



# 奶牛乳腺炎的发病机理及中药治疗效应研究进展

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**摘要:** 奶牛乳腺炎是由病原微生物感染引发的乳腺组织炎症反应,严重影响奶牛生产性能和乳制品安全,给畜牧业带来重大经济损失,因此深入阐明其发病机制对预防和治疗具有重要意义。传统观点认为乳腺炎主要由外源细菌感染或物理损伤引起;最新研究发现,胃肠道微生物及其代谢产物可通过“肠-乳轴”对乳腺健康产生系统性影响,这为理解乳腺炎的发病机制提供了新视角。本文在前期研究基础上,系统综述了奶牛乳腺炎的发病机制,并指出传统抗生素治疗因耐药性加剧及乳腺菌群失调问题面临严峻挑战。与此同时,中草药凭借多组分、多靶点协同作用以及肠-乳轴调节功能,在乳腺炎防治中显示出独特优势,已成为当前研究热点。本文从病原微生物感染引发的炎症级联反应与免疫调控机制入手,重点探讨中草药通过作用于病原体、炎症反应及免疫系统等多途径治疗乳腺炎的效应机制,以期奶牛乳腺炎的绿色防控提供新思路。

**关键词:** 奶牛乳腺炎;胃肠道菌群;肠-乳轴;中草药;代谢产物;免疫调控

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## Research Progress on the Pathogenesis of Cow Mastitis and Treatment Mechanism of Traditional Chinese Medicine

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**Abstract:** Bovine mastitis is an inflammatory response of the mammary tissue triggered by pathogenic microorganism infections, which severely impairs dairy production performance and compromises milk product safety, leading to substantial economic losses in the livestock industry. Consequently, elucidating its pathogenesis is of critical importance for prevention and treatment strategies. Conventionally, mastitis has been attributed primarily to exogenous bacterial infections or physical trauma; however, recent studies reveal that gastrointestinal microbiota and their metabolites can

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systemically influence mammary health via the "gut-mammary axis," offering novel insights into the disease's mechanistic underpinnings. Building on prior research, this review systematically summarizes the pathogenesis of bovine mastitis and highlights the escalating challenges posed by traditional antibiotic therapies due to rising antimicrobial resistance and disruption of mammary microbiota. In parallel, herbal medicines have emerged as a promising research focus, exhibiting distinctive advantages in mastitis prevention and treatment owing to their multi-component, multi-target synergistic actions and regulatory effects on the gut-mammary axis. Starting from the inflammatory cascade and immune regulation mechanisms initiated by pathogenic infections, this article focuses on the multi-pathway mechanisms through which herbal medicines exert therapeutic effects—by targeting pathogens, modulating inflammatory responses, and regulating immune functions—thereby offering innovative perspectives for the green prevention and control of bovine mastitis.

**Keywords:** cow mastitis; gastrointestinal flora; gut-mammary axis; traditional Chinese medicine; metabolite; immune regulation

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奶牛乳腺炎是影响世界奶业发展的主要疾病之一<sup>[1]</sup>,不仅导致奶牛的产奶量和乳品质下降,还可能引起乳腺组织永久性损伤,增加治疗成本甚至造成淘汰,严重危害奶牛健康和生产性能,给奶牛养殖带来巨大经济损失。该病病因复杂,全球平均临床发病率可达30.49%,经济损失占比21%<sup>[2]</sup>。据统计,全球每年因乳腺炎造成的经济损失高达350亿美元<sup>[3]</sup>,其中我国养殖场每头奶牛的年治疗成本为29~135美元<sup>[4]</sup>。值得注意的是,当前临床治疗过度依赖抗生素,导致耐药菌检出率持续攀升。国内研究显示,乳腺炎奶牛乳汁中分离出的大肠杆菌,超过70%对多种抗生素耐药<sup>[5]</sup>,严重威胁食品安全与公共卫生。因此,开发新型防治策略已成为保障奶业健康发展和乳品安全的迫切需求。

近年来,中药复方因其多组分协同作用、不易产生耐药性及良好的代谢调控能力<sup>[6]</sup>,成为奶牛乳腺炎防治的研究热点。例如由蒲公英、王不留行、黄芩、当归等组成的中药复方对临床奶牛乳腺炎治愈率达70%<sup>[7]</sup>;由黄连、金银花和连翘等配伍的复方制剂能有效降低乳腺炎的发生<sup>[8]</sup>。然而,尽管这些复方在临床上表现出清热解毒、活血通乳等功效,其具体作用靶点及分子机制尚不完全明确,有待深入解析。

本文系统综述了奶牛乳腺炎的发病机制并重点探讨中草药通过调节胃肠道微生物和免疫屏障功能缓解和治疗奶牛乳腺炎的研究进展,以期为该病的防治提供新的思路和理论依据,推动中草药在

奶牛养殖业中的应用,为保障乳制品安全和提高养殖经济效益提供科技支撑。

## 1 诱发奶牛乳腺炎的外源性途径

外源性乳腺炎主要由外部环境中的病原微生物引起,这些微生物可通过奶牛的皮肤、乳头或污染设备进入乳腺。常见的外源性病原体包括大肠杆菌、金黄色葡萄球菌、链球菌等<sup>[9]</sup>。这类感染往往与奶牛的饲养管理和卫生条件密切相关,尤其是在拥挤或卫生不佳的养殖环境中更易发生<sup>[10]</sup>。

