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植物类黄酮的生理功能与抗菌机制

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摘 要:类黄酮是植物产生于不同部位的一大类次生代谢小分子,在植物各器官履行多种生理功能;对人类健康有广泛的药理和有益作用,包括抗氧化活性、自由基清除能力、预防冠心病、抗动脉粥样硬化、保肝、抗炎和抗癌活性,已获得医药及保健业的高度关注;研究表明:类黄酮还能通过破坏细菌细胞膜、抑制细菌脂肪酸、粘肽层、核酸与电子传递链和 ATP 合成、抑制细菌金属酶活性等,发挥抗菌抑菌作用;在细胞水平上可阻止细菌粘附到宿主受体,抑制细菌生物膜形成,不仅选择性地针对细菌细胞,也抑制毒性因子以及其他形式的微生物威胁;一些植物类黄酮能明显逆转抗生素的抗药性,提高其药效;开发和应用类黄酮药物,对抗生素耐药感染可能是一有前途的方法。

关键词:类黄酮;生理功能;抗菌机制
中图分类号:TS201. 2 **文献标志码**:A **文章编号**:1672-058X(2021)06-0008-13

病原微生物自从起源以来,作为人类发病率和死亡率的主要原因,一直威胁人类健康。在 1930 年代人类发现青霉素与磺胺类药物前,尽管人类尝试不同种类植物提取物抗传染病产生了各种结果[1-2],但除了毒砷,这还是唯一抗传染病的方法。

过去几十年,抗生素在治疗细菌和真菌引起的传染病中发挥了重要作用,但由于它们在医学、兽医,特别是农业领域不负责任、不适当或过度被使用,导致其耐药菌株持续产生,已对人类健康构成严重威胁[3]。同时,自 1970 年代以来,开发或获得批准的抗生素锐减[4],寻找新的抗菌药物迫在眉睫。

类黄酮是一大类植物药效成分之一,具有抗氧化、抗炎、抗过敏、抗癌、抗病毒和抗真菌等特性[5],在国内外民间医学中,用于抗菌与治疗人类疾病,已被其活性成分制剂成功使用所支持。如万寿菊,含六羟黄酮阿拉伯半乳糖苷,在阿根廷民间广泛用于治疗各种传染病[6]。菅属花提取物包含甘草黄酮 C 和 Derrone,对革兰氏阳性和革兰氏阴性细菌有抗菌活性。雏菊,含有大量类黄酮如芹菜素、山柰酚、木犀草素、槲皮素及各类黄酮苷,在伊朗民间广泛用作消毒剂和治疗某些疾病[7]。

植物来源的药物临床使用悠久,到目前已试验约 100 000 种植物的药用价值[8-9],在患者中有良好的耐受和接受性,似乎是抗菌药物可靠来源之一[3]。从类黄酮成分中筛选抗菌活性成分是国内外研究的热点。

1 类黄酮化合物的结构

类黄酮化学结构由 A 和 B 两苯环通过中央三碳连接含 C6-C3-C6 框架的系列化合物。根据中央三碳是否构成 C 环及 C 环不饱和与氧化程度、B 环与 C 环连接位置等特点,类黄酮可以分成黄酮(图

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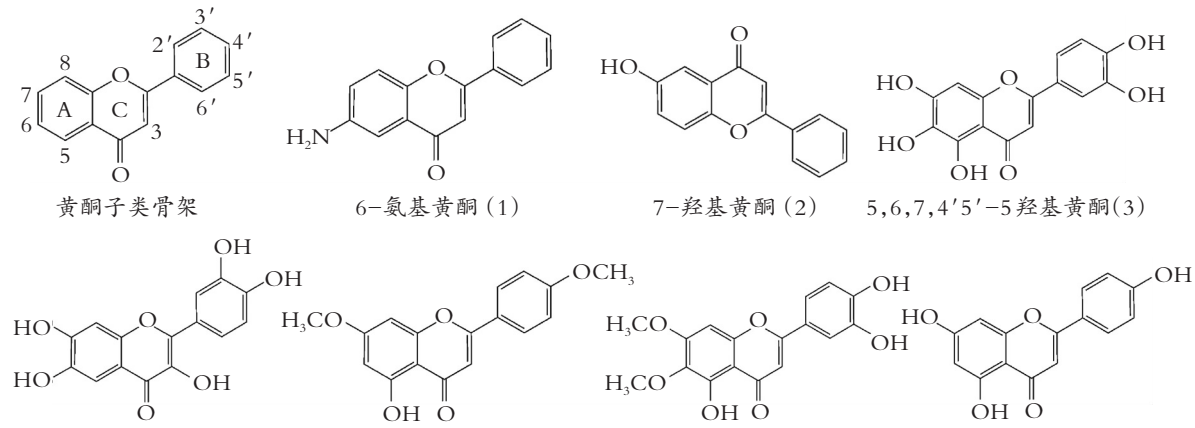
1)、异黄酮(图 2)、黄酮醇(图 3) 黄烷醇(也称为儿茶素,图 4)、黄烷酮(图 5)、黄烷酮醇(图 6)、查尔酮、二氢查耳酮(图 7)、花青素和橙酮各子类(图 8)[10]。其化学结构如下:



