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# 没食子酸抗炎作用的研究进展

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## 摘　要

**没食子酸(gallic acid, GA)，又称五倍子酸，化学名3,4,5-三羟基苯甲酸，化学式$C_6H_2(OH)_3COOH$，作为我国传统中药材五倍子、石榴、掌叶大黄等的主要成分之一，是化学结构最简单的天然多酚类化合物。具有抗炎、抗氧化、抑菌、抗病毒、抗肿瘤、心血管保护等多种生物活性，并且广泛用于医药、食品等领域，具有很大的应用价值。近年来，没食子酸因其强大的抗炎作用而受到越来越多的关注。本文对没食子酸的化学性质、来源、药代动力学和毒性等特性进行阐述，着重针对没食子酸在炎症性疾病中的药理作用及相关分子机制，以期为没食子酸的深入研究和开发应用提供参考。**

## 关键词

**没食子酸，抗炎，NF-κB信号通路，丝裂原活化蛋白激酶信号通路**

# Research Progress on Anti-Inflammatory Effects of Gallic Acid

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## Abstract

**Gallic acid (GA), also known as pentaspermic acid, chemical name 3,4,5-trihydroxybenzoic acid, chemical formula $C_6H_2(OH)_3COOH$. It is one of the main components of traditional Chinese medicinal materials pentaphyllum, pomegranate, palm leaf rhubarb, etc. And it is the simplest chemical structure of natural polyphenol compounds. It has a variety of biological activities such as anti-inflammatory, anti-oxidant, bacteriostatic, anti-viral, anti-tumor, cardiovascular protection, etc.,**

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**and is widely used in medicine, food and other fields. In recent years, GA has received increasing attention for its powerful anti-inflammatory effects. In this paper, we will summarize the chemical properties, source, pharmacokinetics and toxicity of GA, focus on its pharmacological role and related molecular mechanisms in inflammatory diseases, in order to provide a reference for the in-depth research and development of GA.**

## Keywords

**Gallic Acid, Anti-Inflammatory, NF-κB Signal Path, MAPK Signal Path**

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## 1. 没食子酸的化学性质和来源

没食子酸是一种只含有一个苯环结构的有机酸，具有苯酚和羧酸的性质。它的分子式是 $C_7H_6O_5$，在苯环的 3、4、5 位有 3 个相邻羟基，在 1 位有一个羧基。没食子酸为白色或浅棕色针状晶体或粉末，熔点为 235℃~240℃，它的结构不稳定，加热到 100℃~120℃时失去结晶水，加热到 200℃以上时失去二氧化碳，其常见溶剂溶解度如下：沸水 > 丙酮 > 乙醇 > 甘油 > 水(25℃) > 乙醚 > 苯氯仿 ≈ 石油醚。

大量研究表明，没食子酸广泛存在于许多药用植物的根、茎、叶、果实、果皮、花和种子中，如叶下珠(euphorbiaceae)、苦瓜(cucurbitaceae)、茯苓(asteraceae)、薄荷(lamiaceae)和胡芦巴(malvaceae) [1] [2] [3] [4] [5]。然而，从这些药用植物中分离出的没食子酸含量差别很大，介于 0.001 至 135.08 毫克/克之间。在所有草本植物中，叶下珠中没食子酸的含量最高，其次是苦瓜和阿希勒草，这为大量萃取富集没食子酸提供了可靠有效的参考[6]。

## 2. 没食子酸的药代动力学

研究药物在体内的代谢动力学过程，有助于我们了解药物在体内的吸收、分布、代谢和排泄过程。Yu 等人在 SD 大鼠上对没食子酸的药代动力学性质进行全面检测，他们发现没食子酸达到峰值浓度的平均时间为 1.5 h、最大血药浓度为 0.83 μg/mL、终末消除半衰期为 2.56 h、血药浓度时间曲线为 0.137 mg/min/mL、平均停留时间为 2.67 h、清除率为 0.37 L/min/kg 和容积分布为 78.52 L/kg [7]。有研究结果表明，没食子酸在大鼠组织中分布迅速且普遍，在肾脏中分布最高，其次是心脏、肝脏、脾脏和肺[8]。然而，Liu 等人发现没食子酸在大鼠体内主要分布在肾脏和肝脏，而不是其他器官[1]。这两项研究共同揭示了肾脏可能是没食子酸的主要代谢器官。研究总结，没食子酸首先被肠粘膜吸收，然后主要分布在肾脏，分别由肝脏代谢和肾脏排泄[9]。值得注意的是，甲基化、糖苷酸化和硫酸化产物是体内没食子酸的主要形式。

## 3. 没食子酸的毒性

研究结果表明，浓度不超过 200 μM 时没食子酸对 hepg2 细胞无细胞毒性作用，浓度大于 200 μM 时对 B16F10 细胞和 RAW264.7 细胞有轻度细胞毒作用[10]。Haute 等人发现，1000 μM 没食子酸对中性粒细胞的细胞活性没有影响[11]。整体上看，没食子酸的体内毒性也相对较弱。体内实验表明，210 mg/kg 剂量的没食子酸对 BALB/c 小鼠也无毒性作用[12]。另外，一项为期 28 天、剂量为 900 mg/kg 的亚急性毒性研究显示，没食子酸没有改变小鼠的行为、形态学和组织病理学参数[13]。这些结果表明，中低浓度的没食子酸在细胞和动物模型中是安全有效的，而在较高的浓度时具有毒性。