### 1.1 诱发外源性乳腺炎的因素

外源细菌感染是引起乳腺炎的主要因素之一。根据感染来源,外源性乳腺炎可分为环境性和传染性两类。环境性乳腺炎由环境中的机会性病原菌引起<sup>[11]</sup>,通过污染的水源、垫料或挤奶设备等多种途径传播,也可经粪便、尿液和其他污染物扩散<sup>[12]</sup>。其症状通常表现为急性感染,如高热、乳腺红肿等,但病程短,较少形成慢性感染。粪便是环境病原体的主要来源<sup>[13]</sup>,而金黄色葡萄球菌和链球菌是最常见且传染性较强的病原体<sup>[14]</sup>。传染性乳腺炎则由其他感染部位的病原微生物传播引起的,其主要宿主包括胃肠道和生殖道等<sup>[15]</sup>。病原体在挤奶过程中通过感染乳汁传播至健康乳腺,逐渐侵入乳导管。传染性乳腺炎易转为慢性或亚临床感染,生物膜的形成增加了抗生素治疗的难度,复发率较高。此外,环境条件和管理因素也显著影响外源性乳腺炎的发生。不良的牛舍卫生、粪便和尿液积聚等<sup>[4]</sup>

均可增加发病风险。气候、季节和温度变化同样与发病率相关<sup>[16]</sup>。饲养管理不当,如营养不均衡、饲料质量差、饮水不足等可能导致奶牛免疫力下降,从而增加感染机会;挤奶操作不当、挤奶设备清洁不干净或消毒不彻底等也是外源性乳腺炎发生的重要原因<sup>[17]</sup>。

## 1.2 宿主对病原的免疫防御机制

外源性乳腺炎表现为乳腺组织的物理、化学和细菌学变化<sup>[18]</sup>。当病原体入侵乳腺后,局部免疫反应被激活,引起炎症反应。当机体的防御功能减弱时,感染容易发生<sup>[19]</sup>。

乳腺上皮细胞是抵御外界细菌入侵的第一道防线,在感染早期发挥关键保护作用<sup>[20]</sup>。乳腺上皮细胞能够检测到腺泡中活跃的细菌:它们通过模式识别受体(pattern recognition receptors, PRRs),尤其是 toll 样受体(toll-like receptors, TLRs),识别细菌释放的病原相关分子模式(pathogen-associated molecular patterns, PAMPs),进而释放 IL-6、TNF- $\alpha$  等促炎因子,招募中性粒细胞和巨噬细胞,启动炎症反应<sup>[1]</sup>。Wang 等<sup>[22]</sup>发现挤奶过程中的负压可激活乳腺上皮细胞机械敏感通道,引起钙离子外流和炎症因子释放,从而诱发乳腺炎症。这种机械性损伤加速乳腺屏障破坏,为病原微生物的侵入创造了条件。乳腺上皮细胞还可与上皮内白细胞的相互作用精细调控多酶复合体(multi-enzyme complex, MECs)反应,分泌多种促炎蛋白参与细菌防御<sup>[23]</sup>。乳腺上皮细胞之间的紧密连接是血乳屏障的核心组成,感染中期,该结构受损,细胞间间隙变大<sup>[24]</sup>,病原体穿透乳导管的物理屏障,进入乳池,引发乳汁中的免疫细胞反应,从而加剧炎症。

乳汁中的白细胞构成第二道防线<sup>[25]</sup>。中性粒细胞是炎症反应最活跃的免疫细胞,作为组织损伤和炎症部位的主要病原体清除者<sup>[26]</sup>,通过中性粒细胞胞外陷阱(neutrophil extracellular traps, NETs)捕获和杀死病原体<sup>[27]</sup>,直接参与乳房对微生物的防御。与中性粒细胞一样,巨噬细胞和淋巴细胞同样发挥重要作用,在感染过程中吞噬和清除细菌。淋巴细胞产生免疫球蛋白和淋巴因子,其中免疫球蛋白作为生物调理素增强吞噬细胞功能,淋巴因子则促进白细胞浸润并激活其杀菌特性<sup>[28]</sup>。

此外,特异性细胞和体液免疫也参与防御。活化的 T 细胞和 B 细胞分泌多种细胞因子,如白细胞介素(interleukin, IL)、TNF- $\alpha$ <sup>[29]</sup>和类二十烷酸<sup>[30]</sup>

等,这些因子的差异表达导致炎症过程异质性,临床表现从无明显异常到产奶量下降、乳汁成分改变、乳腺红肿、硬化、敏感、疼痛、瘙痒,甚至全身性症状<sup>[31]</sup>。在乳腺炎症中,适应性 T 细胞被激活,分泌 IL-17,促进乳腺纤维化和炎症细胞的迁移,加重病情。研究还发现<sup>[32]</sup>,乳腺上皮细胞分泌的黏液 IgA 在炎症中显著减少,可能与病原体持续定植和炎症反应有关。

## 1.3 诱发外源性乳腺炎的关键信号通路

多条信号通路参与乳腺炎症反应,包括 PI3K/AKT<sup>[33]</sup>、p38/MAPK<sup>[33-35]</sup>、IKK/NF- $\kappa$ B<sup>[26,33-37]</sup>、TLR4<sup>[35-36,38]</sup>和 JAK-STAT<sup>[39]</sup>等。LPS(lipopolysaccharides, LPS)作为革兰阴性菌细胞壁表面的主要致病因子<sup>[40]</sup>,被细胞表面的 TLR4 识别后,激活 NF- $\kappa$ B 信号通路、MAPK 信号通路和 AKT 通路<sup>[33]</sup>,进而诱导 IL-6、IL-1 $\beta$ 和 TNF- $\alpha$ 等促炎因子表达(图 1)。正常情况下,细胞质中核因子  $\kappa$ B(nuclear factor kappa-B, NF- $\kappa$ B)与其抑制蛋白 I $\kappa$ B 结合处于失活状态<sup>[41]</sup>。免疫反应启动后,受体信号激活 IKK 激酶使 I $\kappa$ B 磷酸化,NF- $\kappa$ B 亚基 p65 与之解离并转入核内<sup>[42]</sup>,调节炎症基因表达<sup>[43]</sup>,促进 IL-6、IL-1 $\beta$ 、TNF- $\alpha$ 、iNOS、髓过氧化物酶(myeloperoxidase, MPO)等炎症介质产生<sup>[40]</sup>。

丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)激活后参与细胞表面至核内的信号转导,通过磷酸化转录因子、细胞骨架蛋白、激酶等影响基因表达、代谢、细胞分裂、形态和存活<sup>[44]</sup>。在奶牛乳腺炎中,三大 MAPK 家族——细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)、p38 MAPK 和应激活化蛋白激酶(c-Jun N-terminal kinase, JNK)发挥重要作用<sup>[40]</sup>。磷酸化 MAPK 激活转录因子激活蛋白-1(activating protein 1, AP-1),并参与 PI3K/Akt 通路的调控<sup>[45]</sup>。研究表明,JNK 和 p38 MAPK 通路主要响应细胞应激和凋亡,而 ERK/MAPK 通路细胞增殖和分化密切相关,在细胞信号转导网络中起关键作用<sup>[46]</sup>。JAK-STAT 通路受 IFN、LTA 或生长因子的调控<sup>[1]</sup>。革兰阳性菌的细胞壁成分被 TLR2 受体识别后,主要通过 MyD88 信号通路激活 NF- $\kappa$ B 通路和 MAPK 通路。先天免疫系统通过模式识别受体(PRRs),特别是 toll 样受体识别病原体配体后,激活 JAK,导致 STATs 被受体酪氨酸磷酸化,STAT 二聚体入核调节转录,介导促炎细胞因子产生<sup>[39]</sup>,引起炎症反应。

