lipid metabolism in humans and animals through nutritional intervention.

Keywords: naringenin; adipose tissue; lipid metabolism; gut microbiota

脂质过度积累是危害人类及动物健康的核心代谢因素,不仅直接导致肥胖、非酒精性脂肪肝等一系列慢性系统疾病,也在畜牧业中造成饲料转化效率降低、畜禽产品品质下降及代谢紊乱,严重制约其可持续发展^[1]。世界卫生组织将肥胖这一全球性流行病定义为“可能损害健康的异常或过多脂肪堆积”^[2],其作为一种慢性复发性疾病,常伴随着炎症反应,且会显著增加死亡率和并发症风险^[3]。随着全球健康养殖理念的深化及抗生素在养殖业中限制使用政策的推进,开发安全、高效且能精准调控脂质代谢的天然替代方案,已成为当前医学与畜牧领域共同关注的重点与难点。

在众多天然活性物质中,柚皮素(Naringenin, Nar)作为广泛存在于柑橘类水果中的二氢黄酮类化合物,凭借其显著的抗炎、抗氧化及免疫调节功能,逐渐成为研究热点^[4]。已有研究证实,柚皮素在调节脂质代谢、缓解脂类代谢异常相关疾病方面展现出潜在活性,但早期研究多聚焦于“单器官、单通路”的作用模式,难以全面阐释其在机体多器官互作网络中的整体调控效应^[5]。值得注意的是,柚皮素作为难被上消化道吸收的多酚类化合物,其大部分需进入结肠后经肠道微生物代谢

转化,这提示肠道菌群的结构与功能变化可能是其发挥作用的关键环节。

目前,尽管已有诸多研究从不同角度揭示了柚皮素调节脂质代谢的能力,但大多数仍局限于单一通路或单一效应的观察,缺乏对其多层次、多靶点整合机制的全面梳理,特别是如何系统地阐释其直接调控作用与间接的抗氧化、抗炎效应之间的内在联系,尚待深入总结。因此,本文旨在深化对黄酮类化合物系统生物学功能的理解,为开发基于柚皮素的精准营养干预策略提供理论依据,同时推动其在畜禽绿色健康养殖中的实践应用。

1 柚皮素的特性与代谢调控概述

1.1 柚皮素的化学特性、生物活性与利用度挑战

柚皮素在化学上被称为4,5,7-三羟基黄酮,广泛存在于柑橘类植物(橙子、柑橘和葡萄柚)中,属于二氢黄酮类化合物,是柚皮苷水解掉一分子葡萄糖和鼠李糖后得到的苷元,结构式如图1所示。常温(10~30℃)储存,相对分子质量为272.25,常溶于乙醇、乙醚和苯,几乎不溶于水。