## 4. 没食子酸在炎症性疾病的药理活性

### 4.1. 类风湿性关节炎

类风湿性关节炎(Rheumatoid arthritis, RA)是一种以滑膜异常增生和炎性细胞浸润滑膜为特征的炎症性疾病，可引起关节炎症和破坏。滑膜是类风湿性关节炎的主要病理部位，成纤维细胞样滑膜细胞(Fibroblast-like synovial cells, FLS)在类风湿性关节炎滑膜炎和关节破坏的发生和持续中起着关键作用[14]。当滑膜开始发生炎症反应时，FLS 开始增殖，激活的炎症细胞产生各种促炎介质，包括细胞因子如 IL-1$\beta$、IL-6、TNF-$\alpha$，趋化因子如 CCL-2/MCP1、CCL-7/MCP-3、基质金属蛋白酶(MMPs)和环氧化酶(COX)-2，导致滑膜炎加重和关节完整性被破坏[15]。有研究表明没食子酸治疗的浓度不会对 RA FLS 细胞活力产生不利影响，并能抑制 RA FLS 细胞中促炎介质的表达，包括促炎细胞因子 IL-1$\beta$、IL-6、TNF-$\alpha$、趋化因子 CCL-2/MCP1、CCL-7/MCP-3 和基质金属蛋白酶 MMP-9 [16]。AMP 活化蛋白激酶(AMPK)作为 AMP/ATP 的重要“能量传感器”，可以调节细胞内代谢和能量平衡[17]。激活的 AMPK 可通过增加 NAD+浓度增加依赖脱乙酰酶的沉默信息调节因子 1 (SIRT1)的表达，从而抑制 NF-κB [18] [19]的表达。有证据表明，没食子酸可以通过选择性抑制磷酸二酯酶 4 (PDE4)的活性来提高 cAMP 水平，从而有助于改善局部 RA 的炎症反应[20]。因此，我们认为没食子酸可能通过激活 cAMP 激活的 AMPK/SIRT1/NF-PDE B 信号通路。除此以外，没食子酸可通过促进凋亡蛋白 Caspase-3，Bax 和 p53 蛋白的表达而诱导凋亡，同时抑制抗凋亡蛋白 Bcl-2 和 p-AKT 蛋白的表达[21]。众所周知，RA 的发病机制在炎性细胞增殖方面与癌症细胞增殖相似，而没食子酸能有效地对抗异常增殖[22] [23]。因此，没食子酸具有良好的抗炎活性和对肿瘤恶性增殖的抑制作用，可作为 RA 治疗的候选药物。这些发现表明没食子酸可能为类风湿性关节炎的治疗提供一种新的治疗或联合保护方法。

### 4.2. 过敏性炎症

#### 4.2.1. 特应性皮炎

特应性皮炎(Atopic dermatitis, AD)是作为一种常见的过敏性皮肤病，特征是红、肿、干、厚[24]。AD 也被称为湿疹，是最常见的慢性过敏性皮肤病，在世界范围内的患病率正在增加，大约 70%的病例发生在 5 岁之前[25]。AD 的典型症状包括皮肤极度瘙痒、发炎和干燥，发炎区域可以是红色、肿胀、破裂、结垢、网状和结皮[26]。没食子酸通过调节细胞内丝裂原活化蛋白激酶和 NF-κB 通路参与炎症和过敏性疾病。通过抑制 NF-κB 和 p38MAPK 的活化，减少炎性细胞因子 TNF-$\alpha$ 和 IL-6 的表达[3]。Liu 等人在皮肤系统的研究中表明没食子酸可抑制 IL-33 诱导的 KU812 细胞中 p38MAPK、JNK 和 NF-κB 的表达，从而减少细胞间黏附分子(ICAM-1)、趋化因子和炎症因子的释放[27]。这提示没食子酸能有效缓解特应性皮炎症状，且作用机制与调节丝裂原活化蛋白激酶和 NF-κB 通路有关。

#### 4.2.2. 过敏性鼻炎

过敏性鼻炎是最常见的过敏性疾病之一，是鼻气道的过敏性炎症。过敏性鼻炎(Allergic rhinitis, AR)的特征是鼻塞、鼻漏、打喷嚏和瘙痒。过敏性鼻炎患者呈现一种炎症 IgE 介导的反应，其特征是过敏原 2 型辅助 T 细胞(T helper 2 cell, Th2)免疫模式，肥大细胞和嗜酸性粒细胞激活和释放炎症介质以应对过敏原的暴露[28] [29]。1 型辅助 T 细胞(Th1)/Th2 的失衡被认为是 Th17 细胞上调增加 AR 风险的重要免疫机制[30]。研究表明没食子酸可减轻鼻部变态反应症状，减轻鼻黏膜厚度，减轻鼻黏膜杯状细胞增生和嗜酸性粒细胞浸润，降低鼻腔积液中 IL-4、IL-5、IL-13、IL-17 和 ROR-$\gamma$t 水平，降低血清中 OVA (卵清蛋白)特异性 IgE 和 OVA 特异性 IgG1 水平，增加 IFN-$\gamma$ 和 IL-12 的表达。综上所述，这些结果提示没食子酸可作为变应性鼻炎的潜在治疗药物。

#### 4.2.3. 哮喘

哮喘是一种以支气管高反应性、肺炎性细胞浸润和气道重塑为特征的常见病[31]。目前，哮喘的发病机制与 Th2 细胞、2 型固有淋巴细胞(Type 2 innate lymphoid cells, ILC2s) [32]、以及 Th2 细胞和 ILC2s 释放的 Th2 相关细胞因子有关。此外，白细胞介素-33 (Interleukin-33, IL-33)可以促进 Th2 相关细胞因子的产生，增强 Th2 型免疫应答，从而导致哮喘的发生[33]。在环境刺激下，上皮细胞分泌的 IL-33 与 ST2 结合，募集髓系分化主要反应基因(MyD88)、肿瘤坏死因子受体相关因子 6 (TNF receptor associated factor 6，TRAF6)和 IL-1 受体相关激酶(IRAK) [34]。这激活了丝裂原活化蛋白激酶(MAPKK)。同时，TRAF6 激活 NF-κB，诱导 Th2 型相关细胞因子基因表达。有研究表明没食子酸能够改善卵清蛋白(Ovalbumin, OVA)诱导的哮喘小鼠的促炎细胞浸润和气道高反应性。其作用可能与 IL-33/MyD88/NF-κB 信号通路失活 IL-2，从而减轻卵泡灌洗液/IL-33 诱导的炎症细胞浸润和 2 型固有淋巴细胞的数量抑制 IL-5 和 IL-13 的释放有关[35]。这些研究均表明没食子酸有助于减轻哮喘患者的气道高反应性。