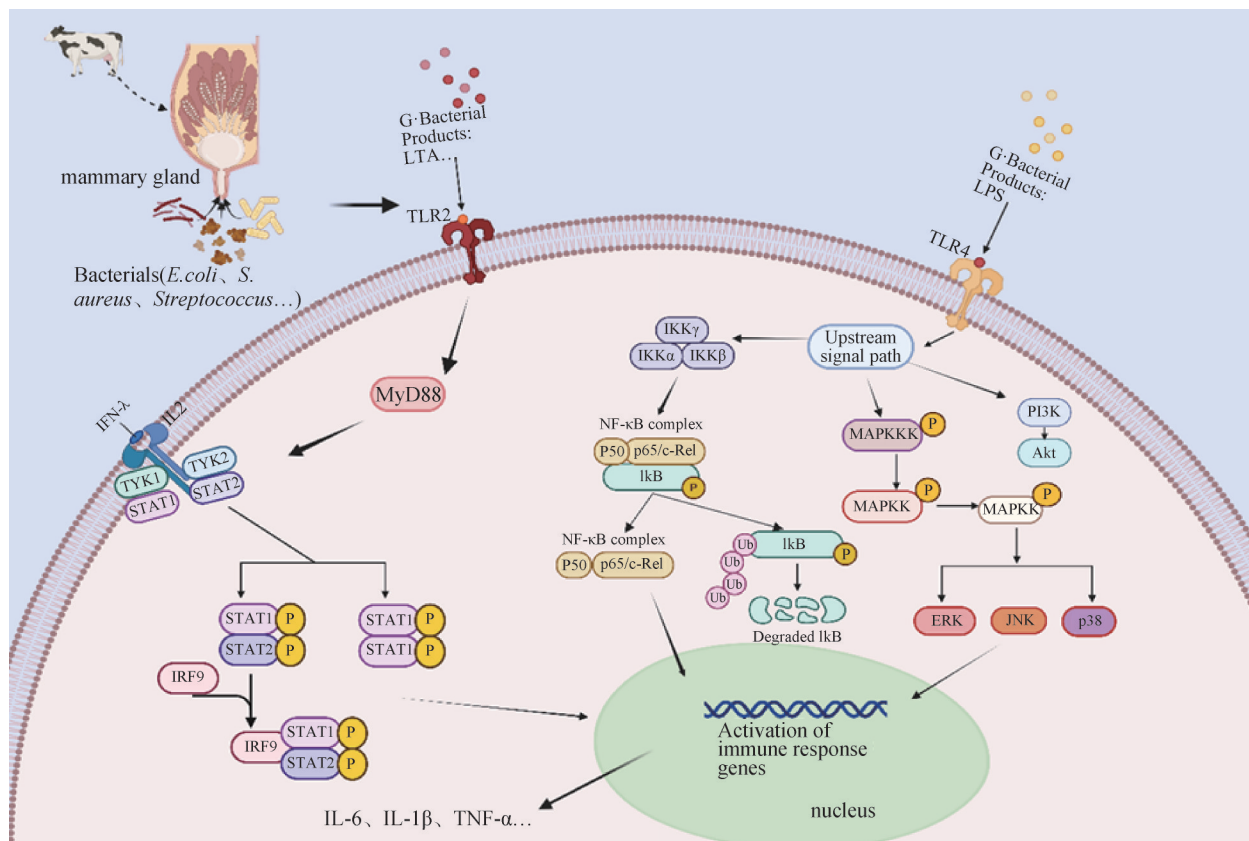


图1 奶牛乳腺炎多条信号通路

Fig. 1 Multiple signaling pathways of cow mastitis

#### 1.4 肠道菌群紊乱与外源性乳腺炎的互动机制

近年来的研究发现,肠道微生物稳态的破坏可能通过“肠-乳轴”间接促进外源性病原体入侵乳腺。肠道菌群失调导致宿主全身免疫防御降低,短链脂肪酸(short-chain fatty acids, SCFAs)合成减少,免疫细胞活性降低<sup>[47]</sup>,肠道屏障受损,使得肠道病原菌产生的LPS进入血液循环,引发全身慢性炎症<sup>[48]</sup>,使外界病原菌更易突破乳头导管屏障并在乳腺组织定植。同时,部分外源性乳腺炎病原菌可能具备肠道和乳腺的双重定植能力。肠道屏障受损时,内源菌群可通过血液循环或淋巴系统迁移至乳腺。临床研究发现,乳腺炎奶牛乳汁中分离的肠杆菌菌株与肠道菌株基因型高度相似<sup>[49]</sup>;同时热应激、高精料饲喂<sup>[50]</sup>等环境应激不仅直接增加病原体接触风险,还可通过破坏肠道菌群结构、加剧肠漏和氧化应激,协同削弱乳腺上皮修复能力,形成“肠道-乳腺”双重损伤,进一步促进外源性病原菌的入侵与定植,增加乳腺炎发生风险。

## 2 诱发奶牛乳腺炎的内源性途径

奶牛乳腺炎发病机制涉及病原微生物侵袭、宿主免疫失衡及乳腺微环境紊乱等多重互作。近年来研究发现,肠道菌群失调“肠-乳轴”引发调控异常,SCFAs代谢紊乱<sup>[51]</sup>及LPS迁移<sup>[58]</sup>导致乳腺组织TLR4/NF-κB等通路过度激活,形成促炎微环境,血乳屏障紧密连接蛋白表达下调,通透性异常,炎症因子跨膜扩散形成级联放大效应,最终诱发乳腺炎症。

### 2.1 肠-乳轴调控失衡

胃肠道菌群通过“肠-乳轴”对乳腺微环境产生系统性调控<sup>[52-58]</sup>。内源性乳腺炎又称为肠源性乳腺炎,其主要原因与肠道菌群紊乱密切相关。研究表明,即使在无外源病原菌感染的情况下,抗生素诱导的肠道菌群失调也可导致血乳屏障通透性增加,促进乳腺炎发生<sup>[47]</sup>。肠道菌群紊乱后,LPS经血液循环迁移至乳腺,激活乳腺免疫细胞中的TLR4/MyD88通路,触发系统性炎症反应,并通过抑制宿

主碱性磷酸酶(alkaline phosphatase, ALP)活性加重乳腺炎<sup>[59]</sup>。Ma等<sup>[52]</sup>将临床乳腺炎奶牛的粪便细菌移植到无菌小鼠成功诱发乳腺炎,证实肠道菌群在疾病发生中的关键作用。当厚壁菌门(Firmicutes)与拟杆菌门(Bacteroidetes)比例失衡时,肠道菌群代谢模式发生改变,LPS及促炎因子经门静脉循环进入体循环,并优先富集于乳腺组织,破坏血乳屏障,诱发奶牛乳腺炎症<sup>[59]</sup>。动物试验表明<sup>[52]</sup>,高F/B值小鼠乳腺中TLR4/NF- $\kappa$ B信号通路显著激活,促炎因子IL-6、TNF- $\alpha$ 表达量增加,而益生菌干预可逆转这一过程。乳酸杆菌属(*Lactobacillus*)丰度下降与乳腺导管上皮紧密连接破坏呈正相关,提示特定菌株可能具有直接保护效应。研究还证实<sup>[52]</sup>,移植乳腺炎奶牛粪便菌群的小鼠肠道菌群失调后,乳腺促炎细胞因子水平显著升高,表明肠道与乳腺免疫细胞存在直接交互。

## 2.2 肠道菌群代谢产物介导的免疫反应

肠道菌群的代谢产物可能对炎症性疾病的发病机制有深远的影响。短链脂肪酸(SCFAs)、次级胆汁酸和色氨酸代谢物等通过特异性分子机制调控乳腺免疫微环境。色氨酸经肠道菌群代谢为犬尿氨酸,激活吲哚胺2,3-双加氧酶(indoleamine 2,3-dioxygenase, IDO),通过芳香烃受体(aryl hydrocarbon receptor, AHR),调控乳腺T细胞分化,抑制过度免疫反应,AHR信号受损会加剧乳腺炎<sup>[60]</sup>。次级胆汁酸通过法尼醇X受体(farnesoid X receptor, FXR)调控乳腺巨噬细胞极化,抑制金黄色葡萄球菌诱导的乳腺炎症<sup>[61]</sup>。肠道菌群失调导致次级胆汁酸合成减少,削弱乳腺局部抗炎能力。短链脂肪酸(SCFAs)<sup>[50]</sup>、醋酸酯(C2)、丙酸酯(C3)<sup>[62]</sup>和丁酸酯(C4)<sup>[63]</sup>是肠道微生物群的发酵终产物,通过G蛋白偶联受体(GPCRs)如GPR43、GPR109a等和抑制组蛋白去乙酰化酶(HDAC)活性,调控调节性T细胞(Treg)分化,抑制肠道炎症并维持内环境稳态。SCFAs可调节能量代谢,增强免疫力,抑制炎症反应,稳定肠道益生菌,通过支持肠上皮细胞保护黏膜屏障的完整性。它们还有助于恢复血乳屏障功能,降低其通透性,抑制病原体及其LPS或LTA等代谢物入侵<sup>[50]</sup>。共生菌群产生的丙酸可直接介导对沙门菌的定植抗性,并通过破坏细胞内pH稳态限制其生长<sup>[62]</sup>。丁酸通过调节巨噬细胞稳态减少细菌感染,通过抑制组蛋白去乙酰化酶(histone deacetylase, HDAC)维持Treg细胞功