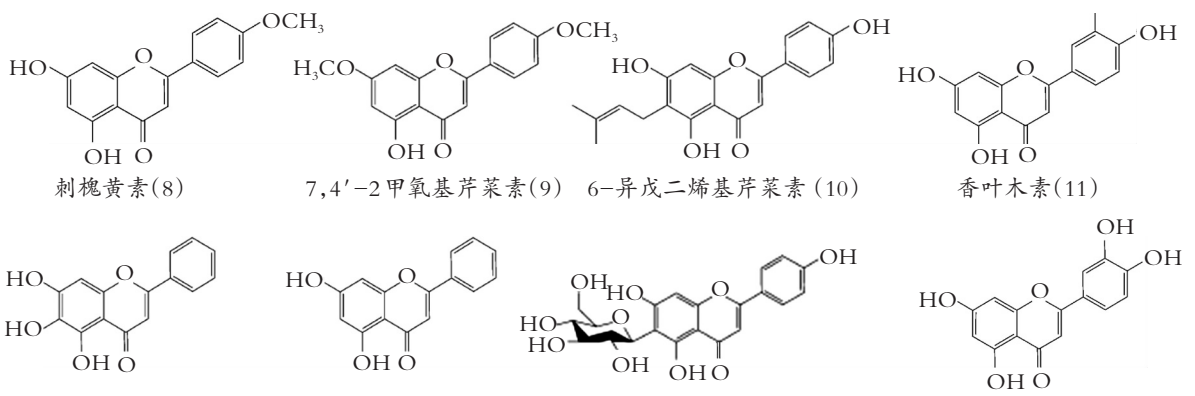


图 1　黄酮的化学结构

Fig. 1　Chemical structures of flavones

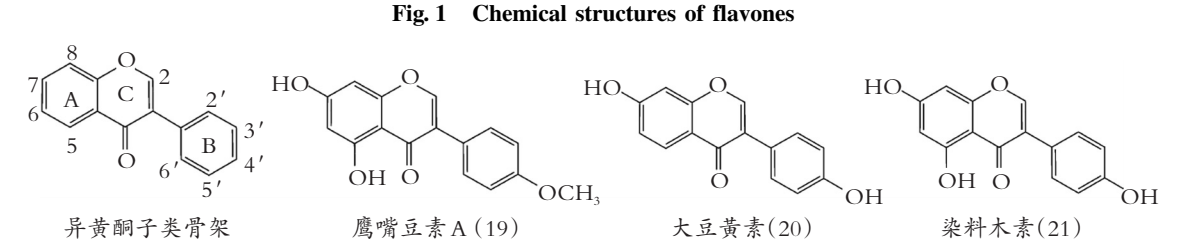
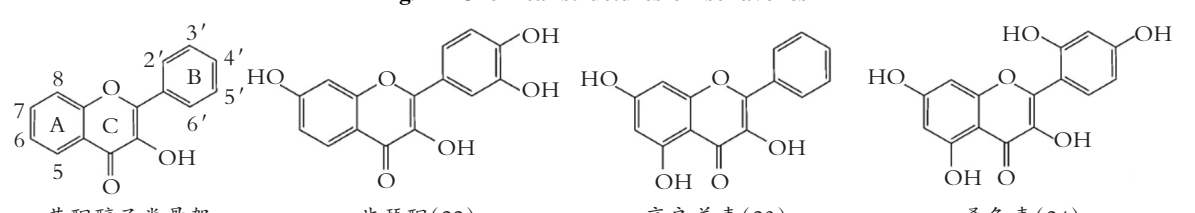
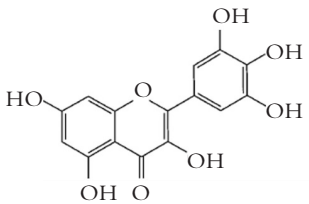
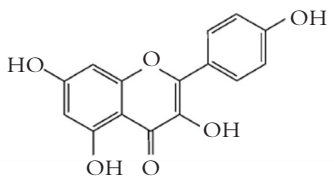


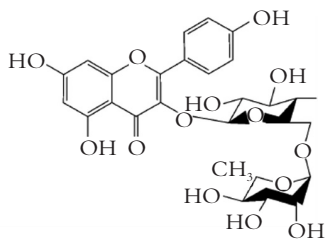
图 2 异黄酮的化学结构

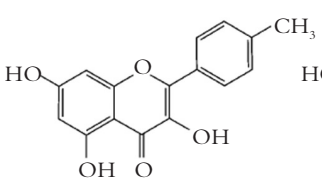
Fig. 2　Chemical structures of isoflavones

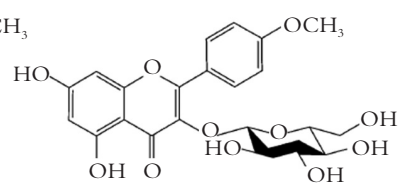


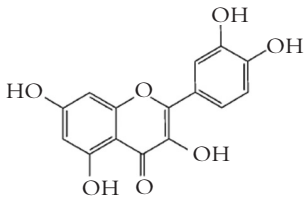

杨梅酮(25)

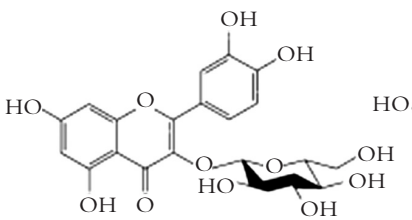

山柰酚(26)