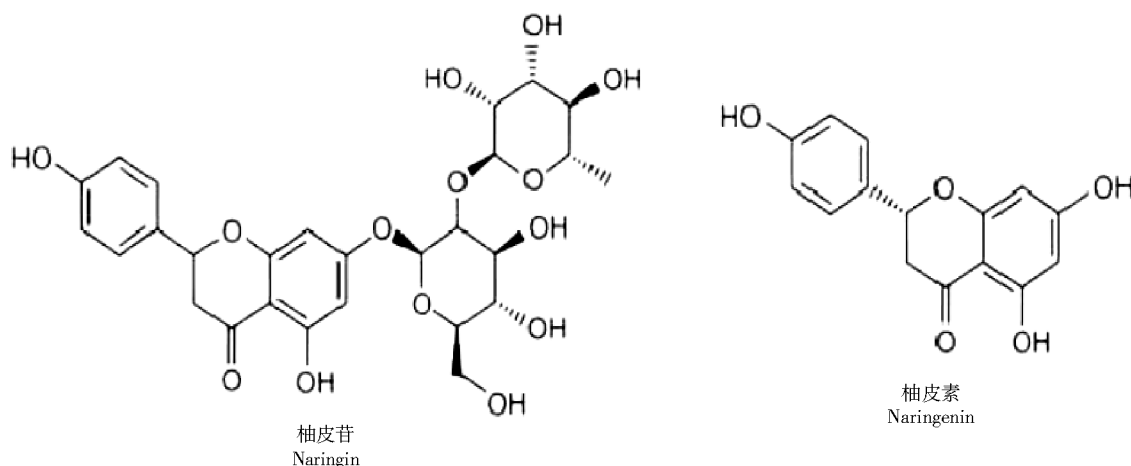


图1 柚皮苷和柚皮素的化学结构

Fig.1 Chemical structures of naringin and naringenin

柚皮素具有抗炎、抗氧化、抗肿瘤、清除活性氧(ROS)等广泛的药理活性,能够有效降低组织中多余的脂质,从而有效缓解脂类代谢异常及其

相关的慢性代谢疾病^[6]。然而,其实际应用受限于较低的生物利用度,有研究表明,柚皮素的口服生物利用度约为15%,柚皮苷经肠道菌群去糖基化

后转化为柚皮素再被吸收的口服生物利用度仅为5%~9%^[7]。该限制主要归因于其自身较差的水溶性和较高的脂溶性,导致其在胃肠道的溶出度和吸收率低下^[8]。此外,柚皮素在体内经历广泛的II相代谢反应,特别是在肠道和肝脏中迅速被葡萄糖醛酸化和硫酸化形成水溶性结合物后被快速排出体外,并受肠道菌群代谢与P-糖蛋白外排作用的影响^[9],使得原形药物进入体循环的量显著降低。目前,为克服其生物利用度低这一瓶颈,研究者们已探索多种先进的纳米递送策略,如制备纳米乳液、磷脂复合物和固体脂质纳米粒,能有效提高其在水相中的分散性和稳定性,并通过增强肠道淋巴吸收等途径绕过首过效应,从而促进其吸收^[10]。另一种有前景的策略是用天然甜味剂莱鲍迪苷A(Rebaudioside A, RA)构建一种可在水中自发组装成纳米胶囊的递送系统,以克服柚皮素水溶性差、口服生物利用度低的缺陷,同时通过抗炎和抗氧化机制缓解吡啶美辛诱导的肠道损伤^[11]。

1.2 肠道微生物群与屏障功能

胃肠道是一个复杂的生态系统,定殖着数万亿个与宿主相互作用的共生微生物^[12],统称为肠道菌群。肠道菌群包括细菌、真菌、寄生虫和病毒,其中细菌群落占相关微生物的绝大部分,并以拟杆菌门(Acteroidetes)、厚壁菌门(Firmicutes)为优势菌群,通过与宿主互作在维持代谢稳态中发挥核心作用^[13]。在健康个体中,肠道正常菌群通过特异性和非特异性免疫参与机体局部和全身性的免疫调节作用,两者间形成一个动态平衡状态^[14]。若这种稳态被打破,将导致肠道外和肠道内的疾病,例如由肠道菌群紊乱引起的炎性肠病和代谢性疾病等^[15]。据报道,肠道菌群对于维持肠道屏障功能及免疫稳态至关重要^[16]。其免疫调节作用主要体现在2个方面。一方面,菌群通过诱导分泌性免疫球蛋白(IgA)的产生,如靶向病原体的IgA1和结合共生菌的IgA2,实现对特定微生物的精准识别与清除^[17]。据报道,无菌小鼠中肠道黏膜中的分泌型免疫球蛋白A(SIgA)的浆细胞数量大大减少,但当向无菌小鼠移植如*Filamentous*、*Clostridium*或*Alcaligenes*等细菌后能诱导肠黏膜分泌成熟的IgA,以维持肠道免疫系统的平衡^[18]。另一方面,肠道菌群通过促进调节性T细胞(Treg)等免疫细胞的分化并分泌白介素-10(Interleukin 10, IL-10)等细胞因子,主动抑制炎症反应。