### 4.3. 溃疡性结肠炎

溃疡性结肠炎(Ulcerative colitis, UC)是一种影响结肠和直肠粘膜层的慢性复发性炎症性疾病。UC 的特征是腹痛、便血、粘膜溃疡和反复腹泻[36]。髓过氧化物酶(myeloperoxidase, MPO)是中性粒细胞浸润的标志，pandurangan 等人发现没食子酸通过抑制葡聚糖硫酸钠诱导的 UC 中 IL-6/STAT-3 和 IκB/NF-κB 信号通路降低 MPO 的表达[37]。NF-κB 通路的持续激活是 UC 的主要发病机制[38]，IκB$\alpha$ 是 NF-κB 的重要抑制剂，IκB$\alpha$ 的降解是对某些促炎细胞因子分泌的响应，IκBa 的磷酸化导致 NF-κB 信号的激活。有研究表明，没食子酸预处理降低了 I-κB$\alpha$ 的降解和 NF-κB 的核转位(P65)，而增加了 I-κB 和 NF-κB 的表达。提示没食子酸可抑制 UC 中 NF-κ 的活化[39]。且该研究评估了没食子酸对正常人肠上皮细胞(HIEC-6)和 2,4,6-三硝基苯磺酸(TNBS)诱导的 UC 小鼠模型的影响，结果表明，没食子酸可提高 IL-4、IL-10 水平，降低 IL-1$\beta$、TNF-$\alpha$、IL-6、IL-12、IL-17、IL-23、TGF-$\beta$ 的 mRNA 表达，且没食子酸能明显改善临床症状，减轻结肠炎症。除此之外，Panduran 等人提出没食子酸通过抑制 IL-6/STAT-3 和 I-κB/NF-κB 信号通路降低 UC 中髓过氧化物酶的表达[40]。没食子酸还可通过抑制 NF-κB 信号通路，降低促炎因子 COX-2 和 iNOS，从而逆转 1,2-二甲基肼诱导的 UC [41]。综上所述，没食子酸可通过 NF-κB 途径抑制炎症，对溃疡性结肠炎具有保护作用。

### 4.4. 肺炎

慢性阻塞性肺疾病(COPD)可引起肺炎，导致小气道阻塞(慢性支气管炎)和实质破坏(肺气肿) [42]。氧化应激在慢性阻塞性肺疾病的发病机制和进展中起着关键作用。来自外源和内源的过量氧化剂通过破坏脂质、蛋白质和核酸使氧化应激长存，从而导致直接或间接的肺损伤[43]。此外，氧化应激通过激活氧化还原敏感的转录因子如 NF-κB 而引发炎症反应，这些转录因子也通过上调各种促炎症因子在 COPD 的发病机制中发挥关键作用[44]。进一步的研究表明，蛋白酶包括 MMP-2 和 MMP-9 的表达也依赖于 NF-κB 的激活[45]。有趣的是，据报道，COPD 患者的 MMP-2 和 MMP-9 水平较高，并与这些患者的疾病严重程度有关[46]。Singla 等人研究证实，没食子酸通过恢复氧化还原失衡和抑制 I-κB/NF-κB 信号通路，抑制 COPD 相关的促炎因子和蛋白酶的表达，从而有效缓解小鼠慢性阻塞性肺疾病的肺部炎症和肺气肿[47]。

### 4.5. 肝损伤相关炎症

氟西汀是一种抗抑郁症药物，其副作用可引起氧化抗氧化系统的氧化损伤，导致肝组织和血清标志物的变化[48]。研究表明，活性氧类在氧化应激的起始和发育过程中起着关键作用，因此氟西汀会导致肝

损伤，引发炎症[49]。有研究表明没食子酸对氟西汀所致肝损伤导致的炎症具有保护作用[50]。没食子酸的抗炎和抗氧化作用可能与其提高肝脏超氧化物歧化酶和过氧化氢酶活性，降低肝脏 TNF-$\alpha$ 表达有关[51]。除了其强大的抗氧化作用，没食子酸还通过抑制 NF-κB 途径减少 COX-2 和 TNF-$\alpha$ 的含量[52]。在脂质负载的 HepA1-6 肝细胞和 RAW 264.7 巨噬细胞的共同培养中，没食子酸降低了 TNF-$\alpha$ 和 IL-1$\beta$ 的表达[53]。根据上述分析，在这些研究中观察到的没食子酸的潜在作用可能在预防和治疗药物性肝损伤所致的炎症及其并发症方面有效。

### 4.6. 盆腔炎

女性盆腔炎性疾病(Pelvic inflammatory disease, PID)描述了由于下生殖道的上行感染而导致的上生殖道和周围结构的炎症，细菌直接从子宫颈扩散到子宫内膜并传播到上生殖道[54]，是女性上生殖道病原体引起的最常见疾病，主要包括子宫内膜炎、输卵管炎、输卵管卵巢炎、盆腔腹膜炎及其他疾病[55]。没食子酸能显著改善子宫肿大、出血和化脓，研究表明其机制是通过抑制子宫组织 IκB/NF-κB 通路减少中性粒细胞浸润，调节细胞凋亡信号通路，且口服没食子酸，IL-1$\beta$、TNF-$\alpha$ 和 MCP-1 显著降低，而 IL-10 则以不同的方式增加[56]。