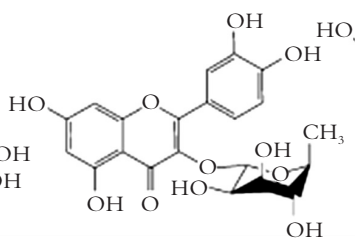

山柰酚-3-芦丁糖甙(27)

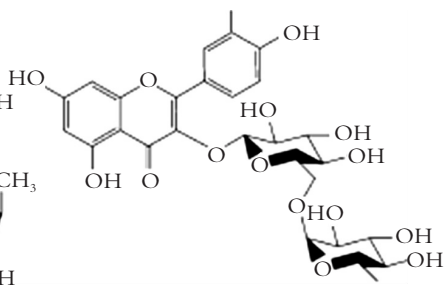

山奈素(28)

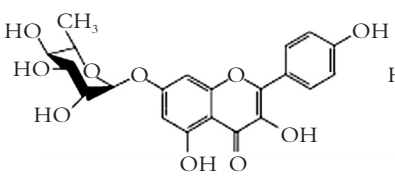

山奈素-3-葡萄糖苷(29)

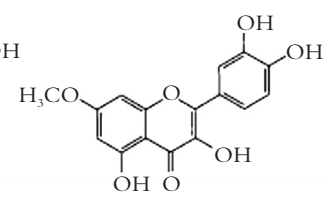

槲皮素(30)


栎皮酮-3-葡萄糖苷(31)


栎皮酮-3-鼠李糖苷(32)


芦丁(33)


栎皮酮-7-葡萄糖苷(34)


鼠李黄素(35)

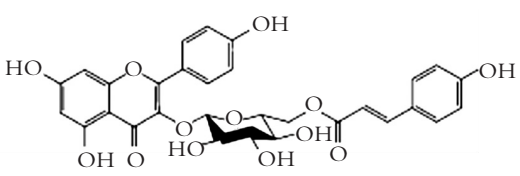
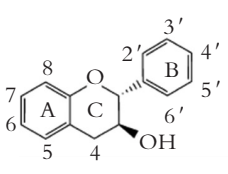
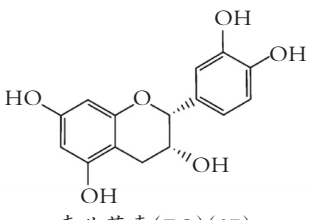
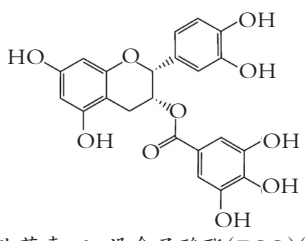

银椴苷(36)

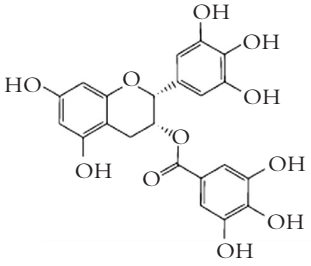
图3 黄酮醇的化学结构

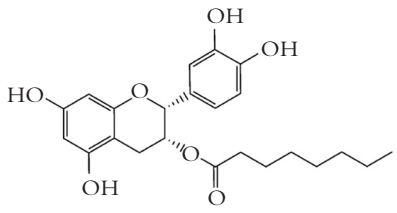
Fig. 3 Chemical structures of flavonols


黄烷醇(儿茶素)子类骨架


表儿茶素(EC)(37)


表儿茶素-3-没食子酸酯(ECG)(38)


表没食子儿茶素-3-没食子酸酯(EGCG)(39)


3-O-辛酰-表儿茶素(40)

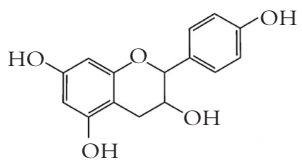

3,5,7,4′-3羟基黄烷醇(41)

图4 黄烷醇(儿茶素)的化学结构

Fig. 4 Chemical structures of flavanols (catechins)