1.3 脂肪组织的类型与代谢调控网络

脂肪组织是调控动物全身代谢与影响胴体品质的关键器官。根据形态与功能,主要分为白色脂肪(WAT)、米色脂肪和棕色脂肪(BAT)。白色脂肪以单房大脂滴和有限的线粒体为特征,通过甘油三酯的形式储存能量,并以脂肪酸的形式释放能量,为生物体提供燃料以响应全身需求^[19]。同时作为重要的内分泌器官,白色脂肪组织分泌参与胰岛素敏感性与糖代谢调控的脂联素、瘦素、抵抗素;分泌参与脂代谢与血压调节的视黄醇结合蛋白4、血管紧张素原;分泌参与炎症与免疫反应的肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)、白介素-6(Interleukin-6, IL-6)、白介素-1 β (Interleukin-1 β , IL-1 β)和白介素-8(Interleukin-8, IL-8)^[20]。其中,瘦素的表达受到胰岛素、糖皮质激素及炎症因子的调控,其信号经JAK2-STAT3通路在下丘脑发挥厌食效应^[21]。以低分子质量(LMW)三聚体、中分子质量(MMW)六聚体和高分子质量(HMW)多聚体形式存在的脂联素,能够通过受体AdipoR1/AdipoR2激活AMPK与PPAR α 通路,促进脂肪酸氧化和葡萄糖摄取,并发挥抗炎、抗纤维化作用^[22]。相比之下,米色和棕色脂肪以其丰富的线粒体和多房脂滴为特征,通过燃烧包括脂肪酸和葡萄糖在内的底物,产生热量以响应寒冷^[23]。它们不仅能通过非颤抖性产热抵抗肥胖,还能清除血液中的甘油三酯、葡萄糖及支链氨基酸等有害代谢物,从而显著改善全身胰岛素敏感性^[24]。许多研究表明,在人源白色脂肪细胞(hADSC)及小鼠棕色脂肪中,柚皮素显著上调解偶联蛋白1(Uncoupling Protein 1, UCP1)、过氧化物酶体增殖物激活受体 γ 共激活因子-1 α/β (Peroxisome Proliferator-activated Receptor- γ Coactivator-1 α/β , PGC-1 α/β)和肉碱棕榈酰转移酶1 β (Carnitine Palmitoyltransferase 1 β , CPT1 β)表达,升高线粒体耗氧率(OCR),从而诱导棕色脂肪产热并促进白色脂肪“棕色化”^[25]。

除了上述功能差异外,脂肪组织的发育过程同样关键。其通过脂肪生成过程完成,即由中胚层间充质干细胞(MSCs)首先“定型”为具有特定分化潜能的前脂肪细胞,随后“终末分化”形成成熟的脂肪细胞,该过程受到复杂的转录与信号通路级联调控^[26]。然而,脂肪组织的过度发育会导致肥胖,进而损害胴体品质并诱发胰岛素抵抗等代

谢并发症^[27]。在肥胖状态下,WAT中由M1型巨噬细胞等分泌的促炎脂肪因子(如抵抗素、TNF- α)占主导,它们通过激活IKK β /NF- κ B等通路诱发胰岛素抵抗^[28]。值得注意的是,脂质分解与脂质合成也是脂质代谢中的核心调控机制,二者共同维持机体的能量稳态与脂质储存平衡。据报道,脂质分解由激素敏感脂肪酶(HSL)和脂肪甘油三酯脂肪酶(ATGL)主导,脂质合成则受到胰岛素-PI3K-AKT通路调控,AKT通过调控固醇调节元件结合蛋白-1c(SREBP-1c)的转录活性,上调乙酰辅酶A羧化酶(ACC)、脂肪酸合酶(FAS)等关键酶的表达^[29]。

1.4 肝脏脂质代谢

肝脏作为机体脂质代谢的核心调控器官,通过一套精密而复杂的网络维持全身脂质稳态^[30]。首先,在脂肪酸代谢方面,肝脏承担着摄取、合成与分解的动态平衡调节。具体而言,肝细胞通过CD36等特异性转运蛋白摄取循环中的游离脂肪酸,当营养过剩时,SREBP-1c通路激活可上调脂肪酸合成酶等生脂基因表达,促进脂肪酸从头合成并酯化为甘油三酯,进而储存于脂滴^[31]。而在能量需求增高时,AMPK通路被激活,通过磷酸化抑制乙酰辅酶A羧化酶,降低丙二酰辅酶A水平,从而解除对肉碱棕榈酰转移酶-1的抑制,最终驱动脂肪酸进入线粒体进行 β -氧化以供能^[32]。在胆固醇代谢方面,肝脏发挥着合成、转化与清除的核心作用。其不仅通过HMG-CoA严格控制内源性胆固醇合成,还借助低密度脂蛋白(LDL)受体有效摄取循环中的外源性胆固醇^[33]。同时,肝脏将胆固醇转化为胆汁酸并经胆道排泄,这是机体清除多余胆固醇的关键途径,该过程受到肝X受体(LXR)与法尼醇X受体等核受体通路的精密调控^[34]。最后,在脂蛋白代谢层面,肝脏负责合成、分泌与回收的全过程调控。它将内源性合成的甘油三酯和胆固醇酯与载脂蛋白(ApoB)-100组装为极低密度脂蛋白并分泌入血,从而启动内源性脂质转运^[35]。

2 柚皮素调控脂质代谢的相关机制

2.1 对脂质代谢的直接调控作用

柚皮素在LXR α 激动剂存在下表现出对LXR α 的拮抗活性,还显著下调ATP结合盒转运体A1(ATP-binding cassette sub-family A member 1,

