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Hans汉斯

没食子酸在抗微生物感染中药理作用的研究进展

尹　娇，彭旭东*，张　杰，田　雪，张冉冉

青岛大学附属医院眼科，山东　青岛
Email: *doctorpxd@126.com

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摘　要

没食子酸(Gallic acid, GA)是一种低分子天然多酚类化合物，广泛存在于自然界各种植物，具有多种生物活性。在查阅国内外GA的最新文献基础上，综述了GA在抗细菌、抗真菌、抗病毒、抗寄生虫、抗炎、抗氧化以及在肿瘤、代谢、心血管、神经心理疾病等方面的药理作用研究进展，重点围绕其抗微生物作用，进行分析总结，以期为没食子酸的深入研究或开发应用提供参考。

关键词

没食子酸，抗微生物，抗菌，氧化应激，抗炎，药理作用

Pharmacological Research Progress on Antimicrobial Infection of Gallic Acid

Jiao Yin, Xudong Peng*, Jie Zhang, Xue Tian, Ranran Zhang

Department of Ophthalmology, The Affiliated Hospital of Qingdao University, Qingdao Shandong
Email: *doctorpxd@126.com

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Abstract

Gallic acid (GA) is a low-molecular natural polyphenolic compound that is widely present in various plants of nature and has a variety of biological activities. On the basis of consulting the latest domestic and foreign literature of GA, the research progress of pharmacological effects of GA in

*通讯作者。

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antibacterial, antifungal, antiviral, antiparasitic, anti-inflammatory, anti-oxidant, and tumor, metabolism, cardiovascular, neuropsychological diseases and other aspects is reviewed. Analyze and summarize the antimicrobial effect in order to provide a reference for the in-depth research or development and application of GA.

Keywords

Gallic Acid, Antimicrobial, Antibacterial, Oxidative Stress, Anti-Inflammatory, Pharmacological Action

1. 引言

没食子酸(gallic acid, GA)，化学名 3,4,5-三羟基苯甲酸，是一种淡黄色结晶化合物，广泛分布于自然界各种植物[1]，是植物界中最丰富的酚酸之一，在食品和制药工业中得到广泛应用[2]。作为一种化学结构最简单的天然多酚类化合物，没食子酸已被证明具有抗菌、抗病毒、抗肿瘤、抗炎、抗氧化等多种生物活性[3]。笔者就没食子酸的多种药理作用进行分析总结，重点围绕抗微生物感染方面，希望能为其合理开发利用提供参考和依据。

2. 抗细菌作用

2.1. 革兰氏阳性菌

2.1.1. 葡萄球菌

研究者从泰国的一种植物(*Caesalpinia mimosoides*)中分离出抗菌活性物质 GA，并证明其对金黄色葡萄球菌及表皮葡萄球菌均具有抗菌活性[4]。Anabela 等后来发现 GA 能够抑制金黄色葡萄球菌运动和粘附以及预防其生物膜形成[5]。另外，GA 亦显示出对耐甲氧西林金黄色葡萄球菌的抑制作用[6]。有研究表明[7]，GA 的这些抗菌活性很可能与邻苯三酚基团位点和羟基数有关。

2.1.2. 单核细胞增生李斯特菌

Saavedra [8]等在评估几种简单的酚类物质抗菌活性时发现，GA 对细胞增生李斯特菌的抑菌活性可能与酚类化合物使细菌氨基酸或蛋白质失活有关。亦有研究[9]发现，这种抗菌活性与 pH 值密切相关，这可能归因于酚酸影响细菌膜通透性。

2.1.3. 变形链球菌

Kang [10]等在研究口腔变形链球菌时发现了 GA 的抗菌作用(MIC = 4 mg/ml)，且 GA 可以显着抑制变形链球菌生物膜的体外形成。最近的一项研究[11]发现 GA 通过影响钙离子在细胞中的外流而影响口腔细菌定殖。Sendamangalam 等[12]证明，GA 的抗菌活性可能与其羟基和羧基的存在有关。