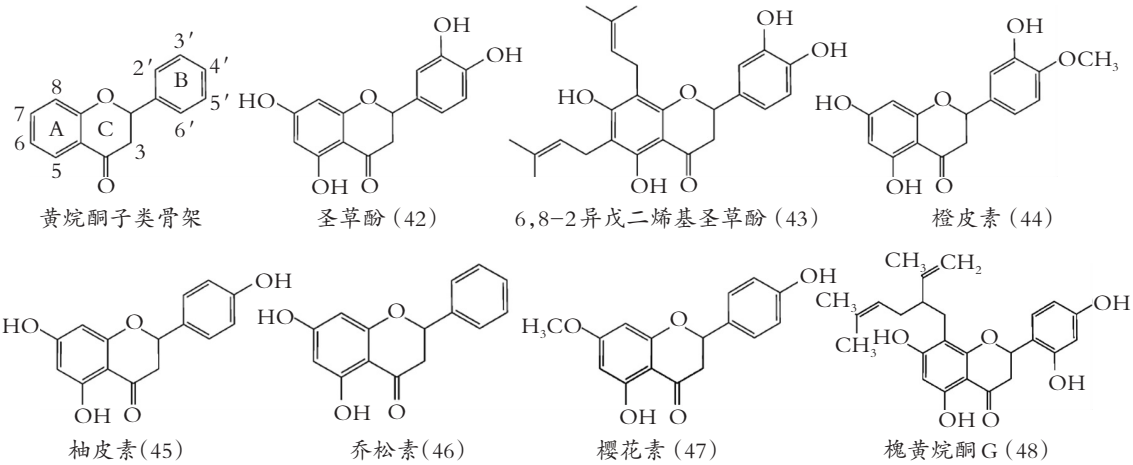


图 5　黄烷酮的化学结构

Fig. 5　Chemical structures of flavanones

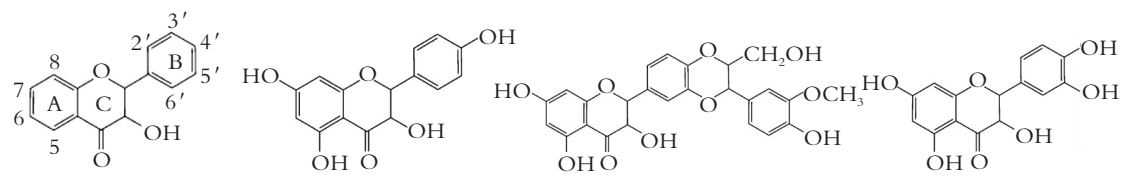


图 6　黄烷酮醇的化学结构

Fig. 6　Chemical structures of flavanonols

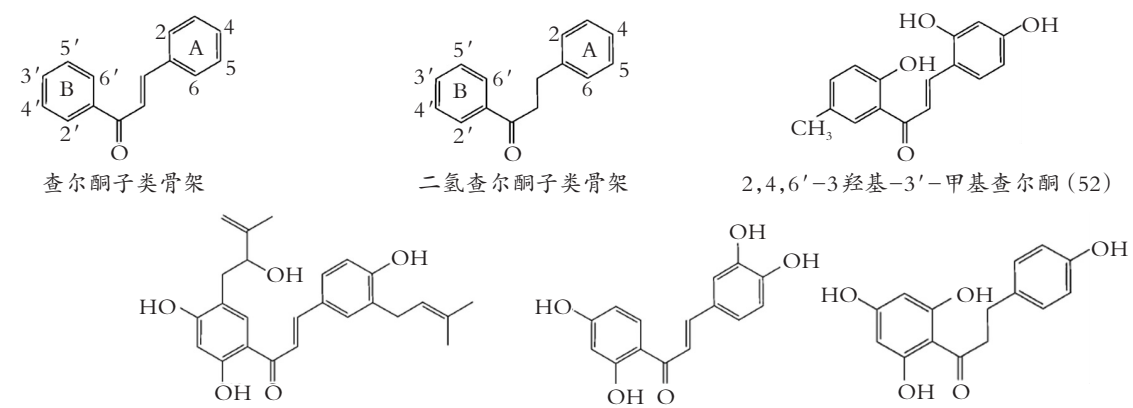
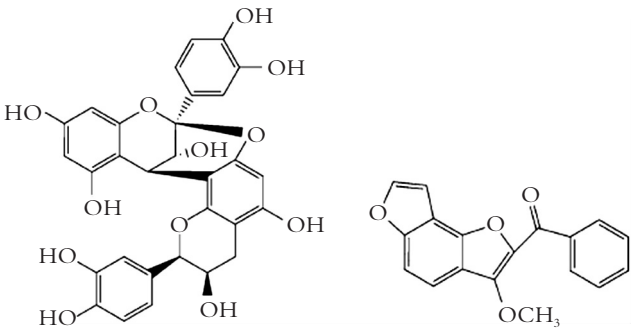


图 7　查耳酮的化学结构

Fig. 7　Chemical structures of chalcones.



A-型 原花青素(62) 橙酮(63)

图8 其他类黄酮化合物的化学结构

Fig. 8 Chemical structures of other flavonoids

类黄酮化合物频繁的化学修饰,形成丰富多样的结构[11]。类黄酮、类黄酮苷与它们的异戊二烯基化、香叶基化、甲氧基化、羟基化、乙酰基化以及聚合物,使得它与植物、微生物和动物各亚细胞中的靶标相互反应,以发挥不同的生理功能与抗菌作用[12]。

2 类黄酮的生理功能

类黄酮是植物长期进化过程中,在非生物和生物应力(如营养、阳光强度、紫外线辐射、冷、热、干旱、盐碱、食草动物与病原微生物侵蚀等因子)刺激下,产生的一大类植物次生代谢物。其化学结构、含量与分布随不同植物、不同组织和植物年龄发生变化[13]。相同种类植物会产生相似的类黄酮[13-14]。

在植物器官,这些化合物履行多种生理功能。呈现花和水果颜色的花青素,与其他类黄酮色素,起吸引传粉者与种子传播的作用[15]。在植物组织,受应力刺激产生的花青素和其他非色素类黄酮,如黄酮和黄酮醇等也对应力起抑制作用,保护组织免受伤害[16-17]。类黄酮还参与植物能量转移、光合作用、形态形成、生长因子与性别决定等过程[18]。