ABCA1)、ABCG1和脂肪酸合酶(Fatty acid synthase, FAS)等脂质合成关键基因的表达。其调节脂代谢的机制涉及多条信号通路:在分子层面,柚皮素可促进AMPK与ACC磷酸化,抑制HMGCR表达,从而减少细胞内的脂质积累^[36]。在HepG2细胞及高脂饮食小鼠模型中,它通过激活AMPK,抑制其下游靶点ACC与SREBP-1c,在减少脂肪酸合成的同时促进 β -氧化,有效缓解肝细胞脂质沉积^[37]。此外,柚皮素还通过激活Nrf2/HO-1信号通路,上调超氧化物歧化酶(Superoxide Dismutase, SOD)、过氧化氢酶(Catalase, CAT)及谷胱甘肽(Glutathione, GSH)等抗氧化酶活性,并抑制MDA、TNF- α 与IL-6等炎症因子的释放,从而减轻肝脏氧化应激与炎症反应^[38]。研究还发现,肠道菌群可将柚皮苷水解为活性形式柚皮素,后者通过抑制ROS/NLRP3炎症小体,改善肝细胞脂质沉积与氧化应激,这一机制在非酒精性脂肪肝模型中得到了验证^[39]。有研究发现,柚皮苷通过减少脂肪酸摄取和从头脂肪生成以及增强脂肪酸氧化来增强肝脏的脂质代谢^[40]。另有研究指出,柚皮素可通过调节脂质消化、促进逆转胆固醇转运及上调LDL受体表达等多种途径综合调节血脂,并能够通过抑制NF- κ B信号通路,减少细胞色素C释放及Caspase-3活化,进而缓解炎症与细胞调亡。

2.2 抗炎与抗氧化作用机制

肥胖状态下的脂肪组织肥大,是驱动脂肪细胞炎症的核心因素,此炎症过程由多种机制共同调节,包括内质网应激、游离脂肪酸及自然杀伤(NK)细胞、中性粒细胞和巨噬细胞等免疫细胞的聚集^[41]。研究表明,柚皮素具有调节炎症反应的作用。在高脂饮食诱导的肥胖小鼠模型中,为期14 d的柚皮素干预可显著抑制巨噬细胞向脂肪组织浸润,并下调MCP-1和MCP-3的表达,提示其缓解脂肪组织炎症的潜力^[42]。此外,在RAW264.7巨噬细胞与前脂肪细胞共培养模型中,柚皮素(0~200 μ mol/L, 3 h)能显著降低促炎细胞因子的生成,说明其可调节脂肪细胞与巨噬细胞之间的相互作用,进而抑制脂肪组织炎症^[43]。有研究表明,炎症的发生往往伴随着氧化应激的产生。氧化应激是糖尿病与心血管疾病等慢性病的重要诱因,其本质是体内氧化/抗氧化系统失衡导致的自由基与氧化剂过度积累^[44]。柚皮素凭借其酚羟基结

构,能够直接清除活性氧(ROS)与活性氮物种(RNS),保护DNA免受氧化损伤,并有效增强多种内源性抗氧化酶的活性^[46]。研究显示,柚皮素在体内不仅直接发挥抗氧化作用,还可通过上调相关基因表达与酶活性,系统性增强机体的抗氧化防御能力。例如,有研究表明,以50 mg/kg剂量的柚皮素干预30 d,可显著提高SOD、CAT、谷胱甘肽过氧化物酶(GPx)和谷胱甘肽还原酶(GR)的活性^[47]。此外,柚皮素可与细胞膜等生物膜结构发生相互作用,改变其流动性、水合作用与通透性,从而减少自由基与脂质之间的反应,进一步强化其抗氧化效果^[48]。