2.1.4. 乳酸菌

GA 可通过影响乳酸菌细胞膜通透性、酸化细胞质、引起蛋白质变性来发挥抗乳酸菌活性[13]。Campos [14]等发现多种 GA 对 *O. oeni* 乳酸菌最大生长速率的抑制作用与酚酸浓度有相关性。

2.1.5. 蜡状芽孢杆菌

当 GA 浓度为 2.5 mg/mL 时，显示出对蜡状芽孢杆菌的抗菌活性[6]，Han 等不仅证明了 GA 可抑制蜡状芽孢杆菌生物活性，并且发现富含 GA 的植物(红色剑豆皮)也同样发挥抗菌作用[15]。

2.2. 革兰氏阴性菌

2.2.1. 大肠杆菌

有实验证明[16]，GA 对大肠杆菌的 MIC 为 8 mg/mL，在 25℃和 37℃时，GA 显著影响了大肠杆菌的生长曲线，并且 GA 对细菌生长和生物膜的抑制作用均受到营养水平、温度和处理时间的影响。GA 亦显示出对一种多重耐药菌(产 ESBLs 的大肠杆菌)的抗菌活性[6]。Shao 等[16]证实，GA 不仅对革兰氏阴性菌的抗菌活性比革兰阳性细菌高，且在减少革兰氏阴性细菌形成的生物膜的质量方面显示出更高的活力。

2.2.2. 伤寒沙门氏菌

当 GA 浓度为 2.5 mg/mL 时，显示出鼠伤寒氏沙门杆菌的抗菌活性[6]。Puupponen 等[17]在研究鞣花单宁结构成分的抗微生物活性时发现，GA 强烈抑制了鼠伤寒沙门氏菌生长，并推测这可能与 GA 抑制细胞外微生物酶、剥夺微生物生长所需的底物、抑制微生物代谢氧化磷酸化等有关。另外，Ratttanata 等[9]发现天然没食子酸(nGA)和商品没食子酸(cGA)以相同的方式抑制食源性致病菌沙门氏菌的生长，这与酚酸在细菌细胞膜上的作用有关。

2.2.3. 假单胞菌

有研究[5]发现，GA 可大幅降低铜绿假单胞菌生物膜的代谢活性、减少生物膜质量。Rauha 等[18]通过孔板扩散法亦证明 GA 对铜绿假单胞菌明显的抗菌活性。Yang 等[19]从一种山茶花中鉴定出没食子酸，并验证了 GA 抑制铜绿假单胞菌 PAO1 菌株的生长及致病因子绿脓素的生成。其次，GA 亦对耐碳青霉菌的铜绿假单胞菌显示出抗菌活性[6]。Borges 等[20]证明 GA 的抗铜绿假单胞菌活性可能是由于 GA 改变细胞膜疏水性，或者在膜上形成局部破裂或孔，从而导致细胞内成分泄漏。

2.2.4. 气单胞菌

研究发现，GA 通过破坏细菌的膜完整性表现出抗气单胞菌活性，并以剂量依赖性方式引起细菌内膜的严重收缩和不规则形态[21]。

2.3. 其他

一项新的研究[22]发现，GA 对一种植物细菌病原体(*Ralstonia solanacearum*)显示出抗生物膜形成及粘附潜力。GA 还显示出对弗氏链球菌、耐多药鲍曼不动杆菌[6]、幽门螺杆菌[23]、叶缘焦枯病菌[24]、产气荚膜梭菌、副溶血性弧菌、密歇根棒状杆菌[7]、粪肠球菌、肺炎克雷伯菌[25]等的体外生长抑制作用。GA 抑制了几种不同弯曲杆菌菌株的生长(MIC 15.63~250 μg/mL)，但在易感菌株中没有观察到细胞含量的损失或形态变化，却引起钙离子流失，并推测其潜在机制为造成细胞膜通透性的损害[26]。GA 作为传统草本植物大戟素提取物之一，显示出对痤疮丙酸杆菌强大的抗菌活性[27]。