大量研究表明:在植物整个生命过程中,类黄酮是重要的抗菌素。植物拥有先天免疫能力,包括自身合成类黄酮与不同层次的防御反应,以阻止病原体传播[19]。如黄烷酮-樱花素(47),大量存在于受外界各病原体包括细菌和真菌侵蚀的稻米中[20]。植物为了快速应对病原体的侵蚀,类黄酮大多集中在叶的维管束。此外,许多类黄酮已被确认是化感物质,通过根系分泌或组织脱落方式释放到外界环境,是植物与植物以及植物与微生物之间进行信号交流的媒介,影响周围其他植物或微生物生长[21]。

3 类黄酮的抗菌机制

研究得出,应对植物病原体抗菌活性为特征的许多类黄酮,也可有效应用于对抗人类病原体,且有别于传统抗菌药物的抗菌机制,细菌耐药性较低,逆转抗生素耐药等优点[22]。

3.1 破坏细菌细胞膜

细胞膜负责渗透调节、呼吸和运输过程,以及肽聚糖与脂类的生物合成。细菌细胞膜完整性的破坏会直接或间接引起代谢功能障碍,最终导致细菌死亡[23]。

到目前,类黄酮特别是儿茶素,对革兰氏阳性和革兰氏阴性细菌有广泛的研究。儿茶素(图4)的抗菌作用,首先与细菌脂质双分子层疏水性膜内部的非极性化合物结合,然后与脂质极性基团形成氢键[24],诱导细胞膜结构变化、间接调节膜蛋白分布或功能[25]。

实验证明,儿茶素与脂质结合,灭活、抑制细菌细胞内外酶的合成,使细菌细胞膜破裂[26]。Bouayed 等[27]采用细胞模型,得出类黄酮如表儿茶素(37)、EGCG(39)和槲皮素(30)有助氧化活性。

Fathima 等[28]报道,儿茶素通过高浓度 EGCG 产生活性氧(ROS)爆发,诱导细菌膜渗透性变化与膜损伤引起杀菌作用。Cushnie 等[29]发现,儿茶素导致耐甲氧西林金黄色葡萄球菌(MRSA)膜损伤,产生钾泄漏,且亲脂性更强的3-O-辛酰-表儿茶素(40),比普通表儿茶素(37)有更好抗菌效果,表明

增加亲脂酰基链长度,能提高儿茶素抗菌活性[30]。

其他类黄酮如 2,4,6′-3 羟基-3′-甲基查尔酮(52)导致变形链球菌胞内物质如蛋白质和离子泄漏[31]。来自蜂胶的槲皮素(30)能降低金黄色葡萄球菌质子动力势,增加膜渗透性,提示蜂胶与抗生素如四环素和氨苄青霉素有协同抗菌活性[32]。

此外,黄酮芹菜素(7)、刺槐黄素(8)以及黄酮醇桑色素(24)和鼠李黄素(35),通过扰乱脂的有序与定向排列,引起膜结构不稳,增大胞内物质渗漏[33]。

Tsuchiya 等[34]报道,黄烷酮柚皮素(45)和槐黄烷酮 G(48)对耐甲氧西林金黄色葡萄球菌(MRSA)的抗菌活性,是因降低细胞膜内外流动性引起。槲皮素(30)、芦丁(33)和银锻苷(36)可减小脂双分子层厚度,破坏脂质单层结构[35]。

黄烷酮 C-3 位被亚芳基取代,影响金黄色葡萄球菌、表皮葡萄球菌与粪肠球菌引发细菌细胞聚集,破坏细胞膜完整性,导致细菌生物膜扰动,有高度抗菌活性[36]。

类黄酮-OH 的数量、分布,以及 C 环甲氧基等差异,影响类黄酮与脂质双层之间的相互作用[37]。

3.2　抑制细菌脂肪酸、粘肽层合成

脂肪酸是细胞膜重要组成成分,细菌脂肪酸合成酶 (FAS-II)在许多方面不同于哺乳动物脂肪酸合成酶(FAS-I),这使抗菌剂对 FAS-II 有优良的靶向性。研究报道,很多类黄酮是 FAS-II 抑制剂。

槲皮素(30)、芹菜素(7)与樱花素(47)能抑制幽门螺杆菌的 3-羟脂酰基-ACP 脱水酶[38]。Jeong 等[39]研究了 11 个不同结构的羟基黄烷酮对粪球菌 3-酮脂酰-ACP 合酶的影响,得出圣草酚(42)、柚皮素(45)和紫杉叶素(51)有好的抑制效果。类黄酮 B 环 4′、5′-OH 和 Arg38 和 Phe308 酶氨基酸残基间形成氢键,对抗菌活性起关键作用。

Elmasri 等[40]发现,5,6,7, 4′,5′-5 羟基黄酮(3)和 5-羟基 7,4′-2 甲氧基黄酮(5)下调丙二酰辅酶 A 酰基载体蛋白转酰酶 fabD,调节细菌 FAS-II。因此,这二黄酮被认为是阻断细菌生长有前途的药物。

绿茶 EGCG(39)能抑制细菌 FAS-II 特定还原酶(FabG FabI)[41]。FabG 酶(3-酮脂酰 ACP 还原酶)是已知催化还原细菌包膜 β-酮基同工酶[42]。EGCG(39)还能抑制参与细菌脂肪酸生物合成的其他酶如 3-酮脂酰基-ACP 和烯脂酰-ACP 还原酶[61],这些酶是开发新抗生素理想的靶点。

