



黄酮类化合物调控断奶仔猪肠黏膜屏障功能的研究进展

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摘要 黄酮类化合物是膳食非营养生物活性物质, 广泛存在于各种植物中, 具有抗氧化、抗菌和抗炎等特性. 断奶应激引发的肠黏膜损伤是制约仔猪生长的关键因素. 作为无污染、无残留、抗药性低的抗生素替代物之一, 黄酮类化合物在提高断奶仔猪生产性能和改善肠黏膜屏障功能方面具有广泛的应用价值. 本文结合课题组关于断奶仔猪肠上皮细胞更新的相关研究成果, 综述黄酮类化合物调控肠上皮细胞更新, 肠黏膜屏障损伤修复和肠道菌群平衡的药理作用及分子机制的最新研究进展, 旨在为开发和应用不同种类的天然植物源黄酮类化合物作为改善断奶仔猪肠道功能的饲料添加剂提供理论依据和实践参考.

关键词 黄酮类化合物, 断奶仔猪, 肠上皮细胞, 肠黏膜屏障, 肠道菌群

黄酮类化合物又称类黄酮, 主要由两个具有酚羟基的苯环(A环和B环)通过中央三个不饱和碳原子(C₆-C₃-C₆)作为基本骨架相连构成的一系列化合物, 多以O-糖苷或C-糖苷形式存在. 作为植物次生代谢产物, 黄酮类化合物广泛分布于各种天然农产品中(如蔬菜、水果和谷类作物等), 具有抗肿瘤、抑菌、抗炎、抗氧化和调节免疫力等益生作用^[1]. 食物中的黄酮类化合物往往以糖基化、酯类和聚合物等多种形式存在, 一部分在肠道水解酶的作用下水解成苷元形式, 再被肠上皮细胞吸收后进入血液循环发挥药理作用; 另一部分则通过肠道菌群产生的特异性代谢酶将其转化生成多酚酸类物质后进入循环系统^[2,3]. 目前, 已从不

同来源中分离鉴定出8000多种黄酮类化合物; 随着实验技术的改进, 更多天然黄酮类化合物及其糖苷被提取、分离和鉴定^[4,5].

仔猪早期断奶是生猪养殖过程的一个重要环节, 容易诱发仔猪出现精神状况不佳、采食量和抗病力下降、生长缓慢、肠道菌群失衡以及腹泻为主要特征的“早期断奶综合征”, 最终导致肠道功能紊乱和肠道疾病发生^[6]. 养殖场通常在饲料中添加抗生素等添加剂来控制上述症状, 促进仔猪生长. 由于抗生素残留量和细菌耐药性的增加, 《中华人民共和国农业农村部公告第194号》指出, 2020年7月1日起, 除中草药类外, 饲料生产企业停止生产含有促生长类药物饲料添加剂

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的商品饲料. 研究表明, 黄酮类化合物能通过清除自由基^[7]、调节酶活性^[8]和促进细胞增殖^[9]等方式维护肠黏膜上皮结构和功能; 因具备抗过敏、止泻、抗溃疡和抗炎等潜在药理功效而引起广泛关注^[10]. 因此, 毒副作用小、无残留、抗药性低的黄酮类化合物替代饲用抗生素已成为动物营养研究领域的热点之一^[11]. 本文综述近年来黄酮类化合物在断奶仔猪肠上皮细胞更新、抗氧化作用、肠黏膜屏障损伤修复及调节肠道菌群平衡等方面的功效和分子机理, 旨在为深入研究其改善断奶仔猪肠黏膜屏障功能提供理论基础, 同时也为其作为饲料添加剂在生猪生产中的应用提供科学依据.

1 断奶应激对仔猪肠黏膜结构和屏障功能的影响

1.1 仔猪肠道黏膜上皮结构特征

肠道不仅是仔猪消化食物、吸收营养的主要器官, 同时还承担着机体免疫调节和代谢调节等多种生理功能. 肠黏膜上皮作为哺乳动物体内自我更新速率最快(5~7天)的组织之一, 其功能单位由隐窝-绒毛轴(crypt-villus axis, CVA)组成; 其中, 绒毛结构朝向肠腔内部, 而隐窝结构凹陷入下层间充质^[12,13]. 肠道干细胞(intestinal stem cells, ISCs)位于隐窝的底部, 由LGR5⁺(leucine-rich repeat-containing G protein-coupled receptor 5+)基因标记, 在自我不断更新的同时, 通过分裂增殖产生过渡扩增(transit amplifying, TA)细胞^[13]. 在沿CVA迁移的过程中, TA细胞快速分裂并逐渐分化成为功能不同的吸收型细胞和分泌型细胞系(肠杯状细胞、肠内分泌细胞、Paneth细胞和Tuft细胞); 此外, 肠黏膜上皮还存在M细胞^[14]. 吸收型上皮细胞占绒毛细胞数量的95%以上, 主要负责吸收营养物质; 而分泌型上皮细胞和M细胞与肠黏膜免疫屏障功能密切相关^[15]. 因此, 肠道稳态维持是通过隐窝基底位置的ISCs进行增殖, 从而产生一群快速更新的分化谱系特异性肠上皮细胞(intestinal epithelial cells, IECs); 其中, Paneth细胞成熟后迁移到隐窝底部维持干细胞性并分泌抗菌肽, 其他各细胞在沿CVA迁移至绒毛顶端的过程中逐渐分化成熟并最终在绒毛顶端凋亡脱落入肠腔中; 因此, IECs向绒毛顶端的迁移过程也是其分化成熟并实现生理功能的过程^[13,14]. 在正常情况下, 肠上皮细

胞始终处于不断自我更新的状态, 而这种动态平衡则需要由复杂的信号通路网络来调控IECs的增殖和凋亡; 研究发现, Wnt、Hippo、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)、转化生长因子 β (transforming growth factor-beta, TGF- β)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)和磷脂酰肌醇3-激酶(phosphatidylinositol-3-kinases, PI3K)/蛋白质丝氨酸苏氨酸激酶(protein-serine-threonine kinase, AKT)等信号通路参与哺乳仔猪空肠上皮隐窝-绒毛轴细胞的更新^[16]. 因此, 肠上皮细胞增殖和凋亡的动态平衡在维持肠黏膜结构和功能完整性及其损伤修复过程中发挥关键作用^[14].

