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## 胆汁酸在预防和治疗感染性疾病中的生物活性、机制、生产和潜在应用

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### 摘要

感染性疾病是一个全球公共卫生问题,全世界范围内新发和再发感染性疾病呈上升趋势。因此,感染性疾病的预防和治疗仍然是面临的重大挑战。胆汁酸是宿主和微生物的常见代谢物,这些宿主和微生物在控制脂质、葡萄糖和能量的代谢方面发挥着重要作用。胆汁酸在历史上曾经作为一线有价值的治疗药剂,用于治疗相关的代谢和肝胆疾病。值得注意的是,胆汁酸是牛黄和熊胆的主要活性成分,而牛黄和熊胆作为常见的传统中药,具有清热、解毒和疏风解痉的疗效。近年来,胆汁酸在治疗感染性疾病方面的良好表现已经引起了科学界的注意。本文首次对胆汁酸在治疗和预防感染性疾病方面的生物活性、可能机制、生产路线以及潜在应用进行综述。与之前的综述相比,我们对现有的关于胆汁酸在治疗病原微生物(病原微生物是导致全球性发病和死亡的主要原因)所引起的感染性疾病相关的研究进行了全面的总结。此外,为了确保胆汁酸以可负担的价格进行稳定供应,有必要阐明胆汁酸在体内的生物合成,这将帮助科学家们解释胆汁酸的累积,并发现如何通过化学合成、生物合成和化学-酶法合成的方式对不同的胆汁酸进行改造。最后,我们探索本领域目前面临的挑战,并为以胆汁酸为基础的药物和胆汁酸的可持续生产推荐开发策略。目前的研究表明,胆汁酸是一种治疗感染性疾病的潜在的新颖治疗药剂,并能以可持续的方式进行人工合成。

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## 1. 引言

感染性疾病包括传染性和非传染性两种,主要发生在神经系统、皮肤、肺部、肝脏和肠道。很多感染性疾病是由细菌、病毒、真菌和其他病原体引起的,是导致全球发病和死亡的主要原因之一[1]。人类历史上最致命的传染性疾病包括疟疾、天花、西班牙流感、肺结核、鼠疫、获得性免疫缺陷综合征(AIDS,即艾滋病)和霍乱。疟疾是由疟原虫(一种寄生虫)引起的,在过去的一个世纪中

感染了数十亿人,至今仍然是热带地区严重的公共卫生威胁[2]。结核病是由结核分枝杆菌感染引起的,是全世界主要的致死传染病之一,每年有超过100万人死于结核病[3]。天花是由天花病毒引起的,是最古老和死亡率最高的传染性疾病之一,具有高度接触传染性,致死率约30%[4]。霍乱是一种由霍乱弧菌引起的严重肠道疾病,全世界曾多次暴发霍乱[5]。鼠疫,也被称为黑死病,是由于鼠疫耶尔森菌引起的,一直是最热门的国际公共卫生问题之一[6]。近年来,由严重急性呼吸系统综合征冠状

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病毒2 (SARS-CoV-2) 引起的新型冠状病毒肺炎 (COVID-19) 和由甲型流感病毒引起的 H1N1 流感 (猪流感) 也加入了全球最致命疾病清单[7]。此外, 一些由病原体入侵引起的非传染性疾病, 比如菌血症、败血症、脓毒症和感染性休克等, 是危重症病人的严重并发症, 也是造成分娩、手术、炎症、创伤、烧伤和慢性疾病死亡的主要原因。总的来说, 感染性疾病是全球公共卫生的重要威胁, 其预防和治疗仍然是主要挑战之一。