分枝杆菌是引起一些难以治疗严重疾病的病原菌[43],细菌拥有 FAS-II 和 FAS-I,二者对分枝菌酸的生物合成都很重要。许多类黄酮包括槲皮素(30)、山柰酚(26)、非瑟酮(22)、桑色素(24)、杨梅酮(25)、黄岑素(12)、木犀草素(15)以及 EGCG(39)抑制 FAS-I[43]。这些类黄酮对 FAS-II,包括烯脂酰-ACP 还原酶、β-酮脂酰-ACP 还原酶、β-羟脂酰-ACP 脱水酶,也有抑制活性。紫铆因 (54)、异甘草素(56)和非瑟酮(22),能降低牛结核分枝杆菌卡介苗 FAS-II 活性[44]。

粘肽层是肽聚糖、胞壁质或粘质复合物,抑制其合成是常见传统抗菌药物和类黄酮抗菌作用机制之一。黄岑素(12)有助于 EGCG(39)引起的肽聚糖损伤[45]。高良姜素(23)、山奈素(28)和山奈素-3-葡萄糖苷(29)不仅对耐阿莫西林大肠杆菌有抗菌活性,而且能抑制肽聚糖和核糖体合成,逆转抗菌剂耐药性[46]。儿茶素与肽聚糖化合,干扰细菌细胞壁合成。EGCG(39)和环丝氨酸协同抑制细胞壁合成,与 β-内酰胺(苯唑西林青霉素、甲氧西林、氨苄西林、头孢氨苄)直接或间接靶向肽聚糖,从而增强 β-内酰胺抗菌药物活性[47]。

3.3　抑制核酸合成

类黄酮有拓扑异构酶抑制剂活性,Ohemeng 等[48]发现槲皮素(30)、芹菜素(7)和 3,6,7,3′,4′-5 羟基黄酮(4)抑制大肠杆菌 DNA 促旋酶。得出,槲皮素与促旋酶 B 亚基结合,经 5,7,3′-OH 与 DNA 促旋酶的氨基酸残基形成氢键,封锁 D-丙氨酸-D-丙氨酸连接酶 ATP 结合袋[49]。类黄酮羟基比甲氧基与促旋酶结合能力更强,如白杨素(13)和山柰酚(26)较蜜橘黄素(16)和福橘素(18)能更好地抑制大肠杆菌 DNA 促旋酶,但 5′羟基大大减小了其抑制活性。

类黄酮与 DNA 促旋酶 B 亚基(GyrB)三磷酸腺苷(ATP)结合位点发生竞争反应,是抑制 DNA 成为超螺旋第二种机制。类黄酮与 DNA 结合,稳定 DNA-促旋酶复合物,引起 DNA 裂解感应[50]。3-

OH、5-OH、7-OH 和 4-羰基基团,是类黄酮与 GyrB 残基结合的重要基团[51]。Ulanowska 等[52]发现,异黄酮染料木素(21)以剂量-反应的方式,抑制鳗弧菌的生长,其原因是染料木素介导拓扑异构酶 II-DNA 裂解复合物的稳定性,导致细胞分裂或染色体复制受损。

解旋酶是无处不在的马达蛋白,作用 ATP 水解释放能量,分离、重排核酸双链[53]。类似于拓扑异构酶与促旋酶,是 DNA 复制所必需。研究表明这些蛋白质是类黄酮的分子靶点,其药效基团与核酸的键合能力,已作为解旋酶抑制剂被筛选。

木犀草素(15)及其结构相似的黄酮醇,如莫林(24)杨梅酮(25),被证明抑制复制的解旋酶如 DnaB 和 RecBCD 解旋酶/ E. coli 核酸酶[54]。杨梅酮抑制革兰氏阴性细菌生长,被认为是许多 DNA 和 RNA 聚合酶以及病毒反转录酶和端粒酶的有效抑制剂[55]。

二氢叶酸还原酶(DHFR)是许多药物包括抗菌药物,常见的靶点。DHFR 在叶酸合成途径提供嘧啶和嘌呤前体[56]。据报道,EGCG(39)抑制嗜麦芽寡养单胞菌、结核分枝杆菌和大肠杆菌的 DHFRs[57]。EGCG 与叶酸通路其他抑制剂,如磺胺甲恶唑和乙胺丁醇,有协同效应[57]。

类黄酮插层 DNA,抑制细菌核酸合成,也被认为是一种抗菌机制。Mori 等[58]用 EGCG(39)、杨梅酮(25)和洋槐黄素(17)培养普通变形杆菌和金黄色葡萄球菌,引起 DNA、RNA 和蛋白质合成降低,这是 A 环无 6-OH 和 B 环-3′、4′、5′- 3 OH 结构的类黄酮,与核酸双链插层所致。

大量研究得出,在人类癌症细胞中,类黄酮介导拓扑异构酶抑制和 DNA 插层,是普遍作用机制[59]。

3.4 抑制电子传递链和 ATP 合成

膜电位,生命系统几乎所有化学过程必需的主要能量来源,也是细菌细胞生存和生长最重要的因素。奇特的是,用异补骨脂查尔酮(57)和 6-异戊二烯基芹菜素(10)处理金黄色葡萄球菌,导致细菌膜去极化[60]。Haraguchi 等[61]报道,甘草查尔酮抑制微球菌细胞氧消耗,其抑制位点存在于电子传递链细胞色素 C 和 CoQ 之间,甘草查尔酮 A、B、C、D(58~61)亲脂性的异戊二烯基团,有助于它们渗透到细菌细胞。