本团队建立了低温条件下分离和富集仔猪肠黏膜上皮CVA绒毛细胞和隐窝细胞的螯合剂沉淀技术, 通过多组学测序深度解析断奶应激影响仔猪肠上皮细胞更新的分子机制^[17~20]. 蛋白组学研究显示, 与哺乳仔猪相比, 断奶不同日龄仔猪空肠绒毛细胞中参与能量代谢、细胞分泌、高尔基囊泡运输、离子转运、蛋白氨基酸糖基化、跨膜转运、翻译起始、mTOR信号通路和细胞分化等蛋白表达显著下调^[17]; 而断奶不同日龄仔猪空肠隐窝细胞中参与蛋白质分解代谢、糖酵解、氨基酸代谢和细胞周期阻滞相关蛋白表达显著上调, 与脂肪酸代谢、大分子定位、翻译起始、高尔基体囊泡运输和氧化磷酸化相关蛋白表达显著下调, 上述细胞过程可能受到mTOR信号通路的调控^[18]. 断奶应激导致参与脂肪酸 β -氧化的过氧化物酶体酰基辅酶A氧化酶和长链特异性酰基辅酶A脱氢酶在绒毛细胞中表达下调, 参与三羧酸循环的 α -酮戊二酸脱氢酶和苹果酸脱氢酶在隐窝细胞表达上调, 参与糖酵解的6-磷酸果糖激酶, 果糖二磷酸醛缩酶和三磷酸异构酶在隐窝细胞表达上调, 且mTOR信号通路相关蛋白表达水平显著下降, 暗示能量代谢紊乱可能是造成断奶仔猪肠上皮细胞氧化损伤的重要因素^[19]. 代谢组学分析发现, 早期断奶引发仔猪空肠隐窝细胞脂质组成的重塑; 其中, 磷脂酰胆碱、肉碱、鞘磷脂、磷脂酰乙醇胺和磷脂酰肌醇等发生显著变化, 这可能与断奶引起的炎症有关^[20]. 上述研究表明, 早期断奶通过影响能量代谢、蛋白质合成和脂质代谢等方面导致调控肠上皮细胞功能、更新和修复的分子通路发生紊乱, 而相关差异基因/蛋白和脂质生物标志物为治疗断奶应激诱发的仔猪肠道黏膜上皮损伤提供潜在的分子靶点.

1.2 仔猪肠黏膜屏障功能

肠黏膜屏障最重要的功能之一是为防止病原体、毒素和抗原入侵提供物理屏障; 由黏液层、免疫系统和紧密连接之间的相互作用决定^[21]。肠上皮细胞通过细胞间紧密连接参与屏障功能, 这对仔猪的肠道健康至关重要。研究表明, 断奶应激诱导仔猪IECs上游启动器——半胱氨酸蛋白酶(caspase-8和caspase-9)活性增强, 然后引发caspase级联反应并激活凋亡执行者caspase-3, 导致细胞内DNA片段化, 促进小肠绒毛顶端区域细胞凋亡, 仔猪IECs增殖和凋亡的动态平衡被打破^[22]。肠上皮细胞凋亡加剧引起闭合蛋白(claudin)、闭锁蛋白(occludin)、连接黏附分子(junctional adhesion molecule, JAM)和闭合小环蛋白(zonula occludens, ZO)等紧密连接蛋白表达下降, 进而造成肠黏膜通透性增加, 机械屏障功能受损^[23]。上述变化引起仔猪肠黏膜上皮结构和屏障特性及生理功能发生显著改变, 主要表现为小肠上皮绒毛萎缩脱落, 肠道隐窝细胞有丝分裂加快, 造成隐窝深度增加, 消化吸收功能下降^[24]; 进而诱导肠黏膜上皮组织产生大量活性氧自由基(reactive oxygen species, ROS), 损伤蛋白质、DNA和脂质等细胞内大分子, 诱导细胞稳态失调, 进而触发肠上皮细胞发生多种生物学反应, 包括细胞自噬异常、凋亡及坏死, 引发肠黏膜炎症反应, 导致黏膜结构损伤和屏障功能紊乱, 进而产生肠道疾病^[24,25]。空肠作为仔猪营养吸收的主要场所, 其上皮细胞易受内外环境的影响而产生氧化应激^[26]。研究证实, 断奶应激导致仔猪空肠黏膜IECs的抗氧化能力沿绒毛纵轴逐渐降低^[24,26]。因此, 普遍认为断奶应激引起仔猪肠黏膜上皮组织和细胞内源性ROS稳态失衡是导致肠黏膜屏障损伤和肠上皮细胞凋亡的重要原因, 由此引发的小肠黏膜吸收面积减少和碱性磷酸酶、氨基肽酶N及蔗糖酶等刷状缘酶活性降低直接影响仔猪的生长性能^[27,28]。

2 黄酮类化合物对肠黏膜形态结构的影响及分子机制

肠黏膜上皮形态结构的完整性对营养物质的消化吸收和肠道免疫屏障的建立发挥着重要作用。断奶应激引发的仔猪肠黏膜上皮形态结构发生改变可导致病

原菌入侵, 影响营养物质的消化吸收, 从而导致生长受阻^[29]。众所周知, 绒毛高度与隐窝深度比值(villus height/crypt depth, V/C)可以综合反映仔猪小肠营养吸收的状况, 绒毛长度增加, 隐窝深度降低, V/C值就会增大, 营养吸收的能力随之增加^[30]。因此, 保持肠黏膜形态的完整是仔猪健康的前提。

2.1 改善肠黏膜形态结构

近年来, 一系列研究证实黄酮类化合物对维护断奶仔猪肠黏膜形态结构具有正向调节作用。日粮添加150 mg/kg甘草黄酮能显著降低仔猪盲肠和结肠pH值, 增加断奶仔猪十二指肠绒毛高度和V/C值, 降低隐窝深度^[31]。日粮添加500 mg/kg绿原酸显著提高断奶仔猪空肠黏膜绒毛高度、完整性和小肠长度指数, 提升平均日增重和平均日采食量, 降低料肉比; 日粮添加500 mg/kg橙皮苷通过提升绒毛高度促进生长性能^[32]。日粮添加500 mg/kg绿原酸不仅显著降低断奶仔猪十二指肠隐窝深度, 增加绒毛高度和V/C值; 同时, 还能增加空肠绒毛高度和回肠V/C值, 降低料肉比^[33]。断奶仔猪饲喂杜仲黄酮显著增加空肠V/C值、空肠和回肠绒毛高度, 提高平均日增重和肉料比^[34]。研究发现, 高剂量抗生素暴露会损伤仔猪肠道形态结构, 进而破坏肠黏膜屏障; 饲粮添加500 mg/kg黄芩苷能显著增加高剂量(1000 mg/kg)林可霉素暴露组的断奶仔猪体重, 提高空肠绒毛高度和结肠肌层宽度, 暗示黄芩苷能够有效缓解抗生素对仔猪空肠和结肠黏膜造成的形态损伤^[35]。二氢杨梅素能抑制黄嘌呤氧化酶产生的过氧化, 缓解早期断奶应激对仔猪IECs的损伤, 促进IECs的增殖分化, 提升绒毛高度, 增强肠黏膜上皮结构的自我修复功能^[36]。断奶仔猪日粮中添加0.1%槲皮素能够抑制IECs凋亡, 降低空肠隐窝深度和增加绒毛高度, 进而有效提高V/C值来改善肠黏膜上皮损伤^[37]。槲皮素可通过调控EAAC1, ASCT2和rBAT等氨基酸转运载体、小肽转运载体(PepT1)及mTOR信号通路相关成员(mTOR, eIF4E和eIF4A) mRNA和蛋白的表达来促进猪肠上皮细胞对蛋白质的利用^[38]。