3. 抗真菌作用

3.1. 念珠菌

Pedroso [28]等在秀丽隐杆线虫－念珠菌感染模型中发现，GA 对 5 种不同的念珠菌菌株均显示出较强抗真菌活性(MIC 31.25~1000 μg/mL)，其中，其抗菌作用主要针对光滑念珠菌和克柔念珠菌，抗生物膜

活性主要针对克柔念珠菌。有体外研究表明[29]，GA 还可降低白色念珠菌对口腔上皮细胞的粘附，但是不能降低白色念珠菌毒力因子蛋白酶和磷脂酶的产生。体内实验[30]证实，用 GA 治疗全身感染白色念珠菌的小鼠 7 天后，机体组织真菌载量降低，死亡率显著降低，效果可与氟康唑相当。另外，Sony 等[31]发现，决明子瘘提取物可对氟康唑抗药性念珠菌产生抗菌活性，这可能与 GA 影响真菌细胞膜，导致细胞质含量的泄漏有关，本实验亦证明了 GA 与真菌细胞膜合成途径重要的酶羊毛甾醇 14-α 脱甲基酶(CYP51)具有结合力。

3.2. 毛癣菌

较早的一项研究显示[32]，GA 对红色毛癣菌及须毛癣菌具有抗菌活性，其 MIC 分别为 16 和 31 mg/L。后来的研究[30]发现，GA 对几种毛癣菌属的皮肤真菌株具有广泛抗菌活性(MIC 43.75~83.33 μg/mL)，其中最敏感的丝状菌是红毛癣菌，其效价与氟康唑相当，GA 通过影响麦角固醇生物合成途径中 2 种重要的酶：角鲨烯环氧酶(SE)和 CYP51，作用于真菌细胞膜，从而影响细胞生长和存活。

3.3. 镰刀菌

Nguyen 等[33]发现，GA 通过使茄形镰刀菌菌丝塌陷收缩、抑制分生孢子萌发来抑制菌丝体生长，其抗真菌活性的机制之一可能是产生几丁质酶降解真菌细胞壁的重要组成部分几丁质。Miguel 等[34]证明 GA 对孢镰刀菌和单形镰刀菌 MFC 均为 250 μg/mL。而 Shinsaku 等[35]则证明使用 Natsuaki 教授赠送的茄形镰刀菌发现 GA 对其并无抗菌活性，并推测出现不同的结果可能与菌株的差异有关。

3.4. 霉菌

研究发现[34]，来自墨西哥的塔布灌木表现出对匍枝根霉、灰霉菌的抗菌活性，而其抗菌活性归因于其中的没食子酸和类黄酮。Lam 等[36]证明，GA 及含 GA 的微胶囊均表现出对黑曲霉的抗真菌活性，且后者效果更佳。Carlos 等[37]证明 GA 对黑曲霉 MFA 为 250 μg/ml。Ana [32]等发现 GA 对烟曲霉及黑曲霉 MIC 均大于 62.5 mg/L。

3.5. 新生隐球菌

Nuchanart 等[38]发现，GA 表现出对新生隐球菌的抗真菌活性(MIC > 8000 μg/ml)，而 Gehrke 等[39]则证明从巴西南部的一种植物分离的 GA 对新生隐球菌 MIC 为 100 μg/ml。