据报道,类黄酮能抑制大肠杆菌 F_1F_0 ATP 酶[62]。ATP 合酶是含 F_1 和 F_0 两个部分高度保守的酶。在大肠杆菌中,F_1 是由 α3β3γσεab2c10 组成,而 F_0 由 ab2c10 组成。ATP 水解和合成发生在 F_1 部分 3 个催化位站,而质子迁移发生在嵌入膜的 F_0[63]。

已被证明,各种多酚类黄酮与存在于 ATP 合酶 F_1 部分独特的多酚结合袋 α、β 和 γ 亚基界面结合,阻碍 γ-亚基顺时针或逆时针旋转,抑制 ATP 合成酶[64]。不同物种,包括人、牛、鼠与大肠杆菌,多酚结合袋残留物高度保守,其他微生物容易受到这种抑制[65]。最有效的大肠杆菌 ATP 酶 F_1F_0 抑制剂有:黄芩素(12)、桑色素(24)、表儿茶素 (37)以及水飞蓟素(50)。槲皮素(30)、栎皮酮-3-葡萄糖苷(31)和栎皮酮-3-李糖苷(32),虽不抑制 ATP 合成,但能防止 ATP 水解[65]。EGCG(39)通过抑制变异链球菌 ATP 酶 F_1F_0 活性,抑制产酸和耐酸性能[66]。Ulrey 等[67]发现,用 A 型的原花青素(73)处理绿脓杆菌,下调 ATP 合成过程多蛋白质表达。

3.5 与金属离子形成螯合物

类黄酮与过渡金属离子有很强的螯合能力[68],抑制细菌金属酶活性,对许多其它抗菌物质包括母乳中的乳铁蛋白,这是常见的作用机制。类黄酮的螯合位点包括:A 环或 B 环两邻-OH、C 环 3-OH 与 C 环-4-酮基,或 A 环 5-OH 和 C 环-4-酮基位置。虽然螯合物的抗菌活性很大程度上取决于金属离子,但螯合物的形成优先取决于类黄酮螯合位点和 pH 值[69]。研究表明:槲皮素(30)与 Mn^{2+}、Hg^{2+}、Co^{2+}、Cd^{2+}螯合物对金黄色葡萄球菌、蜡样芽胞杆菌、绿脓杆菌、E 大肠杆菌和肺炎克雷伯菌有杀菌作用。类似地,桑色素(24)Ca^{2+}、Mg^{2+}螯合物对金黄色葡萄球菌和微球菌有抗菌作用[70];7,4′-2 甲氧基芹菜素(9)与 Cu^{2+}、Ni^{2+}、Zn^{2+}、Co^{3+}、Fe^{3+}、Cr^{3+}、Cd^{2+}和 M^{2+}螯合物,对大肠杆菌、金黄色葡萄球菌和普通变形杆菌有抗菌效果[71]。

3.6 抑制细菌生物膜形成

类黄酮除直接与细菌作用,还影响细菌生长、粘附、能动性与群体感应(QS),抑制细菌生物膜建立

与形成[72]。以细菌生物膜为基础的感染,在所有微生物、动物与人的慢性感染以及食物腐败中,占很大比例[73]。与浮游细菌相比,细菌生物膜对抗菌剂和宿主免疫系统具有很强的抵抗力(对抗菌剂的抵抗力,比浮游细菌提高 10 到 1 000 倍),导致严重的临床问题,引起许多慢性和难治感染疾病的反复发作[74]。

细菌生物膜形成是细菌粘附到宿主接触表面的随机事件,由其细胞分裂、发展到成熟所分泌的多糖基质、纤维蛋白、脂质蛋白等活性养分,将自身包绕其中形成的大量细菌聚集三维生物膜[75]。细菌感染通常使用全身抗生素治疗,去除细菌生物膜非常有限。

有趣的是类黄酮支持细菌聚集。Stapleton 等[76]在用 EGCG (39) 和 3-O-辛酰-表儿茶素 (40) 培育金黄色葡萄球菌,发现呈现多细胞聚集。黄酮醇导致细菌细胞聚集,尤其是高良姜素(23),然而细菌聚集后,细菌增长被抑制。可能是类黄酮部分分解诱发细菌聚集,产生细胞膜融合,降低了单位膜面积活性养分的吸收,不利于细菌生物膜形成。Awolola 等得出[77],异牡荆苷(14)、EC(37)、5,7,4′-3 羟基黄酮醇(41)对金黄色葡萄球菌 ATCC 29213,有显著的抗生物膜活性。同样,El-Adawi 等[44]观察,在 EC 2 ~ 15% 下,变异链球菌生物膜形成减少 55 ~ 66%。然而也有报道,来自 *Acacia karroo* 的 EC 对李斯特氏菌生物膜无降低活性[78]。

大肠杆菌、弧菌 spp 和鼠伤寒沙门氏菌生物膜的形成,QS 尤其是自诱导物-2 信号分子被认为是重要的调节因子[79]。研究发现柑橘类黄酮如芹菜素(7)、山柰酚(26)、槲皮素(30)和柚皮素(45),是自诱导物-2 信号分子有效拮抗剂[80]。除此,槲皮素以浓度依赖方式抑制海藻酸盐的产生,导致生物膜形成过程中粘附下降,该类类黄酮还能抑制 N-高丝氨酸内酯(AHL)介导的 QS。