能。肠道菌群紊乱会导致SCFA水平降低,Treg细胞功能受抑制,促炎反应增强,加剧乳腺炎<sup>[51]</sup>。最新研究发现,唾液酸(Sialic acid)通过富集促炎菌群、激活NLRP3炎症小体,加剧肠道菌群失调相关的乳腺炎<sup>[59]</sup>。当其代谢异常时,乳腺组织糖酵解关键酶上调,促进M1型巨噬细胞极化,释放大量的活性氧(reactive oxygen species, ROS)和促炎因子,形成促炎微环境<sup>[64]</sup>。乳腺上皮细胞过氧化物酶体增殖物激活受体- $\gamma$ (peroxisome proliferator-activated receptor- $\gamma$ , PPAR- $\gamma$ )信号抑制导致脂毒性物质累积,诱发内质网应激(endoplasmic reticulum stress, ER stress)和细胞凋亡<sup>[65]</sup>,进一步破坏乳腺屏障功能。

## 2.3 肠-乳轴屏障功能异常

肠道是机体与外界环境之间的重要屏障,能有效阻止有害物质和微生物侵入。肠道菌群通过产生有益代谢产物,如SCFAs<sup>[50]</sup>和神经递质<sup>[66]</sup>维持肠道黏膜完整性。肠道屏障与血乳屏障的结构相似,后者由上皮细胞间的紧密连接蛋白构成,通过桥粒、黏附连接和紧密连接等结构实现细胞间黏附、肌动蛋白细胞骨架的调控以及细胞内信号传导<sup>[67]</sup>。紧密连接(tight junctions, TJs)由Claudin、Occludin和连接黏附分子(JAM)等跨膜蛋白与细胞质支架蛋白(ZO-1、ZO-2和ZO-3)相互作用形成<sup>[34]</sup>。血乳屏障是乳腺组织的重要组成部分,保护乳腺免受外界有害物质和微生物侵袭<sup>[68]</sup>,并调节乳腺内环境稳态。肠道屏障功能受损时,紧密连接蛋白表达下调,导致内毒素(LPS)和活菌易位入血。研究发现,抗生素诱导的肠道菌群紊乱会破坏血乳屏障,使肠道来源的炎性细胞浸润乳腺,引发无菌性乳腺炎<sup>[69]</sup>。

肠道菌群紊乱导致肠道屏障被破坏,肠内有害菌及其代谢物从肠道迁移至乳腺、肝脏等肠外器官,引发相关免疫疾病<sup>[70]</sup>。亚急性瘤胃酸中毒(sub-acute ruminal acidosis, SARA)可导致奶牛乳腺炎:长期高精料饲喂导致瘤胃发酵异常,挥发性脂肪酸(volatile fatty acid, VFA)积累,pH降低,微生物群紊乱,最终导致SARA。SARA状态下,有害菌大量繁殖,释放LPS,损害胃肠道黏膜屏障,使其从消化道转运到血液中并迁移至乳腺<sup>[45]</sup>。血液中LPS流动可能进一步损害肝功能,乳腺中LPS水平升高会破坏血乳屏障功能,降低中性粒细胞进入血乳屏障阈值,导致大量中性粒细胞浸润乳腺,使乳汁中体

细胞数(somatic cell count, SCC)升高,引起乳腺炎的发生<sup>[71]</sup>(图2)。当LPS进入乳腺后,被乳腺上皮细胞和免疫细胞的表面模式识别受体识别。LPS结合受体后,激活NF- $\kappa$ B和MAPK信号通路,诱导乳腺炎症反应,产生大量细胞因子和急性期蛋白<sup>[59]</sup>,促进TNF- $\alpha$ 、IL-1 $\beta$ 和IL-6等促炎因子转录。LPS还会激活一系列的信号通路,改变乳腺上皮细

胞紧密连接蛋白表达,如下调Claudins表达或导致其异常分布,破坏血乳屏障完整性<sup>[35]</sup>。血乳屏障被破坏,有害分子和微生物通过内源性途径侵入乳腺组织,导致乳腺炎症。因此,内源性乳腺炎的治疗和预防需要考虑调控肠道微生态、减少LPS暴露和优化饲料配比等因素。