除脂肪组织肥大驱动的细胞炎症外,另一条不可忽视的核心因素源自肠道屏障破坏引发的系统性低度炎症^[49]。肠道菌群也被证明在脂肪积累中发挥作用,并与肥胖的形成有关^[50]。当肠道通透性增加时,脂多糖通过激活脂肪组织中巨噬细胞表面的Toll样受体4(TLR4),启动下游髓样分化因子88(MyD88)依赖的信号转导通路,促使核因子 κ B(NF- κ B)和c-Jun氨基末端激酶(JNK)活化,进而诱导TNF- α 、IL-1 β 和IL-6等促炎细胞因子的表达与分泌^[51]。此外,菌群紊乱还会激活NLRP3炎症小体,促进Caspase-1介导的IL-1 β 成熟,从而扩大炎症反应并抑制脂肪细胞分化^[52]。有研究证实,奶牛饲喂柚皮素后,血清IL-1 β 、IL-6、丙二醛、天冬氨酸氨基转移酶(AST)、谷氨酸氨基转移酶(ALT)的含量显著降低,且能通过降低非酯化脂肪酸(NEFA)和脂多糖(LPS)水平并增加脂联素表达来减少神经酰胺的积累,从而减少脂肪组织中的炎症和氧化应激,最终改善其全身代谢状态^[53]。另外,通过网络药理学、孟德尔随机化和分子对接整合发现,柚皮素发挥抗氧化与降脂双重作用的核心节点是PPARA、AMPK、Nrf2与TNF- α ,同时进一步证实柚皮素水平升高可显著降低BMI、LDL-C、TG及氧化应激指标^[54]。

2.3 通过内分泌信号网络调节能量平衡

众所周知,较容易被消化的蛋白质在小肠中被水解成氨基酸和多肽,不容易被消化的蛋白质和多肽被大肠中含有的丰富细菌和残余蛋白酶从复杂多糖降解成单糖,并进一步发酵为短链脂肪酸(SCFAs)和气体,而SCFAs是宿主能量的主要来源,也介导了肠道微生物对宿主的影响^[55]。具体而言,乙酸盐、丙酸盐和丁酸盐等短链脂肪酸可

通过激活SCFAs受体包括G蛋白偶联受体(G protein-coupled receptor 41, GPR41)和GPR43调控脂质代谢。其中,丁酸通过激活脂肪细胞GPR43,抑制cAMP-PKA通路,降低激素敏感性脂肪酶(HSL)活性,从而抑制脂解作用^[56]。进一步地,丙酸盐和丁酸盐可通过激活GPR41和GPR43抑制脂解、促进瘦素分泌,并可能通过抑制HDAC影响炎症基因表达,增强肠道屏障完整性^[57]。此外,SCFAs能直接刺激肠嗜铬细胞分泌5-羟色胺(5-HT)和肽YY(PYY),或刺激L细胞分泌胰高血糖素样肽-1(GLP-1),这些激素不仅局部调控肠蠕动和食欲,GLP-1还能通过循环系统直接作用于脂肪组织,微弱地促进脂解和脂肪氧化^[58]。同时,GLP-1通过中枢机制抑制食欲,并直接作用于脂肪组织,通过cAMP-PKA通路增强葡萄糖摄取与脂肪酸氧化,同时减少脂解^[59]。除短链脂肪酸外,肠道微生物还可对另一类重要的宿主衍生分子—胆汁酸进行生物转化,进而系统调控宿主能量代谢^[60]。初级胆汁酸在肠道菌群酶(如胆汁盐水解酶BSH和7 α -脱羟酶)作用下转化为次级胆汁酸,后者作为重要信号分子,可分别通过激活TGR5与FXR受体调节脂代谢。其中,TGR5的激活一方面诱导肠道L细胞分泌GLP-1,进而经cAMP-PKA通路促进脂肪组织产热与脂肪酸氧化^[61]。另一方面,在脂肪细胞中通过诱导II型脱碘酶(DIO2)表达,促使甲状腺激素T4转化为活性T3,刺激产热与能量消耗^[62]。而FXR的激活则表现出组织特异性,在肝脏中通过诱导SREBP-1c表达促进脂质合成,在脂肪组织中则抑制脂解^[63]。柚皮素通过调控多种内分泌信号分子间接调节脂质代谢。有研究表明,以50、100 mg/kg剂量的柚皮素干预4周,可调节脂联素与瘦素水平并影响STAT3磷酸化及下游肥胖相关基因的转录^[64]。同时,它能有效抑制促炎因子的释放,从而缓解脂肪组织慢性炎症与胰岛素信号干扰^[65]。此外,柚皮素还通过改变胆汁酸组成,增加TGR5激动型胆汁酸比例,进而激活肠道L细胞的TGR5-cAMP信号通路,促进GLP-1分泌,间接调控脂代谢^[66]。

2.4 肠道菌群调节功能

作为难被上消化道吸收的多酚类化合物,柚皮素对肠道菌群结构具有显著的调节作用。研究表明,柚皮素干预能增加乳酸杆菌和双歧杆菌等有益菌的丰度,同时抑制脱硫弧菌属和大肠杆菌