奇特的是,槲皮素上调铜绿假单胞菌数个含铁蛋白表达,限制生物膜形成所需 Fe^{3+}[81]。Roy 等发现,山柰酚(28)、ECG(38)和 EGCG(39)介导从 LuxR-type 转录激活蛋白中置换 AHL 分子[82]。白杨素(13)、根皮素(55)和柚皮素(45)可抑制 QS 合酶/受体对 LasI/R 和 RhlI / R[83]。A 型原花青素(62)是铜绿假单胞菌的抗粘附剂,对 Fe^{3+} 等过渡金属离子优良的螯合,抑制细菌生物膜形成[84]。

亲水性类黄酮能与膜表面相互结合,防止有害物质与细胞膜作用,抑制细菌生物膜形成[85]。黄酮如 6-氨基黄酮(1)、7-羟基黄酮(2)、芹菜素(7)、白杨素(13)、异黄酮大豆黄素(20)和染料木素(21)与查耳酮根皮素(55)抑制大肠杆菌 O157: H7 生物膜形成,抗氧化化合物(维生素 C 和维生素 E)没有这种效果,说明类黄酮阻止生物膜形成,抗氧化性不是唯一原因[86]。此外,根皮素显著降低 EO157: H7 大肠杆菌生物膜形成,对浮游细菌生长不产生影响。鱼藤酮(63)对大肠杆菌生物膜抑制有类似效果[87]。

菌毛是细菌生物膜形成的重要因素。由于根皮素(68)抑制 csgA 和 csgB 基因表达,减少大肠杆菌 O157: H7 菌毛形成。根皮素抑制两种毒素基因(溶血素 hlyE 和志贺毒素 2 stx2),诱导抗逆性基因如 marRAB 和 hcsBA 表达[86],对抗生素耐药性有积极影响。

槲皮素(30)、乔松素(46)有细菌外排泵抑制剂(EPI)作用。EPI 不仅能阻止外排泵,而且阻止生物膜形成[88]。研究表明:EGCG (39)能有效抑制浮游粪球菌生长,还能抑制生物膜形成相关基因的表达。来自淫羊藿物种的异戊二烯化类黄酮,能抑制牙龈卟啉单胞菌生物膜的形成[89]。

此外,类黄酮还可抑制与降低细菌毒素。重要的细菌毒素如透明质酸酶,在细菌发病机理中,介导的透明质酸降解,增加结缔组织的渗透率,降低体液黏度[90]。尤其是黄酮醇,如杨梅酮(25)和槲皮素(30)已被确定为无乳链球菌透明质酸裂解酶抑制剂,其抑制作用与类黄酮羟基数量呈正相关[91]。类黄酮特别是儿茶素和原花青素,能中和霍乱弧菌、创伤弧菌、金黄色葡萄球菌炭疽杆菌、肉毒梭状芽胞杆菌的细菌毒素[92]。类似,桑色素(24)抑制金黄色葡萄球菌的外毒素,山柰酚(26)、山柰酚-3-芦丁糖甙(27)和槲皮素糖苷抑制 c 肉毒杆菌的神经毒素[93]。乔松素(46),一蜂蜜黄烷酮,以浓度方式减少金黄色葡萄球菌 α-溶血毒素产生。EGCG(39)和 GCG 抑制从肠出血性 E 大肠杆菌释放志贺样毒素,提示绿茶儿茶素可用来防止大肠杆菌引起的食物中毒。

4 结 论

类黄酮在植物中广泛存在,具有良好的抗菌作用,尤其是对抗生素耐药的细菌依然敏感,并且该类化合物不易产生耐药性。但类黄酮与细胞靶点的作用,仍认识不多,相信随着人们对类黄酮抗菌作用及机制研究的深入,必将对新型抗耐药物的研发提供新的思路和理论依据。

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Physiological Activities and Antimicrobial Mechanism of Plant Flavonoids

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Abstract: Flavonoids are a large class of small molecular secondary metabolic produced in different parts of plants. They perform a variety of physiological functions in various organs of plants and display a wide range of pharmacological or beneficial health effects for humans, which include antioxidative activity, free radical scavenging capacity, coronary heart disease prevention and antiatherosclerotic, hepatoprotective, anti-inflammatory and anticancer activities. Hence, flavonoids are gaining high attention from the pharmaceutical and healthcare industries. Notably, these compounds have been found to be a potent antimicrobial agent by destroying bacterial cell membrane, inhibiting synthesis of bacterial fatty acid, mucopeptide layer, nucleic acid, electron transport chain and ATP, as well as inhibiting the activity of bacterial metal enzyme. At the cellular level, they can also prevent bacteria from attaching to host receptors, and inhibit bacterial biofilm formation. They can not only selectively target bacterial cells but also inhibit virulence factors and other forms of microbial threats. Moreover, some plant flavonoids manifest the ability to reverse the antibiotic resistance and enhance action of the current antibiotic drugs. The development and application of flavonoid-based drugs could be a promising approach for antibiotic-resistant infections.

Key words: flavonoids; physiological function; antimicrobial mechanism

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