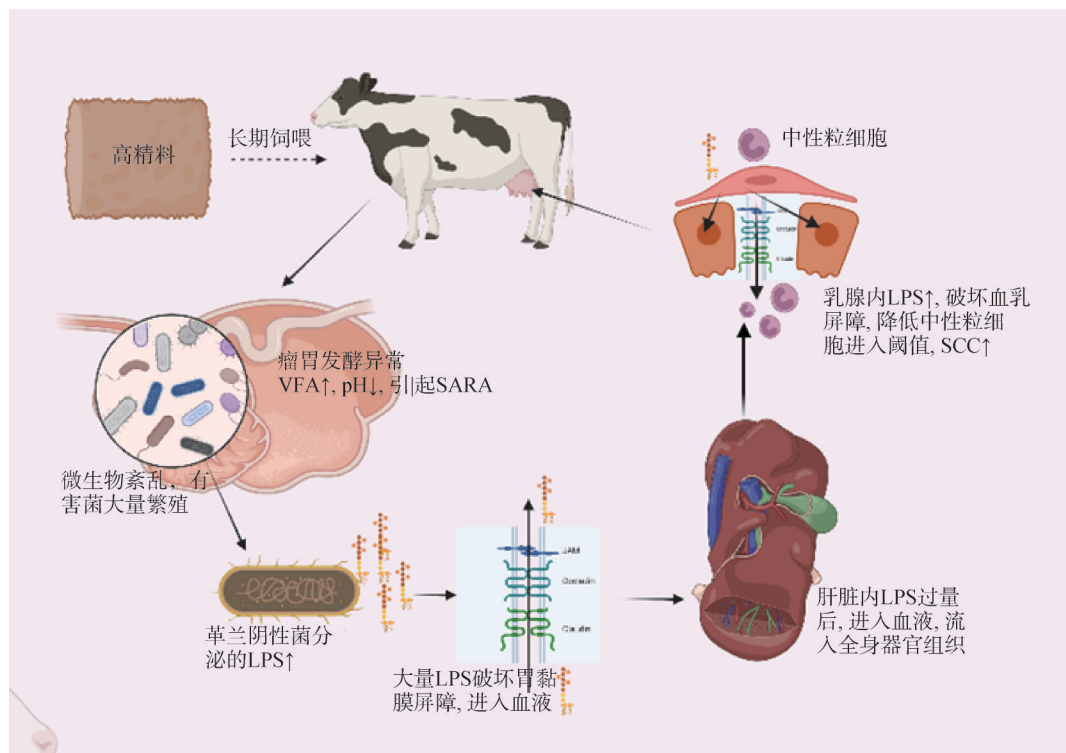


图2 肠源性乳腺炎发病机制

Fig. 2 Pathogenesis of enterogenous mastitis

### 3 中草药防治奶牛乳腺炎的效应机制

研究表明,中草药活性成分不仅通过黄酮类、生物碱等物质直接破坏病原微生物生物膜抑制毒力因子表达<sup>[73-77]</sup>,并能靶向调节TLR4/NF- $\kappa$ B等信号通路以重建乳腺免疫稳态<sup>[78-81]</sup>。中草药还可调控“肠道菌群-短链脂肪酸代谢轴”增强乳腺组织紧密连接蛋白表达,实现“肠-乳”屏障功能协同修复。此外,酚酸类成分通过Nrf2/Keap1通路抑制氧化应激,双向调节促炎/抗炎细胞因子网络进而防治乳腺炎的发生(图3)。

#### 3.1 中草药直接抗菌抑菌作用

中药具有显著的抗菌抑菌作用,可通过破坏细菌细胞壁和细胞膜抑制病原体生长繁殖<sup>[73]</sup>,其抗菌

谱广,适用于细菌性感染治疗。黄连素(小檗碱)与左氧氟沙星联用<sup>[74]</sup>可显著增强对耐甲氧西林金黄色葡萄球菌(MRSA)的抗菌活性,黄连素通过抑制*mecA*基因表达降低金黄色葡萄球菌的耐药性,左氧氟沙星抑制磷脂合成,两者协同加速破坏细菌细胞膜完整性。香叶醇具有镇痛、抗菌、抗炎、抗氧化、抗溃疡、抗真菌和杀虫等多重药理活性。研究发现<sup>[75]</sup>香叶醇对临床分离的乳腺炎病原菌,如大肠杆菌、无乳链球菌、金黄色葡萄球菌和蜡样芽孢杆菌,均表现出优异体外和体内抗菌活性,从而有效治疗乳腺炎。丹参<sup>[76]</sup>可以减少细菌定植,抑制MPO活性,减少炎症细胞浸润,保护大鼠乳腺组织免受过度炎症损伤。体外抑菌试验表明,中药复方乳腺康注射液对大肠杆菌及金黄色葡萄球菌均有明显的抑制