2.2 促进肠黏膜上皮细胞更新的分子机制

体外研究表明, 5 $\mu\text{g/mL}$ 槲皮素处理IPEC-J2细胞(猪小肠上皮细胞)通过降低G0/G1期细胞比例, 促进S期和G2期细胞比例上升, 提高增殖指数进而增强细胞

存活率^[9]。Zhang等人^[39]报道槲皮素通过增加PI3K和Akt的表达水平和抑制磷酸酯酶与张力蛋白同源物(phosphatase and tensin homolog, PTEN)活性,减轻小肠组织病理状况和缓解应激性腹泻。众所周知,PI3K/Akt级联信号通路在细胞分化、增殖、迁移和代谢等肠上皮细胞更新过程中发挥关键作用^[16]。Qin等人^[40]发现绿原酸能通过促进*Lgr5*和*Olfm4*等干细胞标记物表达增加小鼠隐窝类器官面积和出芽肠器官样体的数量;动物实验印证绿原酸能促进小鼠十二指肠绒毛高度和隐窝深度,暗示其通过提高ISCs增殖和分化活性促进肠黏膜上皮更新。细胞迁移是肠黏膜损伤修复的重要环节,主要由隐窝细胞分裂产生的压力驱动,早期修复主要依赖于IECs的快速迁移以重新封闭表面损伤^[41]。在脂多糖(lipopolysaccharide, LPS)诱导IEC-6细胞(大鼠小肠隐窝上皮细胞)氧化应激模型中,10.0 $\mu\text{g/mL}$ 黄芩苷处理能显著提升细胞迁移率,降低细胞凋亡率^[42]。脱氧雪腐镰刀菌烯醇(deoxynivalenol, DON)诱导IPEC-J2细胞氧化应激模型中,二氢杨梅素显著增加细胞活力并抑制细胞凋亡,恢复由DON诱发的谷氨酸代谢、花生四烯代谢和组氨酸代谢等代谢途径的紊乱^[43]。研究发现,20 $\mu\text{mol/L}$ 黄芩苷通过下调Caspase-3和Bax的蛋白表达水平,增加Bcl2/Bax基因相对表达量的比值显著抑制 H_2O_2 诱导的IPEC-J2细胞凋亡率^[44]。Zhu等人^[45]证实黄芩苷通过降低Caspase-3, Caspase-9, Bax和凋亡相关因子配体(factor related apoptosis ligand, FasL)等促凋亡蛋白的表达水平,促进Bcl-2的表达,进而抑制HT-29细胞凋亡。Anderson等人^[46]报道黄酮类化合物(儿茶素、槲皮素、山奈酚、木犀草素和芹菜素)可以通过快速的化学修复,减少DNA单链断裂的发生率和残余碱基损伤,保护ROS诱导的DNA损伤,进而达到细胞损伤修复的目的。上述研究表明,黄酮类化合物可能通过调控断奶仔猪IECs快速更新来促进肠黏膜损伤修复。

由于断奶仔猪的消化系统和免疫器官发育不完善,使蛋白酶、淀粉酶、脂肪酶等消化酶和胃酸分泌不足,引发胃内pH值的大幅度升高,进而降低蛋白质的消化率;蛋白质在肠道细菌作用下发生腐败,生成的有害物质对结肠黏膜产生损伤。相关研究表明,黄酮类化合物通过调控肠黏膜上皮细胞生物学功能来预防和缓解结肠炎病理症状。Miyamoto等人^[47]发现白杨素(5,7-二羟基黄酮)通过显著降低“正常表现”隐窝的有

丝分裂指数,增加隐窝细胞凋亡指数,显著改善氧化偶氮甲烷(azoxymethane, AOM)诱导的小鼠结肠异常隐窝病灶(aberrant crypt foci, ACF)形成,暗示白杨素通过调节隐窝细胞增殖活性和细胞凋亡预防肠道早期病变。Zhang等人^[48]报道100 mg/kg柚皮苷通过抑制粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor, GM-CSF),白介素6(interleukin 6, IL-6)和肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)等促炎因子活性及结肠直肠组织中的NF- κB /IL-6/STAT3级联信号通路降低肠黏膜细胞自噬来减轻AOM诱导的小鼠结肠炎和结肠直肠癌症状。日粮添加100 mg/kg木犀草素通过缓解体重下降以及降低结肠黏膜的组织学损伤来减轻硫酸葡聚糖钠(dextran sulfate sodium salt, DSS)诱导的小鼠结肠炎临床和病理症状;其潜在的机制可能是木犀草素通过激活MAPK/ERK信号通路调控细胞凋亡和自噬,促进结肠组织损伤修复^[49]。

3 黄酮类化合物的抗氧化功效及分子机制

断奶应激诱发仔猪IECs内ROS蓄积,耗尽内源性抗氧化酶,导致氧化系统和抗氧化系统失衡,IECs细胞周期发生阻滞和细胞凋亡,进而引发肠道生理功能障碍及病理反应;因此,抗氧化酶的水平 and 活性可以间接反映组织细胞的氧化应激状态^[50]。

3.1 缓解断奶仔猪肠黏膜氧化应激

黄酮类化合物能通过保护或增强机体主要抗氧化酶,如超氧化物歧化酶(superoxide dismutase, SOD)、过氧化氢酶(catalase, CAT)、过氧化物还原酶(peroxiredoxin, Prx)、谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-px)、血红素加氧酶-1(heme oxygenase 1, HO-1)等,活性来增强机体的总抗氧化能力(total antioxidant capacity, T-AOC)^[51]。日粮添加150 mg/kg甘草黄酮显著提高断奶仔猪的肝脏指数,降低血清天冬氨酸转氨酶活性,增强血清和脾脏中T-AOC活性,进而提升仔猪的免疫功能^[52]。杜仲黄酮显著提高DON诱导的断奶仔猪血清SOD和GSH-Px活性,降低血清丙二醛(malondialdehyde, MDA)和ROS含量;提高平均日增重和料肉比^[53]。日粮添加40 mg/kg苦荞黄酮显著增加断奶仔猪血清T-AOC, SOD, GSH-Px和CAT含量,降低