### 4.7. 其他炎症相关疾病

我们课题组针对烟曲霉菌性角膜炎，研究表明了没食子酸可以有效对抗烟曲霉菌生长，并通过增加 Nrf2/HO-1 信号通路表达来抑制促炎信号因子(如 IL-1$\beta$、TNF-$\alpha$ 等)从而发挥抗炎作用。此外，没食子酸的抗炎作用还有助于改善神经退行性疾病、甲状腺功能障碍和癌症。作为一种组蛋白乙酰转移酶抑制剂，没食子酸可以选择性地抑制阿尔茨海默病动物模型中 NF-κB 的活化，从而抵消淀粉样蛋白引起的神经毒性[57]。Liu 等人指出没食子酸可以逆转 $\alpha$-核蛋白、GFAP 和 EP-1 蛋白，从而抑制 LPS 模拟的帕金森病中 IL-1、NO 和 iNOS 水平[58]。证据显示炎症级联反应可导致甲状腺功能障碍，而 Mohamed 证明没食子酸可用于改善重铬酸钾诱导的白化大鼠的甲状腺功能障碍。其机制可能与血清游离 FT3 和 FT4 水平升高有关，而 NO、iNOS、TNF-$\alpha$、IL-6 和 COX-2 的表达下调[59]。研究也表明没食子酸可以通过抑制 IκB/NF-κB 和 PI3K/AKT 信号通路的活性，抑制胃腺癌细胞 MMP-2/9 的分泌和迁移[60]。同时，抑制 p300/CBP 介导的 p65 乙酰化和 IκB/NF-κB 信号的激活可以降低 A549 肺癌细胞炎症介质的表达。根据上述分析，没食子酸 rcía-rivera 表明没食子酸可以调节 MDA-MB231 乳腺癌细胞的 IκK/IκB/NF-κB、MAPK 和 MEK1/p90RSK/MSK 信号通路。因此，它可以降低 IL-6/8、COX2、CXCR4、XIAP 等炎症、转移下游靶基因的表达。鉴于其强大的药理特性，并且其机制可通过抑制炎症通路的总开关 NF-κB 和 MAPK 信号通路，确实可作为潜在治疗炎症相关性疾病的候选药物。

## 5. 总结与展望

如前所述，没食子酸作为一种天然植物次级代谢产物，已被证明在神经退行性疾病、代谢性疾病、关节炎、癌症和其他病理状况中发挥抗炎作用。常见的靶向抗炎药物是有效的，但它们也容易产生副作用和不良反应，如阿司匹林对肝脏和肾脏的损害和阿莫西林的胃肠道反应。然而，从我们的回顾来看，中、低剂量的没食子酸在动物实验和临床试验中几乎没有表现出毒性，因此它在与炎症性疾病的长期应用中具有潜在作用[10] [11] [12] [13]。本文主要针对其抗炎作用及药效机制进行了综述，没食子酸主要是通过经典的 NF-κB 和丝裂原活化蛋白激酶信号转导途径实现的。在抑制 NF-κB 和丝裂原活化蛋白激酶的活性后，进而抑制炎症因子(TNF-$\alpha$、IL-1$\beta$/6)、趋化因子(CCl-2、ICAM-1、TIMP-1)以及 COX-2 和 NO 等炎症介质的释放。此外，它还可以减少炎症细胞的浸润，从而改善炎症反应。从目前的研究来看，没食子酸的作用机制主要集中在上述两条信号转导途径上，但在炎症相关的疾病中是否存在更多的作用机制，

尚不明确，还需我们更进一步的探索。而我们课题组针对没食子酸在体外和体内对烟曲霉菌性角膜炎的抗真菌和抑炎作用做的研究揭示了没食子酸可以通过增加 Nrf2/HO-1 通路的表达以降低 IL-1$\beta$、TNF-$\alpha$ 等炎症因子的表达，来改善烟曲霉菌性角膜炎预后，这不仅为我们在治疗真菌性角膜炎的研究中提供了新的思路，而且为没食子酸在炎症性疾病中的抗炎机制也提供了更多可能性。

## 参考文献


[1] Wei, L., Zhu, P., Chen, X., Wang, Y. and Xu, Y. (2020) An Ultra High Performance Liquid Chromatography with Tandem Mass Spectrometry Method for Simultaneous Determination of Thirteen Components Extracted from Radix Puerariae in Rat Plasma and Tissues: Application to Pharmacokinetic and Tissue Distribution Study. *Journal of Separation Science*, **43**, 418-437. https://doi.org/10.1002/jssc.201900824

[2] Pereira, G.A., Arruda, H.S., de Morais, D.R., Peixoto Araujo, N.M. and Pastore, G.M. (2020) Mutamba (*Guazuma ulmifolia* Lam.) Fruit as a Novel Source of Dietary Fibre and Phenolic Compounds. *Food Chemistry*, **310**, Article ID: 125857. https://doi.org/10.1016/j.foodchem.2019.125857

[3] Domínguez, R., Zhang, L., Rocchetti, G., Lucini, L., Pateiro, M., Munekata, P.E.S. and Lorenzo, J.M. (2020) Elderberry (*Sambucus nigra* L.) as Potential Source of Antioxidants. Characterization, Optimization of Extraction Parameters and Bioactive Properties. *Food Chemistry*, **330**, Article ID: 127266. https://doi.org/10.1016/j.foodchem.2020.127266