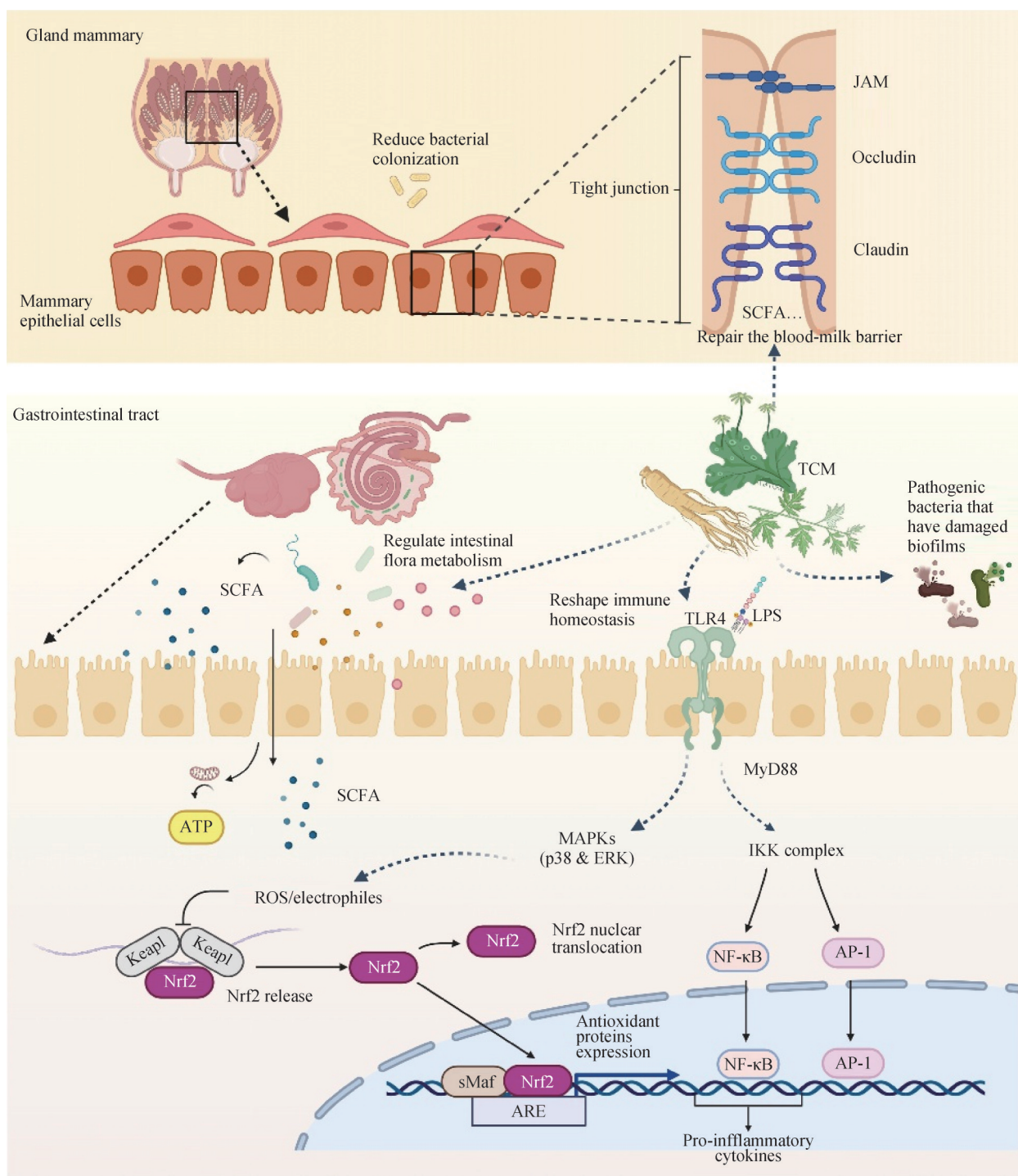


图3 中草药防治乳腺炎机制

Fig. 3 The mechanism of Chinese herbal medicine in preventing and treating mastitis

作用<sup>[77]</sup>。

### 3.2 中草药对免疫稳态的调节作用

中草药治疗乳腺炎在免疫稳态重塑中发挥多靶点调节、整体平衡及炎症控制等作用。其通过免疫调节、抗炎、改善微循环及内分泌平衡等多重效应,重塑乳腺炎免疫稳态。免疫稳态是指免疫系统

的细胞及分子在保护机体免受外来致病因素入侵和避免对自身组织的伤害之间的平衡<sup>[72]</sup>。失衡则导致乳腺炎症。中草药通过调节炎症信号通路,激活免疫细胞,调控相关免疫分子,增强抗菌能力<sup>[78]</sup>。值得注意的是,大肠杆菌和金黄色葡萄球菌感染会引发截然不同的宿主免疫反应模式,中草药复方可

能通过病原特异性的多重调节机制发挥作用。黄芪多糖通过 TLR4 受体激活 MyD88 信号通路,经 miR-21/PTEN 轴促进 M2 型巨噬细胞极化,增强对细菌的吞噬和杀伤能力,提高机体对病原体的清除能力,同时抑制过度炎症,维持免疫平衡<sup>[79]</sup>。连翘酯苷可缓解 LPS 造成的乳腺炎症损伤,降低 IL-1 $\beta$ 、IL-6、TNF- $\alpha$  和 MPO 的表达,激活 Keap1/Nrf2 信号通路,抑制细胞凋亡并促进自噬,增加 Claudin-3、Occludin 和 ZO-1 蛋白的表达,逆转 LPS 对小鼠血乳屏障的破坏<sup>[80]</sup>。中草药通过调节炎症反应、抗菌免疫、免疫微环境重建及自噬-凋亡平衡等机制,减轻乳腺炎症损伤。

### 3.3 中草药对肠-乳轴的修复机制

中草药在调节肠道菌群、促进有益菌生长、抑制有害菌繁殖以及促进 SCFAs 生成等方面作用显著,为奶牛乳腺炎的防治提供了新的思路。中草药通过多种机制恢复肠道菌群平衡<sup>[81]</sup>,与菌群相互作用调节微生态,改变菌群组成、代谢产物和中药成分转化<sup>[82]</sup>,从而保护肠道上皮和紧密连接、调节免疫和代谢过程<sup>[63]</sup>,维持宿主免疫稳态,有助于乳腺炎防治。此外,肠道菌群可以通过水解、氧化还原反应和去乙酰化<sup>[78]</sup>等方式修饰中药成分,影响药效。经方颗粒可抑制低温高湿小鼠 TLR4/NF- $\kappa$ B/NLRP3 通路,上调有益细菌丰度,并通过逆转粪便代谢物水平改善代谢紊乱,具体表现为降低脱硫弧菌属(*Desulfovibrio*)、弯曲杆菌属(*Flexispira*)、不动杆菌属(*Acinetobacter*)和支原体的丰度,增加副拟杆菌(*Parabacteroides*)和另枝菌属(*Alistipes*)的丰度,以及调节花生四烯酸、褪黑素、亚油酸、吡啶乙酸和 L-苯丙氨酸水平,缓解 LTHH 诱导的免疫紊乱和炎症反应<sup>[83]</sup>。Li 等<sup>[84]</sup>发现山茱萸酸通过下调 AKT/NF- $\kappa$ B 和 MAPK 通路及 NLRP3 炎症小体激活,减轻 LPS 诱导的炎症反应并保护血乳屏障,并通过肠道菌群促进乳腺组织屏障蛋白表达,抑制乳腺炎。广东草总黄酮能显著减轻 LPS 对小鼠乳腺组织的损伤,抑制 TNF- $\alpha$ 、IL-1 $\beta$ 、IL-6 等炎性因子分泌,从门水平到属水平调节优势菌群的相对丰度,恢复 LPS 诱导的肠道微生物生态失调,从而缓解炎症反应<sup>[85]</sup>。最新研究发现,中草药可通过调节肠道完整性和屏障功能的黏液降解菌、改善宿主代谢和炎症的 SCFA 产生菌及具有胆盐水解酶活性的细菌等相关益生菌的丰度治疗乳腺炎症,同时减少产 LPS 致病菌丰度,缓解代谢性内毒素血症