MDA含量,提升生长性能^[54]。绿原酸能降低断奶仔猪回肠MDA含量,并通过提高血清GSH-Px活性和十二指肠GSH-Px, CAT活性,上调十二指肠和空肠中Occludin的蛋白表达水平^[33]。日粮中添加300 mg/kg橙皮苷能提高断奶仔猪的血清和肝脏中的GSH-PX, SOD和CAT活性,降低血浆MDA含量及抑制羟自由基能力,进而提升相关生长性能指标^[55]。日粮添加250 mg/kg绿原酸和橙皮苷均能显著提高断奶仔猪血浆和肝组织中T-AOC, T-SOD, CAT, GSH-Px和谷胱甘肽还原酶活力,进而促进肠道健康和生产性能^[32]。上述研究表明,黄酮类化合物主要通过抑制仔猪体内ROS水平来缓解氧化应激造成的肠黏膜损伤。

日粮添加100 mg/kg葛根素通过增强仔猪空肠黏膜上皮Nrf2及其下游酶,包括HO-1, 谷氨酸-半胱氨酸连接酶催化亚基(glutamate-cysteine ligase catalytic subunit, GCLC)及其修饰亚基(glutamate-cysteine ligase modifier subunit, GCLM)的蛋白相对表达水平来缓解敌草快造成的氧化损伤^[56]。Xiao等人^[57]报道日粮添加100 mg/kg杜仲黄酮能提高敌草快诱导的断奶仔猪空肠黏膜Nrf2和Keap1蛋白表达水平及HO-1, NQO-1和GCLC的mRNA表达,降低氧化型谷胱甘肽(oxidized glutathione disulfide, GSSG)浓度和GSSG/GSH比值,暗示黄酮类化合物通过调节Nrf2信号通路缓解仔猪空肠氧化应激。Jia等人^[58]证实槲皮素能缓解敌草快诱导的IPEC-J2细胞(猪小肠上皮细胞)氧化损伤;其作用机制与Nrf2蛋白丰度的升高和细胞内谷胱甘肽(GSH)含量的增加有关。Liang等人^[44]报道黄芩苷通过调节单磷酸腺苷活化蛋白激酶(adenosine 5'-monophosphate (AMP)-activated protein kinase, AMPK)/Nrf2信号通路减轻H₂O₂诱导的IPEC-J2细胞氧化应激。在LPS诱导IPEC-J2细胞的体外氧化应激模型中,16 μg/mL黄芩苷处理细胞通过激活Nrf2/HO-1信号通路缓解肠道细胞氧化应激,进而抑制NF-κB信号通路降低细胞炎症反应,保护肠道细胞的正常生理功能^[59]。

3.2 抗氧化功能的分子机制

已知黄酮类化合物在体内的抗氧化作用有三种途径(图1)。黄酮类化合物的主要抗氧化作用机制是黄酮的酚羟基通过供氢与自由基反应生成共振稳定的半醌式结构,从而终止自由基链式反应,反应式为: [flavone-OH]+R·→[flavone-O·]+RH^[60,61]。抗氧化活性与黄

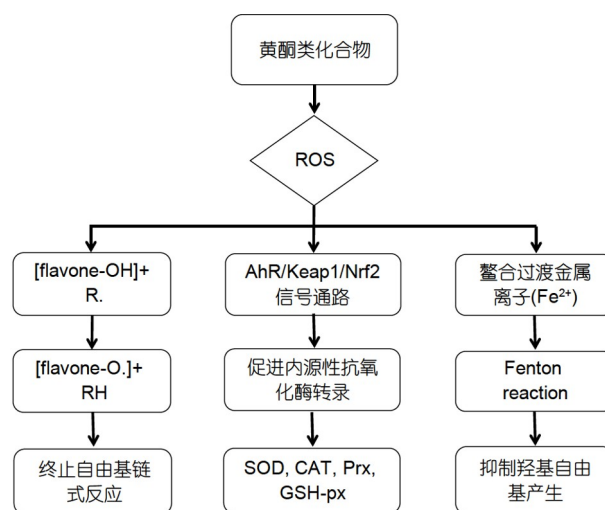


图1 黄酮类化合物抗氧化作用机制

Figure 1 Mechanism of antioxidant action of flavonoids

酮类物质和其酚类物质的总含量呈显著性正相关,酚羟基越多,黄酮类化合物的抗氧化活性越强。Cheng等人^[62]证实苦荞麦抗氧化活性主要归因于各种生物活性化合物,其中苦荞总黄酮含量与苦荞麦的抗氧化活性呈正相关性。黄酮类化合物的抗氧化活性还可能是由胞质芳基烃受体(aryl hydrocarbon receptor, AhR)/核因子-红细胞2相关因子2(nuclear factor-erythroid 2 related factor 2, Nrf2)信号通路介导的;其分子机制是:黄酮类化合物与AhR结合,然后诱导Kelch样环氧氯丙烷相关蛋白1(kelch-like ECH-associated protein 1, Keap1)/Nrf2复合体分离,从而促进Nrf2的细胞核转位,增加内源性抗氧化酶的转录^[63]。第三种途径是螯合过渡金属离子;Fe²⁺, Ca²⁺和Cu²⁺等在ROS产生过程中是必需的,由于黄酮类化合物具有4-酮基,5-羟基的分子结构,且B环3'和4'位的连位羟基含有孤对电子,因而能螯合那些负责产生ROS的过渡金属离子,从而抑制脂氧合酶反应的启动。如槲皮素和芦丁可通过螯合Fe²⁺,通过芬顿反应(Fenton reaction)抑制羟基自由基的生成,从而达到清除自由基的目的^[64]。然而,McAnlis等人^[65]发现黄酮类化合物在非过渡金属依赖性氧化过程中也具有抗氧化能力。最新研究表明,黄酮类化合物还能通过抑制核苷酸结合寡聚化结构域、富含亮氨酸重复序列基因为家族和含热蛋白(pyrin)结构域的蛋白3(NOD-like receptors family pyrin domain containing 3, NLRP3)炎症小体活化,进而减轻氧化应激^[66]。

4 黄酮类化合物对肠黏膜屏障功能的影响

黄酮类化合物具有改善仔猪肠道黏膜屏障的积极作用, 主要包括对肠道屏障机械功能的调节作用; 增强肠道免疫功能, 提升仔猪肠道的免疫应答能力、缓解肠道应激状态; 改善肠道微环境, 增强小肠消化酶功能, 提高仔猪消化吸收能力。