[4] Vuolo, M.M., Batista, A.G., Biasoto, A.C.T., Correa, L.C., Júnior, M.R.M. and Liu, R.H. (2019) Red-Jambo Peel Extract Shows Antiproliferative Activity against HepG2 Human Hepatoma Cells. *Food Research International*, **124**, 93-100. https://doi.org/10.1016/j.foodres.2018.08.040

[5] Figueiredo, F.F., Cechinel Filho, V., Damazo, A.S., *et al.* (2020) *Sorocea guilleminiana* Gaudich.: Wound Healing Activity, Action Mechanisms, and Chemical Characterization of the Leaf Infusion. *Journal of Ethnopharmacology*, **248**, Article ID: 112307. https://doi.org/10.1016/j.jep.2019.112307

[6] Bai, J.R., Zhang, Y.S., Tang, C., *et al.* (2020) Gallic Acid: Pharmacological Activities and Molecular Mechanisms Involved in Inflammation-Related Diseases. *Biomedicine & Pharmacotherapy*, **133**, Article ID: 110985. https://doi.org/10.1016/j.biopha.2020.110985

[7] Yu, X.A., Teye Azietaku, J., Li, J., Wang, H., Zheng, F., Hao, J. and Chang, Y.X. (2018) Ardisiajaponica Simultaneous Quantification of Gallic Acid, Bergenin, Epicatechin, Epicatechin Gallate, Isoquercitrin, and Quercetin-3-Rhamnoside in Rat Plasma by LC-MS/MS Method and Its Application to Pharmacokinetics after Oral Administration of Extract. *Evidence-based Complementary and Alternative Medicine*, **2018**, Article ID: 4964291. https://doi.org/10.1155/2018/4964291

[8] Chen, X., Zhu, P., Liu, B., Wei, L. and Xu, Y. (2018) Simultaneous Determination of Fourteen Compounds of *Hedyotis diffusa* Willd Extract in Rats by UHPLC-MS/MS Method: Application to Pharmacokinetics and Tissue Distribution Study. *Journal of Pharmaceutical and Biomedical Analysis*, **159**, 490-512. https://doi.org/10.1016/j.jpba.2018.07.023

[9] Su, T.R., Lin, J.J., Tsai, C.C., Huang, T.K., Yang, Z.Y., Wu, M.O., Zheng, Y.Q., Su, C.C. and Wu, Y.J. (2013) Inhibition of Melanogenesis by Gallic Acid: Possible Involvement of the PI3K/Akt, MEK/ERK and Wnt/$\beta$-Catenin Signaling Pathways in B16F10 Cells. *International Journal of Molecular Sciences*, **14**, 20443-20458. https://doi.org/10.3390/ijms141020443

[10] Haute, G.V., Caberlon, E., Squizani, E., de Mesquita, F.C., Pedrazza, L., Martha, B.A., da Silva Melo, D.A., Cassel, E., Czepielewski, R.S., Bitencourt, S., Goettert, M.I. and de Oliveira, J.R. (2015) Gallic Acid Reduces the Effect of LPS on Apoptosis and Inhibits the Formation of Neutrophil Extracellular Traps. *Toxicology in Vitro*, **30**, 309-317. https://doi.org/10.1016/j.tiv.2015.10.005

[11] Li, Y., *et al.* (2019) Inflammatory Effect of Feiyangchangweiyan Capsule and Its Main Components on Pelvic Inflammatory Disease in Rats via the Regulation of the NF-$\kappa$B and BAX/BCL-2 Pathway. *Evidence-Based Complementary and Alternative Medicine*, **2019**, Article ID: 9585727. https://doi.org/10.1155/2019/9585727

[12] Variya, B.C., Bakrania, A.K., Madan, P. and Patel, S.S. (2019) Acute and 28-Days Repeated Dose Sub-Acute Toxicity Study of Gallic Acid in Albino Mice. *Regulatory Toxicology and Pharmacology*, **101**, 71-78. https://doi.org/10.1016/j.yrtph.2018.11.010

[13] Huber, L.C., Distler, O., Tarner, I., *et al.* (2006) Synovial Fibroblasts: Key Players in Rheumatoid Arthritis. *Rheumatology*, **45**, 669-675. https://doi.org/10.1093/rheumatology/kel065

[14] Haringman, J.J., Smeets, T.J., Reinders-Blankert, P., *et al.* (2006) Chemokine and Chemokine Receptor Expression in Paired Peripheral Blood Mononuclear Cells and Synovial Tissue of Patients with Rheumatoid Arthritis, Osteoarthritis, and Reactive Arthritis. *Annals of the Rheumatic Diseases*, **65**, 294-300. https://doi.org/10.1136/ard.2005.037176

[15] Yoon, C.-H., Chung, S.-J., Lee, S.-W., *et al*. (2012) Gallic Acid, a Natural Polyphenolic Acid, Induces Apoptosis and Inhibits Proinflammatory Gene Expressions in Rheumatoid Arthritis Fibroblast-Like Synoviocytes. *Joint Bone Spine*, **80**, 274-279. https://doi.org/10.1016/j.jbspin.2012.08.010

[16] Zhang, S., Zhong, B., Chen, M., Yang, L., Yang, G., Li, Y., Wang, H., Wang, G., Li, W., Cui, J., Hoffman, A.R. and Hu, J. (2014) Epigenetic Reprogramming Reverses the Malignant Epigenotype of the MMP/TIMP Axis Genes in Tumor Cells. *International Journal of Cancer*, **134**, 1583-1594. https://doi.org/10.1002/ijc.28487