和炎症<sup>[86]</sup>。

黏膜屏障健康与乳腺炎发生密切相关,黏膜免疫屏障功能对于防止病原体侵入和维持机体健康至关重要。中草药含多糖、生物碱、黄酮类等多种活性成分,可增强乳腺上皮紧密连接,减少病原体 and 有害物质穿透,维护黏膜完整性<sup>[87]</sup>。某些成分还能促进乳腺上皮细胞增殖与修复,增强血乳屏障完整性<sup>[88]</sup>。刺芒柄花素抑制 ERK1/2 和 p38 丝裂原活化蛋白激酶(MAPK)信号通路激活,减少 TNF- $\alpha$ 、IL-1 $\beta$  和 IL-6 等促炎细胞因子释放,增加 LPS 诱导 MCF10A 细胞中抗炎因子 IL-10 表达,增强血乳屏障抗炎作用<sup>[89]</sup>。葛根素减少 ROS 和丙二醛(malondialdehyde, MDA)产生,增加 Nrf2 表达和抗氧化酶活性,降低血液和乳汁中炎症细胞因子水平,保护血乳屏障完整性,减轻奶牛氧化应激和屏障损伤<sup>[90]</sup>。藤黄酸可减轻 LPS 诱导的乳腺炎症和细胞凋亡,抑制促炎因子产生和 MPO 活性,通过抑制 MAPK 和 NF- $\kappa$ B 信号通路保护血乳屏障<sup>[91]</sup>。以上研究表明,中草药通过维持和修复肠道黏膜免疫屏障功能,提高机体免疫力,强化血乳屏障功能等多重机制,对奶牛乳腺炎治疗具有重要意义。

综上,中草药可通过调节肠道菌群结构、改变肠道菌群代谢产物、维持肠道屏障的完整性发挥治疗作用。其在减轻肠道菌群失衡,促进有益菌生长,抑制有害菌过度繁殖,促进 SCFAs 生成<sup>[66]</sup>的同时,还可维持肠道黏膜的免疫屏障功能,提高机体免疫力,防止宿主病情恶化<sup>[63]</sup>。

### 3.4 中草药对氧化应激与细胞因子的调控作用

乳腺炎常伴随氧化应激与免疫失衡。近年来研究发现,中草药在调节氧化应激、平衡细胞因子等方面具有独特优势。其通过清除自由基、调节抗氧化酶活性改善乳腺炎病理进程。氧化应激是指 ROS 与抗氧化系统失衡导致的细胞和组织损伤,与炎症反应形成恶性循环<sup>[92]</sup>。乳腺炎中,病原体感染或乳汁淤积可诱发 ROS 大量生成,激活 NF- $\kappa$ B 等炎症通路,促进 TNF- $\alpha$ 、IL-1 $\beta$  等促炎因子释放,加剧氧化损伤<sup>[93]</sup>。研究表明,乳腺炎患者乳腺组织中超氧化物歧化酶(superoxide dismutase, SOD)活性降低<sup>[94]</sup>,MDA 水平升高<sup>[95]</sup>,提示抗氧化能力下降。中药可通过多靶点干预这一过程,如蒲公英<sup>[96]</sup>和金银花<sup>[97]</sup>含黄酮类、绿原酸等成分可直接清除自由基,其成分具有强抗氧化活性,可中和 ROS,减少脂质过氧化;丹参<sup>[98]</sup>、赤芍<sup>[99]</sup>等活血化瘀类中药

可上调 SOD、谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-Px) 表达, 恢复氧化与抗氧化平衡; 白藜芦醇可通过抑制 NADPH 氧化酶减少 ROS 生成, 并下调 NF- $\kappa$ B 信号, 减弱炎症反应, 打破氧化应激与炎症的恶性循环<sup>[100]</sup>。

细胞因子是乳腺炎免疫反应的核心介质<sup>[101]</sup>, 中草药通过双向调节促炎/抗炎因子平衡, 重塑免疫稳态<sup>[102]</sup>。中草药可抑制促炎因子释放, 含蒲公英、连翘等的复方乳炎消显著降低奶牛乳腺炎模型血清中 TNF- $\alpha$  和 IL-1 $\beta$  水平, 同时促进抗炎因子表达<sup>[103]</sup>; 黄芪等补益类中药能增强 Th2 细胞活性, 促进 IL-10 分泌<sup>[104]</sup>。

#### 4 小结与展望

中草药在治疗奶牛乳腺炎的研究方面取得显著进展。本文系统阐述了中草药在调节肠道微生物群、修复肠道化学屏障、恢复肠道和乳腺机械屏障和提高免疫力方面治疗乳腺炎的潜力。肠道菌群作为特征性生物标志物, 为乳腺炎诊断和中草药调节菌群治疗研究提供新方向。

然而, 当前研究仍存在不足。多数试验限于细胞或小鼠模型阶段, 针对奶牛的实际治疗效果缺乏大规模验证; 中药复方中具体起效成分及其相互作用机制尚未完全明确; 对“肠-乳轴”双向调节机制认识较浅。未来研究应基于中草药的治疗效果与肠道微生物群的结构、组成和代谢产物关系, 建立标准动物模型。使用高通量测序、宏基因组学、宏转录组学和代谢组学等技术, 阐明不同中草药成分与菌群代谢产物的关联, 确定特定指标成分, 探讨多机制与成分间的相关性。通过网络药理学分析, 抗乳腺炎植物药活性成分的预测和提取, 探索中药复方调节乳腺炎奶牛肠道微生物群的关键靶点和机制。此外, 开发中草药与益生菌联用方案, 实现奶牛精准营养调控, 优化给药方式, 研发纳米载药、微生态制剂等新型递送系统, 以期提高疗效, 为奶牛乳腺炎绿色防控提供理论和技术支持。

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