4.1 调节肠黏膜机械屏障功能

紧密连接蛋白是肠黏膜机械屏障的重要组成部分, 其表达、分布和磷酸化水平在维持肠黏膜屏障功能完整性以及调节细胞通透性方面发挥关键作用。研究表明, 黄酮类化合物可通过增加紧密连接蛋白表达水平、增强其在IECs膜上的定位与分布来维持机械屏障的完整性, 保护肠黏膜机械屏障功能。日粮添加40 mg/kg大豆异黄酮能抑制p38和Toll样受体-4(toll-like receptors-4, TLR4)信号通路的激活, 上调肠黏膜中ZO-1和Occludin基因转录水平, 缓解LPS诱导的断奶仔猪肠黏膜机械屏障损伤作用^[67]。免疫荧光结果表明, 副猪嗜血杆菌感染改变仔猪腹膜中紧密连接蛋白的分布, Occludin, ZO-1, Claudin-1和JAM-1蛋白染色减少, 呈现碎片化; 日粮添加50 mg/kg黄芩苷能显著改善紧密连接蛋白的染色紊乱; 暗示黄芩苷能有效缓解细菌诱导的紧密连接完整性的整体损伤^[68]。DON处理IPEC-J2细胞能显著降低细胞跨膜电阻抗值(trans-epithelial resistance, TER)并引发氧化应激, 20 μ mol/L槲皮素预处理细胞能有效维持单层肠道细胞的完整性, 维护肠道机械屏障并缓解氧化应激^[69]。橙皮苷不仅能够增加DSS诱导的小鼠结肠炎中Occludin和ZO-1的表达量; 而且还能有效缓解ZO-1在TNF- α /IFN- γ 诱导Caco-2细胞间连接处相对荧光密度降低和不连续造成的细胞形态损伤, 恢复肠道细胞机械屏障功能^[70]。

研究发现, 细胞内蛋白激酶C(protein kinase C, PKC), PKA, PI3K/Akt, MAPK和Rho/Rho相关蛋白激酶(Rho-associated protein kinase, ROCK)信号通路等参与紧密连接功能的调控^[71]。在LPS诱导Caco-2细胞损伤模型中, 绿原酸显著增加上皮细胞跨膜电阻(trans-epithelial electrical resistance, TEER), 并降低跨膜的溶质通透性; 其分子机制为绿原酸抑制ROCK/肌球蛋白轻链激酶(myosin light chain kinase, MLCK)信号通路的激活, 下调下游磷酸化肌球蛋白磷酸酶靶亚基1(p-

MYPT1), MLCK和p-MLC的表达, 上调紧密连接蛋白Claudin-1, Occludin和ZO-1的表达^[72]。橙皮苷通过激活AMPK介导的紧密连接相关蛋白(Occludin, JAM-1, Claudin-1和Claudin-4)表达增强Caco-2细胞单层膜的肠屏障功能^[73]。

4.2 调节肠黏膜化学屏障功能

肠黏膜化学屏障主要由肠道分泌的各种消化酶、溶菌酶、黏蛋白、黏多糖和抗菌肽等化学物质以及肠道微生物产生的抑菌物质组成, 在维持肠道健康中发挥重要作用^[74]。研究发现, 柑橘类黄酮(槲皮素和橙皮苷)能调控肠道黏蛋白和消化酶的表达和分泌, 表现出潜在的肠黏膜化学屏障保护作用^[75]。日粮添加100 mg/kg葡萄籽原花青素增强断奶仔猪空肠黏膜上皮麦芽糖酶和蔗糖酶活性, 而高浓度原花青素则抑制脂肪酶和淀粉酶的活性, 暗示黄酮类化合物在合适的剂量范围内能促进肠黏膜上皮刷状缘酶活性^[76]。Paniagua等人^[77]采用柑橘类黄酮替代日粮氧化锌方案, 显著提高断奶仔猪的体重和平均日增重, 肠黏膜化学屏障相关基因, 黏蛋白13(mucin 13, Muc13), 蔗糖酶异麦芽糖酶(sucrase-isomaltase, SI)、组胺N-甲基转移酶(histamine N-methyltransferase, HNMT)、胰高血糖素(glucagon, GCG)和二胺氧化酶(diamine oxidase, DAO1)等消化酶, 及营养素转运(SLC13A1和SLC15A1)转录水平显著升高, 表明柑橘类黄酮可通过改善肠黏膜化学屏障最大限度地减少日粮中多种抗菌物质(氧化锌和抗生素)的使用。橙皮苷通过上调肠黏膜上皮中Muc2的表达水平来维持化学屏障功能, 减轻小鼠的结肠炎症状^[78]。黄酮类化合物还能通过上调肠上皮细胞胰高血糖素样肽-2(glucagon-like peptide-2, GLP-2)表达水平来改善肠黏膜化学屏障功能^[79]。

Song等人^[72]发现绿原酸通过抑制葡萄糖调节蛋白78(78-kD glucose-regulated protein, GRP78)、C/EBP同源蛋白(C/EBP homologous protein, CHOP)等内质网标记物的蛋白表达水平和激活转录因子6(activating transcription factor 6, ATF6)的核易位, 从而促进黏蛋白2(mucin-2, Muc2), Muc5AC和分泌因子三叶因子家族3(trefoil factor 3, TFF3)蛋白的表达, 缓解LPS诱导的肠道细胞(Caco-2和LS174T)内质网应激。槲皮素通过PLC/PKC/ERK1-2信号通路诱导LS174T细胞(人肠杯状样细胞系)两种主要肠黏蛋白Muc2和Muc5AC的分

泌^[80]。Klepsch等人^[81]报道Nr2f6^{-/-}小鼠肠道Muc2表达减少并改变肠道通透性, 导致自发性结肠炎; 分子机制为Nr2f6作为上游调节因子通过与Muc2结合后, 激活Muc2的表达来缓解结肠炎症状。

4.3 调节肠黏膜免疫屏障功能

肠黏膜免疫屏障主要由肠上皮细胞、相关淋巴组织(gut-associated lymphoid tissues, GALT)和免疫细胞构成。断奶应激导致仔猪肠黏膜免疫屏障在抗原的刺激下产生白细胞介素(interleukin, IL)、干扰素(interferon, IFN)和免疫球蛋白(immunoglobulin, Ig)等因子来激活肠道免疫系统, 进而大量合成促炎因子引发炎症, 对肠黏膜结构完整性和IECs功能造成损伤^[82]。