[17] Kim, S.H., Jun, C.D., Suk, K., Choi, B.J., Lim, H., Park, S., Lee, S.H., Shin, H.Y., Kim, D.K. and Shin, T.Y. (2006) Gallic Acid Inhibits Histamine Release and Pro-Inflammatory Cytokine Production in Mast Cells. *Toxicological Sciences*, **91**, 123-131. https://doi.org/10.1093/toxsci/kfj063

[18] Baptista, B.J.A., Granato, A., Canto, F.B., Montalvao, F., Tostes, L., de Matos Guedes, H.L., Coutinho, A., Bellio, M., Vale, A.M. and Nobrega, A. (2018) TLR9 Signaling Suppresses the Canonical Plasma Cell Differentiation Program in Follicular B Cells. *Frontiers in Immunology*, **9**, Article No. 2281. https://doi.org/10.3389/fimmu.2018.02281

[19] Jiang, D.X., Zhang, M.H., Zhang, Q., Chen, Y.S., Ma, W.J., Wu, W.P., Mu, X. and Chen, W. (2014) Influence of Gallic Acid on Porcine Neutrophils Phosphodiesterase 4, IL-6, TNF-$\alpha$ and Rat Arthritis Model. *Journal of Integrative Agriculture*, **14**, 758-764. https://doi.org/10.1016/S2095-3119(14)60824-8

[20] Yoon, C.H., Chung, S.J., Lee, S.W., Park, Y.B., Lee, S.K. and Park, M.C. (2013) Gallic Acid, a Natural Polyphenolic Acid, Induces Apoptosis and Inhibits Proinflammatory Gene Expressions in Rheumatoid Arthritis Fibroblast-Like Synoviocytes. *Joint Bone Spine*, **80**, 274-279. https://doi.org/10.1016/j.jbspin.2012.08.010

[21] Liu, P., Wang, J., Wen, W., Pan, T., Chen, H., Fu, Y., Wang, F., Huang, J.H. and Xu, S. (2020) Cinnamaldehyde Suppresses NLRP3 Derived IL-1$\beta$ via Activating Succinate/HIF-1 in Rheumatoid Arthritis Rats. *International Immunopharmacology*, **84**, Article ID: 106570. https://doi.org/10.1016/j.intimp.2020.106570

[22] Cheng, W.X., Huang, H., Chen, J.H., Zhang, T.T., Zhu, G.Y., Zheng, Z.T., Lin, J.T., Hu, Y. P., Zhang, Y., Bai, X.L., Wang, Y., Xu, Z.W., Song, B., Mao, Y.Y., Yang, F. and Zhang, P. (2020) Genistein Inhibits Angiogenesis Developed during Rheumatoid Arthritis through the IL-6/JAK2/STAT3/VEGF Signaling Pathway. *Journal of Orthopaedic Translation*, **22**, 92-100. https://doi.org/10.1016/j.jot.2019.07.007

[23] Tsang, M.S., Jiao, D., Chan, B.C., Hon, K.L., Leung, P.C., Lau, C.B., Wong, E.C., Cheng, L., Chan, C.K., Lam, C.W. and Wong, C.K. (2016) Anti-Inflammatory Activities of Pentaherbs Formula, Berberine, Gallic Acid and Chlorogenic Acid in Atopic Dermatitis-Like Skin Inflammation. *Molecules*, **21**, 519. https://doi.org/10.3390/molecules21040519

[24] Williams, H.C. (2005) Clinical Practice. Atopic Dermatitis. *The New England Journal of Medicine*, **352**, 2314-2324. https://doi.org/10.1056/NEJMcp042803

[25] Asher, M.I., Montefort, S., Björkstén, B., Lai, C.K., Strachan, D.P., Weiland, S.K., Williams, H. and ISAAC Phase Three Study Group (2006) Worldwide Time Trends in the Prevalence of Symptoms of Asthma, Allergic Rhinoconjunctivitis, and Eczema in Childhood: ISAAC Phases One and Three Repeat Multicountry Cross-Sectional Surveys. *The Lancet*, **368**, 733-743. https://doi.org/10.1016/S0140-6736(06)69283-0

[26] Liu, K.Y., Hu, S., Chan, B.C., Wat, E.C., Lau, C.B., Hon, K.L., Fung, K.P., Leung, P.C., Hui, P.C., Lam, C.W. and Wong, C.K. (2013) Anti-Inflammatory and Anti-Allergic Activities of Pentaherb Formula, Moutan Cortex (Danpi) and Gallic Acid. *Molecules*, **18**, 2483-2500. https://doi.org/10.3390/molecules18032483

[27] Galli, S.J., Tsai, M. and Piliponsky, A.M. (2008) The Development of Allergic Inflammation. *Nature*, **454**, 445-454. https://doi.org/10.1038/nature07204

[28] Rivera, J. and Gilfillan, A.M. (2006) Molecular Regulation of Mast Cell Activation. *Journal of Allergy and Clinical Immunology*, **117**, 1214-1225. https://doi.org/10.1016/j.jaci.2006.04.015

[29] Fan, Y., Piao, C.H., Hyeon, E., Jung, S.Y., Eom, J.E., Shin, H.S., Song, C.H. and Chai, O.H. (2019) Gallic Acid Alleviates Nasal Inflammation via Activation of Th1 and Inhibition of Th2 and Th17 in a Mouse Model of Allergic Rhinitis. *International Immunopharmacology*, **70**, 512-519. https://doi.org/10.1016/j.intimp.2019.02.025

[30] Liu, L., Wang, L.P., He, S. and Ma, Y. (2018) Immune Homeostasis: Effects of Chinese Herbal Formulae and Herb-Derived Compounds on Allergic Asthma in Different Experimental Models. *Chinese Journal of Integrative Medicine*, **24**, 390-398. https://doi.org/10.1007/s11655-018-2836-2