4. 抗病毒作用

4.1. 肝炎病毒

研究发现[40]，GA 对丙型肝炎病毒(HCV)具有抗病毒活性，并以时间依赖性方式下调 HCV 蛋白和 RNA 的表达。也有实验证明[41]，GA 呈剂量依赖性显著地抑制 HCV 感染 Huh-7.5 肝癌细胞细胞，主要的机制为灭活未进入细胞的病毒颗粒并阻断其与宿主细胞的结合，而对结合后的病毒进入或融合阶段几乎没有影响。但 Aoki 等[42]却发现 GA 的抗 HCV 活性在病毒进入细胞前后步骤都起作用。而先前的一项基于 Huh-7.5 肝癌细胞的研究[43]却发现浓度为 25 μM 以内的 GA 无论在抑制 HCV 进入细胞或是复制过程中，均没有检测到抗 HCV 活性。另外，有研究[44]分析 GA 的抗乙型肝炎病毒(HBV)机制与抑制病毒包膜或逆转录酶有关。

4.2. 流感病毒

GA 以剂量依赖的方式显示出对甲型流感病毒(H1N1)活性的抑制作用，并通过灭活 NA (一种关键的

病毒蛋白)抑制病毒的释放[45]。类似的研究表明[46]，GA 以浓度依赖的方式在 1~400 μM 的范围内对 A 型和 B 型流感病毒均显示抑制作用，但其仅破坏病毒颗粒，并不抑制血凝反应。亦有研究[47]验证，GA 虽然可抑制甲型流感病毒，但>400 μg/ml 的浓度下不能抑制甲型流感病毒表面蛋白血凝素，其具体机制有待深究。

4.3. 单纯疱疹病毒

Kratz 等[48]检测到 GA 的抗 HSV-1 活性，IC_{50} 值为 23.9 ± 9.4 μM，可能的机制 GA 是抑制病毒附着和渗透或破坏病毒的糖蛋白，在这之前也有研究[49]发现 GA 在较高浓度下表现出对 HSV-1 一定的抑制作用。但 Neli 等[50]却表明，GA 对 HSV-1 没有明显的抗病毒活性，并推测这可能与 GA 的化学结构及其可能的病毒蛋白靶标有关。

4.4. 人免疫缺陷病毒

最近的一项研究[51]显示，在使用 β-半乳糖苷酶测定法多酚的体外抗 HIV 活性时，发现没食子酸的有效活性(CC_{50} 962 μM, IC50 27.74 μM, SI = 34)，这与早先的关于 GA 的抗 HIV-1 活性研究[48]相似(CC_{50} 为 825 μM)。Nutan 等[52]发现从紫薇中提取的 GA 具有抗 HIV 活性，并显示逆转录酶的抑制作用。相反地，有研究[53]表示 GA 在 50 μM 浓度以内均未显示任何抗 HIV 活性。

4.5. 冠状病毒

一项关于 COVID-19 的研究[54]发现，没食子酸有希望是开发用于预防和治疗 SARS-CoV-2 和其他冠状病毒的有效抗病毒剂的起始原料。另外，GA 作为茶树接骨木提取物重要成分之一，减少了人冠状病毒感染细胞的细胞病变，具有潜在的针对 HCoV-NL63 的抗病毒活性，其抑制病毒产量的 IC50 值 71.48 μM [55]。

4.6. 埃博拉病毒

一项体外抗病毒实验显示[56]，GA 对埃博拉病毒的入侵有约 80%的抑制作用，且呈剂量响应性，并证明 GA 主要在病毒进入细胞后期阻止感染，但其具体机制尚有待探究。

4.7. 诺如病毒

GA 在 100 μM 时可对鼠诺如病毒 1 (MNV-1)和猫杯状病毒 F9 (FCV-F9)产生 50%~65%的抑制作用[42]，但是在早先的一项研究[57]却发现 GA 对这两种病毒无抑制活性。相似地，在一项关于诺如病毒的阻断实验中发现 GA 未显示出可检测的抑制活性[58]。