等条件致病菌的生长。这种菌群结构的优化有助于增强肠道屏障功能,减少肠源性脂多糖(LPS)易位,进而减轻肝脏炎症并改善脂质代谢紊乱^[67]。双歧杆菌作为柚皮素富集的关键有益菌之一,其生长与柚皮苷和橙皮苷的干预呈剂量依赖性增强,这进一步强化了其在调节菌群平衡和抑制代谢炎症中的作用^[68]。在高脂饮食动物模型中,柚皮苷干预也被证实可促进丁酸球菌等有益菌的增殖,并减少弯曲杆菌等有害菌的定殖^[69]。而与天然柚皮苷相比,其酰化衍生物(A-Nar)因脂溶性增强而更易被菌群摄取代谢,显著提高丙酸、乙酸及总短链脂肪酸水平^[70]。同时柑橘类黄酮提取物呈剂量依赖性增加有益菌丰度,并通过上调牛磺胆酸、下调毒性脱氧胆酸以优化胆汁酸代谢,从而维护肠道健康^[71]。在动物试验中,日粮添加柑橘黄酮能提高奶牛后肠丁酸浓度,通过抑制 SPTLC2 和 CerS 表达阻断鞘脂从头合成,降低血浆神经酰胺含量^[72]。此外,柑橘提取物可促进代谢综合征患者粪便中乙酸、丁酸与戊酸的生成,并显著改善其全身胰岛素敏感性^[73]。同时有研究表明,柑橘黄酮处理能促进肠道内乳酸杆菌等有益菌增殖,并抑制大肠杆菌等致病菌的定殖^[74]。在日粮中添加 1.5 g/kg 柚皮苷,可显著提升动物肌苷单磷酸含量、SOD 活性、总抗氧化能力及肝脏谷胱甘肽过氧化物酶活性^[75]。

除调节菌群结构外,柚皮素对肠道健康的另一关键作用在于直接强化其物理屏障。肠上皮是黏膜表面的单细胞层,吸收食物来源的营养物质,并起到保护黏膜完整性的作用,物理上防止有害物质的渗透。有研究表明,柚皮素通过 AMPK 信号通路上调 ZO-1、Occludin-1 及 Claudin-1 等紧密连接蛋白表达,从而显著增强肠道屏障功能、降低通透性^[76]。此外,柑橘黄酮还可促进杯状细胞增殖,加厚黏液层以隔离腔内刺激物,并通过抑制 NF- κ B 活性减轻肠道炎症;其代谢产物亦具有相似的屏障保护与抗炎效果^[77]。动物试验进一步证实,柑橘来源的活性成分(如柠檬果皮粉)可提高粪便中乙酸与丁酸水平,并通过强化紧密连接减轻 DSS 诱导的结肠炎^[78]。在热应激条件下的宁都黄鸡模型中,日粮添加 0.5 g/kg 柚皮素亦显示出通过调控 ABC 转运蛋白通路,增强十二指肠屏障完整性的作用^[79]。

多项证据表明,柚皮素对脂质代谢的调控可

能通过一个复杂的“肠-脂肪轴”网络介导。据推测,其作用发端于对肠道菌群及屏障功能的改善,进而促使短链脂肪酸与胆汁酸作为系统信使,通过激活脂肪组织的 GPR43、TGR5 等受体,在抑制脂质储存、促进产热与调节能量平衡中发挥作用。此外,柚皮素及其代谢物也被证实可直接激活 AMPK/Nrf2 等肝脏与脂肪组织中的通路。

3 应用前景与展望

柚皮素作为一种天然黄酮类化合物,凭借其在 AMPK、Nrf2/HO-1 等通路的协同作用,既能通过抑制肝脏脂质合成、诱导白色脂肪“棕色化”以改善肥胖与非酒精性脂肪肝,又能依托肠道菌群调节与屏障修复功能,为早期代谢紊乱人群提供安全的精准营养方案,尤其随着纳米递送技术(如莱鲍迪苷 A 纳米胶囊)的优化,可突破低生物利用度瓶颈,实现靶向释放与高效吸收,填补天然成分在个体化代谢治疗中的空白。在畜禽绿色养殖领域,其不仅能替代抗生素发挥抗炎、促代谢作用,减少药物残留与环境污染排放,还可通过调节肠道菌群结构、优化脂肪组织类型比例,提升畜禽产品的营养价值与风味,为其在畜牧业中的规模化应用提供理论支持和技术保障,最终推动畜牧业向高效、安全、绿色的可持续发展方向迈进。

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