[31] Halim, T.Y., Krauss, R.H., Sun, A.C. and Takei, F. (2012) Lung Natural Helper Cells Are a Critical Source of Th2 Cell-Type Cytokines in Protease Allergen-Induced Airway Inflammation. *Immunity*, **36**, 451-463. https://doi.org/10.1016/j.immuni.2011.12.020

[32] Khaitov, M.R., Gaisina, A.R., Shilovskiy, I.P., *et al*. (2018) The Role of Interleukin-33 in Pathogenesis of Bronchial Asthma. New Experimental Data. *Biochemistry*, **83**, 13-25. https://doi.org/10.1134/S0006297918010029

[33] Xu, L., Li, W., Wang, X., *et al*. (2018) The IL-33-ST2-MyD88 Axis Promotes Regulatory T Cell Proliferation in the Murine Liver. *European Journal of Immunology*, **48**, 1302-1307. https://doi.org/10.1002/eji.201747402

[34] Wang, X., Zhao, H., Ma, C., Lv, L., Feng, J. and Han, S. (2018) Gallic Acid Attenuates Allergic Airway Inflammation

via Suppressed Interleukin-33 and Group 2 Innate Lymphoid Cells in Ovalbumin-Induced Asthma in Mice. *International Forum of Allergy & Rhinology*, **8**, 1284-1290. https://doi.org/10.1002/alr.22207

[35] Wang, Y.J., Parker, C.E., Feagan, B.G., *et al*. (2016) Oral 5-Aminosalicylic Acid for Maintenance of Remission in Ulcerative Colitis. *Cochrane Database of Systematic Reviews*, No. 5, CD000544. https://doi.org/10.1002/14651858.CD000544.pub4

[36] Pandurangan, A.K., Mohebali, N., Esa, N.M., Looi, C.Y., Ismail, S. and Saadatdoust, Z. (2015) Gallic Acid Suppresses Inflammation in Dextran Sodium Sulfate-Induced Colitis in Mice: Possible Mechanisms. *International Immunopharmacology*, **28**, 1034-1043. https://doi.org/10.1016/j.intimp.2015.08.019

[37] Saber, S., Khalil, R.M., Abdo, W.S., *et al*. (2018) Olmesartan Ameliorates Chemically-Induced Ulcerative Colitis in Rats via Modulating NFκB and Nrf-2/HO-1 Signaling Crosstalk. *Toxicology and Applied Pharmacology*, **364**, 120-132. https://doi.org/10.1016/j.taap.2018.12.020

[38] Zhu, L., Gu, P.Q. and Shen, H. (2018) Gallic Acid Improved Inflammation via NF-κB Pathway in TNBS-Induced Ulcerative Colitis. *International Immunopharmacology*, **67**, 129-137. https://doi.org/10.1016/j.intimp.2018.11.049

[39] Pandurangan, A.K., Mohebali, N., Esa, N.M., *et al*. (2015) Gallic Acid Suppresses Inflammation in Dextran Sodium Sulfate-Induced Colitis in Mice: Possible Mechanisms. *International Immunopharmacology*, **28**, 1034-1043. https://doi.org/10.1016/j.intimp.2015.08.019

[40] Shree, A., Islam, J., Vafa, A., *et al*. (2020) Gallic Acid Prevents 1,2-Dimethylhydrazine Induced Colon Inflammation, Toxicity, Mucin Depletion, and Goblet Cell Disintegration. *Environmental Toxicology*, **35**, 652-664. https://doi.org/10.1002/tox.22900

[41] Vogelmeier, C.F., Criner, G.J., Martinez, F.J., Anzueto, A., Barnes, P.J., Bourbeau, J., Celli, B.R., Chen, R., Decramer, M., Fabbri, L.M., Frith, P., Halpin, D.M., Lopez Varela, M.V., Nishimura, M., Roche, N., Rodriguez-Roisin, R., Sin, D.D., Singh, D., Stockley, R., Vestbo, J., Wedzicha, J.A. and Agusti, A. (2017) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. *European Respiratory Journal*, **49**, Article ID: 1700214. https://doi.org/10.1183/13993003.00214-2017

[42] Kirkham, P.A. and Barnes, P.J. (2013) Oxidative Stress in COPD. *Chest*, **144**, 266-273. https://doi.org/10.1378/chest.12-2664

[43] Rahman, I. and Adcock, I.M. (2006) Oxidative Stress and Redox Regulation of Lung Inflammation in COPD. *European Respiratory Journal*, **28**, 219-242. https://doi.org/10.1183/09031936.06.00053805

[44] Rhee, J.-W., Lee, K.-W., Kim, D.-B., Lee, Y.-H., Jeon, O.-H., Kwon, H.-J., *et al*. (2007) NF-B-Dependent Regulation of Matrix Metalloproteinase-9 Gene Expression by Lipopolysaccharide in a Macrophage Cell Line RAW 264.7. *BMB Reports*, **40**, 88-94. https://doi.org/10.5483/BMBRep.2007.40.1.088

[45] Vernooy, J.H.J., Lindeman, J.H.N., Jacobs, J.A., Hanemaaijer, R. and Wouters, E.F.M. (2004) Increased Activity of Matrix Metalloproteinase-8 and Matrix Metalloproteinase-9 in Induced Sputum from Patients with COPD. *Chest*, **126**, 1802-1810. https://doi.org/10.1378/chest.126.6.1802

[46] Singla, E., Dharwal, V. and Naura, A.S. (2020) Gallic Acid Protects against the COPD-Linked Lung Inflammation and Emphysema in Mice. *Inflammation Research*, **69**, 423-434. https://doi.org/10.1007/s00011-020-01333-1