日粮添加150 mg/kg甘草黄酮通过降低断奶仔猪十二指肠IL-1 β 、IL-8和诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)的mRNA丰度, 改善生长性能和肠黏膜屏障功能^[31]。日粮添加1000 mg/kg绿原酸可能通过抑制TLR4/NF- κ B信号通路和激活Nrf2/HO-1信号通路上调Toll作用蛋白(toll-interacting protein, Tollip)和细胞因子信号传导抑制蛋白1(suppressor of cytokine signaling 1, SOCS1)相对表达水平, 下调结肠和回肠黏膜中关键炎症因子, 如IL-1 β 、IL-6、TNF- α 和NF- κ B的表达水平来维护断奶仔猪肠黏膜免疫屏障^[83]。一系列研究证实, 黄酮类化合物对LPS诱导IPEC-J2细胞免疫屏障功能氧化损伤有较好的保护作用。分别采用50 μ mol/L槲皮素和衍生物(3-o-甲基槲皮素)处理IPEC-J2细胞, 结果表明两种物质均能显著抑制细胞内ROS的产生和IL-6活性^[84]。木犀草素通过下调IL-6和IL-8的分泌来抑制胞内ROS的产生和培养基中H₂O₂的含量, 促进肠上皮细胞活力^[85]。芹菜素及其衍生物(芹菜素-三甲基醚)均显著降低胞外H₂O₂的水平, 并下调IL-8和COX-2 mRNA表达水平, 有效缓解炎症反应^[86]。杜仲黄酮通过增加p-Akt、p-I κ B α 和p-IKK α / β 蛋白活性, 下调Bax和Caspase-3蛋白的表达量抑制细胞凋亡, 提升IPEC-J2细胞活力和抗氧化能力; 杜仲黄酮和PI3K抑制剂(LY29400)联合处理细胞, 下调PI3K、p-Akt、p-IKK α / β 、p-NF- κ B和Bax的蛋白表达水平, 细胞增殖率和SOD活性降低, 暗示杜仲黄酮可能介导PI3K/NF- κ B信号通路干预肠道炎症性疾病^[87]。

橙皮苷通过调节肠系膜淋巴结中调节性T细胞的激活、分化和效应细胞的浸润^[88], 以及促进肠道中的

免疫球蛋白A(secretory immunoglobulin A, SIgA)^[89]和IgM^[90]分泌, 维护肠黏膜免疫屏障。日粮添加大豆异黄酮可能通过提高断奶仔猪辅助性T细胞与细胞毒性T细胞比率(CD4/CD8)来缓解猪繁殖与呼吸综合征病毒感染症状, 暗示大豆异黄酮通过促进CD4⁺ T细胞分化并激活机体免疫功能, 从而对病毒感染有显著的治疗作用^[91]。黄芩苷可减少副猪嗜血杆菌(*H. parasuis*)感染断奶仔猪血清中IL-1 β 、IL-6、IL-8、IL-10和TNF- α 等炎症因子的释放, 并抑制外周血单核巨噬细胞MAPK信号通路的激活和高迁移率族蛋白B1(high mobility group box 1, HMGB1)表达水平, 减少细胞凋亡, 减轻细菌诱导的炎症反应^[92]。在*H. parasuis*诱导断奶仔猪单核巨噬细胞炎症模型中, 胞内ROS升高, 细胞周期阻滞, 并通过PKC/MAPK信号通路促进细胞凋亡; 日粮添加黄芩苷能显著降低ROS生成, 抑制PKC/MAPK信号通路的激活并降低促凋亡cleavage of caspase-3蛋白活性, 从而下调单核巨噬细胞中p-JNK、p-p38、p-ERK、p-PKC- α 和PKC- δ 表达^[93]。Fu等人^[94]证实黄芩苷能下调*H. parasuis*诱导断奶仔猪单核巨噬细胞中IL-6、IL-8、IL-10、COX-2、IL-1 β 、IL-18和TNF- α 等促炎因子的mRNA表达水平; 通过抑制NF- κ B和炎症小体NLRP3信号通路激活减少胞内ROS产生和细胞凋亡发生。Ye等人^[95]报道黄芩苷可抑制LPS诱导仔猪单核巨噬细胞中ROS、IL-1 β 、IL-18和TNF- α 活性, 下调IL-1 β 、IL-18、TNF- α 和NLRP3的mRNA相对表达水平及Cleaved-Caspase-1 p20的蛋白表达量。上述研究表明, 黄酮类化合物可能通过介导NF- κ B、NLRP3和MAPK等信号通路来调节免疫细胞分化、减轻炎症反应及氧化应激损伤, 改善肠黏膜免疫屏障功能(图2)。

5 黄酮类化合物对断奶仔猪肠道菌群的影响

在正常情况下, 肠黏膜表面会附着大量厌氧细菌, 如双歧杆菌(*Bifidobacteria*)和乳酸杆菌(*Lactobacilli*)等益生菌, 它们与肠黏膜上皮紧密黏附, 阻碍致病菌在肠道中的定植^[96,97], 进而促进IECs增殖, 增强机体免疫力^[98]。仔猪在断奶期间, 因尚未建立稳定的肠道微生态系统, 机体抵抗力较弱, 易受大肠埃希氏菌属(*Escherichia coli*, *E. coli*)和轮状病毒等各种病原微生物的侵袭, 导致肠道菌群结构失衡, 抑制IECs蛋白质合成, 损伤肠绒毛结构, 破坏肠黏膜屏障, 引发腹泻^[99]。

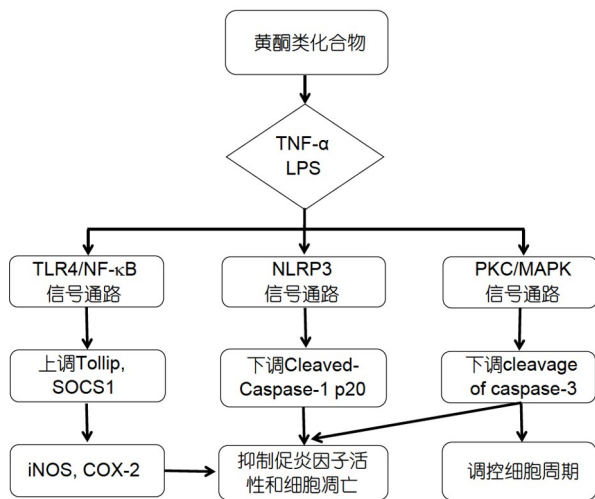


图2 黄酮类化合物调控断奶仔猪肠黏膜免疫屏障机制
Figure 2 Mechanism of flavonoids regulate the intestinal mucosal immune barrier of weaned piglets