4.8. 其他

Andrea 等[59]从番石榴中分离纯化的 GA，在病毒感染细胞前后均显示出对登革热病毒抑制作用，并推测可能与抑制病毒复制和组装过程中必不可少的酶(α-葡萄糖苷酶)有关。GA 亦显示出轻微的抗马尔堡病毒活性[56]。GA 以 100 μg/mL 的浓度抑制了人鼻病毒 HRV2 和 HRV3 复制，主要是通过减轻 HRV 诱导的细胞病变效应(CPE)并与 HRV 颗粒直接作用[60]。另外，从金缕梅花中分离的 GA 显示出对肠道病毒 71 (EV71)强大的抗病毒活性[61]。

5. 抗寄生虫作用

5.1. 锥虫

高浓度 GA 在以前被测定出可抗布鲁氏锥虫[62]。近来的研究[63]也发现，GA 作为一种具有铁螯合

特性的酚酸，同时在基因和蛋白水平以剂量依赖性方式显示出抗布鲁氏锥虫活性(IC_{50} 14.2 ± 1.5 μM)。但是先前的一项研究[64]却证明 GA 的衍生物没食子酸酯具有很强的杀锥虫活性而 GA 本身却完全无活性，并推测这可能归因于亲脂质基团对麦角固醇作用更有效。

5.2. 利什曼原虫

GA 通过时间和剂量依赖方式控制利什曼原虫的生长，可能的机制为对利什曼原虫重要酶(Try-R 和 Try-S)发挥抑制作用和 DNA 损伤作用[65]。Deniz 等[66]证明 GA 不仅以浓度依赖性抑制利什曼原虫的生长，还可以减少被感染的巨噬细胞数量、诱导巨噬细胞能力激活以及增加溶酶体量、NO 合成和胞质钙释放。Rogério 等[64]从巴西的一种植物分离出的 GA 亦表现出良好的抗利什曼原虫活性(IC_{50} 1.7 μg/ml)，这比一项早期的研究[67]显示出 GA 更强抗原虫效力(IC_{50} > 30 μg/ml)。

5.3. 线虫

研究发现[68]，从植物分离出的 GA 具有抗盘尾丝虫活性。更早的一项研究[69]表明 GA 还对野生型秀丽隐杆线虫和秀丽隐杆线虫耐药突变体有不同程度抑制活性。GA 亦显示出对捻转血矛线虫的抑制活性，包括对其卵孵化和运动方面的抑制作用[70]。

5.4. 其他

当 GA 浓度为 300 μg/mL，显示出对三种贾第鞭毛虫滋养体菌株的抑制活性[71]。GA 对细粒棘球绦虫具有有效的杀虫作用，当浓度为 25 mg/mL 时可显示出 100%的杀卵活性[72]。

6. 其他药理作用

6.1. 抗炎

最近的一项体外研究[73]证明，GA 抑制涉及子宫肌层收缩和胎膜破裂的促炎介质的产生而发挥抗炎作用。几项研究验证，GA 可通过 NF-κB 通路下调炎症因子表达，从而缓解结肠炎[74] [75]、哮喘[76]。GA 还可通过影响 Th1，Th2 和 Th17 细胞因子的表达，从而减轻小鼠过敏性鼻炎[77]。另外，GA 的抗炎活性亦表现在其他炎症性疾病，例如肺部炎症[78]、牙周炎[79]、特应性皮炎[80]、类风湿关节炎[81]。

6.2. 抗氧化

最新的一项动物实验[82]表明，GA 可通过减少细胞活性氧的产生并提高抗氧化防御系统酶的活性，从而发挥肝保护作用。并且先前多项研究已证明 GA 可降低多个系统的氧化应激水平，发挥器官保护作用，例如心脏和脾脏[83]、脑和肝[84] [85]、肾[86]、呼吸道[87]。另外，GA 可抑制生殖系统氧化损伤，调节精子功能特性以及生殖系统有关的激素水平[88] [89]。