[47] Nabavi, S.M., Nabavi, S.F., Eslami, S. and Moghaddam, A.H. (2012) *In Vivo* Protective Effects of Quercetin against Sodium Fluoride-Induced Oxidative Stress in the Hepatic Tissue. *Food Chemistry*, **132**, 931-935. https://doi.org/10.1016/j.foodchem.2011.11.070

[48] Shanthakumari, D., Srinivasalu, S. and Subramanian, S. (2004) Effect of Fluoride Intoxication on Lipidperoxidation and Antioxidant Status in Experimental Rats. *Toxicology*, **204**, 219-228. https://doi.org/10.1016/j.tox.2004.06.058

[49] Karimi-Khouzani, O., Heidarian, E. and Amini, S.A. (2017) Anti-Inflammatory and Ameliorative Effects of Gallic Acid on Fluoxetine-Induced Oxidative Stress and Liver Damage in Rats. *Pharmacological Reports*, **69**, 830-835. https://doi.org/10.1016/j.pharep.2017.03.011

[50] Tanaka, M., Sato, A., Kishimoto, Y., Mabashi-Asazuma, H., Kondo, K. and Iida, K. (2020) Gallic Acid Inhibits Lipid Accumulation via AMPK Pathway and Suppresses Apoptosis and Macrophage-Mediated Inflammation in Hepatocytes. *Nutrients*, **12**, 1479. https://doi.org/10.3390/nu12051479

[51] Soper, D.E. (2010) Pelvic Inflammatory Disease. *Obstetrics and Gynecology*, **116**, 419-428. https://doi.org/10.1097/AOG.0b013e3181e92c54

[52] Savaris, R.F., Fuhrich, D.G., Maissiat, J., Duarte, R.V. and Ross, J. (2020) Antibiotic Therapy for Pelvic Inflammatory Disease. *Cochrane Database of Systematic Reviews*, **8**, CD010285. https://doi.org/10.1002/14651858.CD010285.pub3

[53] Li, Y., Yang, Q., Shi, Z.H., Zhou, M., Yan, L., Li, H., Xie, Y.H. and Wang, S.W. (2019) The Antiinflammatory Effect of Feiyangchangweiyan Capsule and Its Main Components on Pelvic Inflammatory Disease in Rats via the Regulation of the NF-κB and BAX/BCL-2 Pathway. *Evidence-Based Complementary and Alternative Medicine*, **2019**, Article ID: 9585727. https://doi.org/10.1155/2019/9585727

[54] Kim, M.J., Seong, A.R., Yoo, J.Y., Jin, C.H., Lee, Y.H., Kim, Y.J., Lee, J., Jun, W.J. and Yoon, H.G. (2020) Gallic Acid, a Histone Acetyltransferase Inhibitor, Suppresses $\beta$-Amyloid Neurotoxicity by Inhibiting Microglial-Mediated Neuroinflammation. *Molecular Nutrition & Food Research*, **55**, 1798-1808. https://doi.org/10.1002/mnfr.201100262

[55] Talebi, S., Karimifar, M., Heidari, Z., Mohammadi, H. and Askari, G. (2020) The Effects of Symbiotic Supplementation on Thyroid Function and Inflammation in Hypothyroid Patients: A Randomized, Double-Blind, Placebo-Controlled Trial. *Complementary Therapies in Medicine*, **48**, Article ID: 102234. https://doi.org/10.1016/j.ctim.2019.102234

[56] Mohamed, H.M. and Abd El-Twab, S.M. (2016) Gallic Acid Attenuates Chromium-Induced Thyroid Dysfunction by Modulating Antioxidant Status and Inflammatory Cytokines. *Environmental Toxicology and Pharmacology*, **48**, 225-236. https://doi.org/10.1016/j.etap.2016.08.019

[57] Ho, H.H., Chang, C.S., Ho, W.C., Liao, S.Y., Wu, C.H. and Wang, C.J. (2010) Anti-Metastasis Effects of Gallic Acid on Gastric Cancer Cells Involves Inhibition of NF-$\kappa$B Activity and Downregulation of PI3K/AKT/Small GTPase Signals. *Food and Chemical Toxicology*, **48**, 2508-2516. https://doi.org/10.1016/j.fct.2010.06.024

[58] Choi, K.C., Lee, Y.H., Jung, M.G., Kwon, S.H., Kim, M.J., Jun, W.J., Lee, J., Lee, J.M. and Yoon, H.G. (2009) Gallic Acid Suppresses Lipopolysaccharide-Induced Nuclear Factor kappaB Signaling by Preventing RelA Acetylation in A549 Lung Cancer Cells. *Molecular Cancer Research*, **7**, 2011-2021. https://doi.org/10.1158/1541-7786.MCR-09-0239

[59] García-Rivera, D., Delgado, R., Bougarne, N., Haegeman, G. and Berghe, W.V. (2011) Gallic Acid Indanone and Mangiferin Xanthone Are Strong Determinants of Immunosuppressive Anti-Tumour Effects of *Mangifera indica* L. Bark in MDAMB231 Breast Cancer Cells. *Cancer Letters*, **305**, 21-31. https://doi.org/10.1016/j.canlet.2011.02.011

[60] Baigent, C., Landray, M., Leaper, C., Altmann, P., Armitage, J., Baxter, A., Cairns, H.S., Collins, R., Foley, R.N., Frighi, V., Kourellias, K., Ratcliffe, P.J., Rogerson, M., Scoble, J.E., Tomson, C.R., Warwick, G. and Wheeler, D.C. (2004) First United Kingdom Heart and Renal Protection (UK-HARP-I) Study: Biochemical Efficacy and Safety of Simvastatin and Safety of Low-Dose Aspirin in Chronic Kidney Disease. *American Journal of Kidney Diseases*, **45**, 473-484. https://doi.org/10.1053/j.ajkd.2004.11.015