5.1 抑制有害菌群繁殖

黄酮类化合物对肠道致病菌的影响主要表现为抗菌作用。Kovács等人^[100]报道原花青素和木犀草素能有效降低LPS诱导IPEC-J2细胞ROS的产生；体外抑菌试验发现，高浓度(2048 g/mL)原花青素能抑制猪源细菌(*E.coli*和鼠伤寒沙门氏菌(*Salmonella enterica*, *S. enterica*))增殖；而木犀草素显示出更强的抑菌效果，能够在最小抑菌浓度(minimum inhibitory concentration, MIC)为256 g/mL浓度下抑制*E.coli*和*S. enterica*生长。日粮添加绿原酸显著抑制断奶仔猪肠道*E.coli*菌群生长，增加结肠内容物中*Lactobacilli*菌群丰度；提升短链脂肪酸(丙酸和丁酸)浓度，进而改善肠道健康和生长性能^[33]。黄芩苷能抑制大肠埃希氏菌(*Escherichia spp.*)的丰度，进而降低β-葡萄糖醛酸酶活性，暗示其可能通过改变腹泻肠道菌群的代谢功能来缓解仔猪感染性腹泻^[101]。Donovan等人^[102]报道大豆异黄酮主要通过降低病毒在上皮细胞的附着能力来降低轮状病毒的感染性。黄酮类化合物主要的抗菌要机制是通过影响病原微生物细胞膜的通透性结构或破坏其细胞膜的磷脂双分子层等方式来抑制肠道*E.coli*，金黄色葡萄球菌(*Staphylococcus aureus*)和轮状病毒等病原微生物的繁殖，降低对机体的生物毒性^[103,104]。

5.2 优化肠道菌群结构

作为有益菌群，*Bifidobacteria*和*Lactobacilli*具有

改善胃肠道环境和维护肠道菌群稳态的作用^[105]，其丰度和数量在一定程度上反映肠道的健康状态^[106]。日粮添加杜仲黄酮能显著增加断奶仔猪回肠中乳酸杆菌属(*Lactobacillus spp.*)种群数量，抑制*E.coli*的定植，缓解仔猪腹泻^[34]。日粮添加250 mg/kg原青花素显著提升断奶仔猪结肠腔中梭菌科(*Clostridiaceae*)菌群丰度，改善结肠内容物中细菌的丰度和多样性，增加丙酸和丁酸浓度^[107]。槲皮素通过增加断奶仔猪直肠内纤维菌(*Fibrobacteres*)、嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*)、丁酸梭菌(*Clostridium butyricum*)和普雷沃氏菌(*Prevotella copri*)的相对丰度，降低变形菌(*Proteobacteria*)、乳杆菌(*Lactobacillus coleohominis*)和布氏瘤胃球菌(*Ruminococcus bromii*)的相对丰度，增强肠道菌群的厌氧特性和碳水化合物代谢功能，进而提升肠道抗氧化能力^[37]。在肠道微生物体外发酵模型中，儿茶素显著增加毛螺菌科(*Lachnospiraceae*)，*Bifidobacteria*和*Lactobacilli*菌群的生长，并对*E.coli*和溶组织梭菌属(*Clostridium histolyticum*, *C.histolyticum*)的生长具有显著的抑制作用^[108]。锦葵色素能促进体外微生物发酵模型中*Bifidobacterium spp.*，*Lactobacilli*和肠球菌(*Enterococcus spp.*)丰富，抑制*C.histolyticum*生长^[109]。柚皮素处理体外微生物共生培养能促进*Bifidobacterium catenulatum*增殖，并抑制*Enterococcus caccae*生长；RNA测序结果显示，*Bifidobacterium catenulatum*内参与分子运输、DNA修复和细胞代谢相关基因表达上调，参与代谢和胸腺嘧啶核苷生物合成的基因表达下调；*Enterococcus caccae*内参与蛋白转运和基因转录调控相关基因表达上调，负责嘌呤合成与糖转运的基因表达下调^[110]。黄酮类化合物作为肠道菌群的代谢底物，不仅可在菌群互作中发生代谢转化作用形成酚酸或芳香酸，与肠上皮细胞膜受体结合后调控下游相关基因表达发挥生理功能^[111]，也可以反作用于肠道微生物，通过抑制或促进部分菌属的增殖，从而优化肠道菌群结构，维持肠道黏膜屏障完整^[112]。主要黄酮类化合物对肠道微生物多样性的影响见表1。

5.3 调控肠道菌群平衡的分子机制

黄酮类化合物调节肠道菌群平衡的作用机制可能与氧化应激反应有关。Ma等人^[113]发现GSH，SOD和ROS含量与肠道菌群分布密切相关；其中，GSH与脱硫弧菌属(*Desulfovibrio*)、毛螺菌科(*Lachnospiraceae*)

表 1 黄酮类化合物对肠道菌群结构的影响

Table 1 Effects of flavonoids on composition of gut microbiota

黄酮种类	对肠道菌群结构的影响		实验模型	参考文献
	抑制菌属	促进菌属		
绿原酸	大肠埃希氏菌属	乳酸杆菌属	断奶仔猪	[33]
杜仲黄酮	大肠埃希氏菌属	乳酸杆菌属	断奶仔猪	[34]
槲皮素	变形菌, 乳杆菌, 布氏瘤胃球菌	纤维菌, 嗜黏蛋白阿克曼菌, 丁酸梭菌, 普雷沃氏菌	断奶仔猪	[37]
原花青素	大肠埃希氏菌属, 鼠伤寒沙门氏菌	/	体外发酵	[98]
木犀草素	大肠埃希氏菌属, 鼠伤寒沙门氏菌	/		
黄芩苷	大肠埃希氏菌属	/	断奶仔猪	[99]
原花青素	/	梭菌科	断奶仔猪	[104]
儿茶素	大肠埃希氏菌属, 溶组织梭菌属	毛螺菌科, 双歧杆菌, 乳酸杆菌	体外发酵	[105]
锦葵色素	溶组织梭菌属	双歧杆菌属, 乳酸杆菌, 肠球菌属	体外发酵	[106]
柚皮素	肠球菌	链状双歧杆菌	体外发酵	[107]