6.3. 抗肿瘤

GA 通过不同信号通路以及引起线粒体功能障碍抑制膀胱癌细胞增殖、迁移和侵袭，从而发挥抗肿瘤活性[90] [91]。GA 以剂量依赖性的方式抑制 HeLa 宫颈癌细胞生长，这会诱导谷胱甘肽耗竭，导致细胞死亡[92]。GA 对癌细胞的毒性作用也表现在乳腺癌[93]、急性髓细胞性白血病[94]、口腔癌[95]、鼻咽癌[96]。

6.4. 抗糖尿病

最近的研究[97]发现，GA 可降低 db/db 小鼠及果糖中毒大鼠的血糖、HbA1c 水平，增加胰岛素敏感

性，这与过去的几项大鼠体内实验[98] [99]类似。但是 Lizielle 等[100]在先前的一项体内研究中却未观察到 GA 的降血糖作用。另外，GA 可减轻 2 型糖尿病引起的大鼠肾脏损害[101]、神经变性[102]、高甘油三酸酯血症和脂肪积累[103]、DNA 氧化损伤[104]。

6.5. 心血管保护

体内实验[105]发现，GA 通过抑制内皮型一氧化氮合酶的降解来减轻血管紧张素 II 诱导的小鼠高血压和血管功能障碍。Du 等[106]发现 GA 对乌头碱引起的心律失常具有保护作用，这与其对电压门控 Na 通道的抑制作用有关。并且，GA 可以降低原发性高血压大鼠的收缩压以及心脏组织中丙二醛水平[107]，是治疗心血管疾病潜在药物。

6.6. 其他

一项新的研究[108]发现，GA 可减轻阿尔兹海默病小鼠认知障碍并改善其病理变化。GA 通过抑制组蛋白 H3K27me3 脱甲基酶活性和表达来减弱脊髓损伤后的血脊髓屏障破坏，从而发挥神经保护作用[109]。Wang 等[110]发现 GA 通过抑制 AKT/ERK 信号通路，阻止瘢痕疙瘩成纤维细胞(KFs)向伤口区域的迁移起到治疗疗瘢痕疙瘩作用。GA 可调节中风后抑郁小鼠的抑郁状态[111]。GA 以剂量依赖性方式通过刺激 Fox 蛋白 N1 表达和细胞增殖来对抗胸腺的退化[112]。

7. 总结与展望

综上所述，大量的研究已经肯定了没食子酸的抗微生物作用。首先，GA 的抗细菌作用主要依赖于其特殊的化学结构及其对细胞膜通透性的影响；其次，无论是在抑制菌体生长还是生物膜方面，GA 对革兰氏阴性菌的活性都优于革兰氏阳性细菌[16]。GA 的抗真菌作用主要集中于念珠菌属，推测它似乎对丝状真菌更有效。与抗细菌一致的是，GA 也作用于真菌细胞膜，导致胞质泄漏，但其抗真菌机制还可能涉及真菌细胞膜的合成[30]或真菌细胞壁的降解[33]，但是具体机制尚不明确。GA 发挥的抗病毒作用的时机以及是否有特定的蛋白或酶靶标还有待深究。GA 的抗寄生虫活性与其抗氧化性有密切关系，且有一部分抗寄生虫特性与免疫机制有关。因此，关于没食子酸在抗微生物感染中药理作用的机理尚需探讨。

另外，GA 还具有抗炎、抗肿瘤、抗氧化、心血管保护等生物活性，并在消化道、心血管、代谢、神经心理等多个系统发挥药理作用。作为一种天然低分子天然化合物，GA 特殊的三羟基苯酚结构在其生物学功能扮演重要的角色，并且它无论作为单体还是植物基质的组成部分，都能在不同程度上发挥其生物活性。GA 涉及广泛的信号传导通路，其抗炎和抗氧化的生物活性贯穿各大领域的预防或治疗。但是，这些药理作用目前仅局限于细胞和动物实验，GA 是否可以早期进入临床实验有待探究，同时也需要进一步探索 GA 分子水平的药理作用机制，使其更安全并有效地发挥药物最大的利用空间。

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