呈正相关, 与梭菌目(*Clostridiales*)、另支菌属(*Alitipes*)、粪杆状菌属(*Faecalibaculum*)、黄曲霉属(*Flavonifractor*)、粪芽孢菌属(*Coprobacillus*)等呈负相关; SOD 与乳杆菌属(*Lactobacillus*)、毛螺菌科(*Lachnospiraceae*)和脱硫弧菌属(*Desulfovibrio*)呈正相关, 与另支菌属(*Alistipes*)、拟杆菌属(*Bacteroides*)、粪杆状菌属(*Faecalibaculum*)和粪芽孢菌属(*Coprobacillus*)等呈负相关; ROS与另支菌属(*Alistipes*)、拟杆菌属(*Bacteroides*)、粪杆状菌属(*Faecalibaculum*)和螺杆菌属(*Helicobacter*)呈正相关, 与毛螺菌科(*Lachnospiraceae*)呈负相关。日粮添加黄酮类化合物(杜仲黄酮, 绿原酸和苦荞黄酮等)能显著增加断奶仔猪GSH和SOD的含量, 降低ROS含量, 维护肠黏膜屏障, 改善生长性能^[32,53,54]。另外, 肠道微生物代谢生成的吲哚及其衍生物大多为芳烃核受体(aryl hydrocarbon receptor, AhR)的配体, AhR信号通路被认为在调控应激诱导的肠道菌群失调效应中发挥关键作用^[114]。Wu等人^[115,116]报道健康小鼠饮食饲喂橙皮素单糖苷后, 盲肠内容物中以吲哚-3-乙醇(Indole-3-acetic acid, IAA)和吲哚-3-丙酸(Indole-3-propionic acid, IPA)为代表的色氨酸相关代谢物含量显著上调; 与之相关的乳杆菌(*Lactobacillus*)、瘤胃球菌(*Ruminococcus*)、嗜胆汁菌(*Bilophila*)、丁酸蓖麻单胞菌(*Butyricimonas*)和假单胞菌(*Pseudomonas*)等菌群丰度显著性变化, 显著提高肠道微生物群的多样性。因此, 黄酮类化合物还可能通过调控AhR信号通路干预微生物代谢产物的生成, 进而调节肠道菌群平衡。

6 总结与展望

黄酮类化合物作为具有广泛应用潜力的抗生素替代品, 在生猪养殖过程中起到营养和药物的双重功效。目前, 国内外关于黄酮类化合物在畜禽健康养殖方面的研究较多, 其作为替抗饲料添加剂在生猪养殖中的作用已得到广泛应用, 但大部分研究主要集中在促进动物生长性能、提高免疫力和改善肠道菌群等宏观方面; 然而, 黄酮类化合物在动物胃肠道的吸收分布及体内代谢的路径并不清楚, 且“黄酮类化合物-肠道菌群”的互作机制也尚不明晰。因此, 本文综述黄酮类化合物通过优化肠道形态学结构、缓解氧化应激、减轻肠道炎症和改善肠道菌群等方面调控断奶仔猪肠黏膜屏障功能的药理作用及相关分子机制的最新研究进展(图3)。

由于天然植物源黄酮类化合物数量种类繁多、结构类型复杂多样, 在养殖过程中的添加剂量与饲喂功效的关系、安全性和潜在的毒副作用以及生物活性的分子机理目前尚不完全明确, 对于如何更好地在生产实践中进行替抗应用仍缺乏许多理论指导。首先, 在断奶仔猪养殖过程中不同种类黄酮类化合物添加剂量差异较大, 其浓度差异必然会影响胃肠道对它的生物利用率, 这也是制约黄酮类化合物在动物生产实践中的开发应用难点之一; 其次, 需要对黄酮类化合物在断奶仔猪生产中的功效进行系统探究, 深入研究并揭示其促进生长性能、降低腹泻发生率、调控肠道菌群

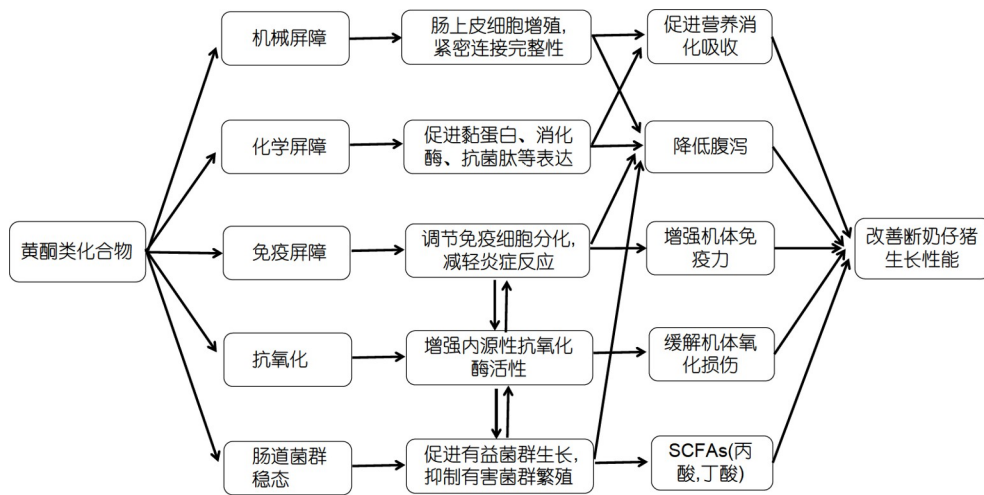


图 3 黄酮类化合物调控肠黏膜屏障功能促进断奶仔猪生长性能

Figure 3 Flavonoids regulate the intestinal mucosal barrier function to promote the growth performance of weaned piglets

结构和改善肠黏膜屏障功能的具体分子机理; 最后, 在探究黄酮类化合物各种功效的同时需要特别关注其安全性, 必须对可能存在的毒副作用进一步深入研究, 避免因过量或者不恰当摄入而影响营养物质的吸收代谢和干扰体内激素合成, 进而对动物生长发育带来不良影响。

综上, 黄酮类化合物作为抗生素替代品在饲料添

加剂市场具有广阔的应用潜力。为促进其在生猪健康养殖中的推广应用, 需要在进一步丰富和加强对天然植物源黄酮类化合物的开发 and 安全性分析的基础上, 深入探究其在动物胃肠道消化吸收代谢规律及与肠道微生物之间相互作用促进肠道健康的分子机理, 逐步规范并建立应用标准, 从而为更加精准地开发黄酮类化合物用于饲用减抗、替抗产品奠定理论和实践基础。

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Current advances on the regulation of intestinal mucosal barrier function in weaned piglets by flavonoids

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Flavonoids are dietary non-nutrient bioactives that are widely found in various plants and possess antioxidant, antibacterial and anti-inflammatory properties. The intestinal mucosal damage caused by weaning stress is a critical factor restricting the growth performance of piglets. As one of the pollution-free, residue-free, low-resistance alternative to antibiotics, flavonoids have extensive application value in improving the growth performance of piglets and protecting intestinal mucosal barrier. Combined with the relevant studies of our group on the renewal of intestinal epithelial cells in weaned piglets, we attempt to sum up recent studies that the pharmacological effects and molecular mechanism of flavonoids in protecting intestinal epithelial cells, repairing damaged intestinal mucosal barriers, and regulating intestinal microbiota homeostasis in improving intestinal health of early weaned piglets. This review could provide valuable theoretical basis and practical evidence for the development and application of various natural plant-derived flavonoids as feed additives to improve intestinal function in weaned piglets.

flavonoids, weaned piglets, intestinal epithelial cells, intestinal mucosal barrier, intestinal microbiota

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