传统中医药用于治疗感染性疾病已经有几千年的历史, 其疗效已经获得了全世界人民的认可。在中国, 传统中医药在 COVID-19 疫情期间发挥了尤为重要的作用, 政府多次推荐传统中医药作为主要治疗手段[8]。“扶正祛邪”是中医治疗疾病的基本原则, 而且传统中医药在预防病原体入侵、减轻毒素损伤、抑制药物抗性、改善临床表现、阻断细胞因子风暴和增强免疫系统方面都具有独一无二的优势[9]。“君臣佐使”是中药方剂的配伍原则[10], 其中“君药”是指在疾病治疗中起主要作用的植物药, 而“臣药”则起到支持作用, “佐药”有助于解毒, 而“使药”协调或加强其他药物的疗效。很多经典方剂已经被广泛用于治疗各种传染病。例如, 八宝玉枢丸、片仔癀和时疫清瘟丸已经用于治疗感染性疾病和流行病[11–12]。牛黄解毒丸、牛黄上清丸、梅花点舌丸、六神丸和熊胆丸已经广泛用于治疗喉咙肿痛、牙龈肿胀、角膜炎和结膜炎[13–17]。安宫牛黄丸、熊胆牛黄胶囊和痰热清注射液 (TRQ) 已经用于治疗上呼吸道感染、急性肺炎、支气管炎、高烧和重症流感[18–20]。在这些方剂中, 牛黄和熊胆都是主要成分, 由于其在清热、解毒和疏风解痉方面的潜在疗效, 数千年看来一直被广泛使用。在中国, 牛黄被广泛用于 650 多种知名方剂中, 而熊胆则被认为是“四大名贵中药”之首。胆汁酸是牛黄和熊胆的主要活性成分, 而且有越来越多的证据表明, 胆汁酸可能在预防和治疗感染性疾病方面具有重要作用。

本课题组致力于传统中医药抗菌领域研究十余年, 重点关注 TRQ。TRQ 由黄芩、熊胆粉、山羊角、金银花和连翘组成, 主要用于治疗上呼吸道感染、支气管炎和肺炎[21–22]。TRQ 自 2003 年开始使用, 已经被列入国家卫生和计划生育委员会 (NHFP) 及国家中医药管理局 (SATCM) 临床指南, 用于治疗人禽流感、甲型 H1N1 流感、甲型 H7N9 流感、小儿手足口病、登革热和埃博拉病毒。此外, TRQ 还在《新型冠状病毒感染诊疗方案 (试行第六版、第七版和第八版)》中连续被列为推荐用药。尽管 TRQ 的临床效果已经在中国得到了大量患者的认可, 但其药效物质基础和药理机制仍需要进一步的科学研究。

我们已经发现, 熊胆和 TRQ 的主要生物活性成分胆汁酸对一系列病原性细菌引起的疾病表现出潜在有前景的治疗效果[23–24]。因此, 结合这些发现和现有的研究, 我们推测, 胆汁酸是一种有前景的药剂, 可以开发为抗感染药物, 用于治疗感染性疾病。

胆汁酸广泛分布于动物、人类和微生物体内, 对于控制脂质、葡萄糖和能量的代谢具有至关重要的作用。它们在调节营养吸收、宿主免疫和微生物发病机制方面发挥着重要作用, 是治疗相关代谢性疾病 [如 2 型糖尿病、肥胖症和非酒精性脂肪肝 (NAFLD)] 的有价值的一线治疗方案[25–26]。目前已上市了多个用于治疗肝胆疾病的胆汁酸药物, 如优思弗 [熊去氧胆酸 (UDCA) 胶囊]、滔罗特 [牛磺熊去氧胆 (TUDCA) 胶囊]、胆酸钠片、鹅去氧胆酸 (CDCA) 胶囊、胆酸 (CA) 胶囊和奥贝胆酸 (OCA), 这些产品已被证明可以溶解胆固醇结石并促进胆汁分泌, 通过抑制疏水性胆汁酸的细胞毒性以及诱导细胞凋亡来保护胆管细胞和肝细胞[27–32]。近年来, 胆汁酸在治疗感染性疾病方面的良好表现已经引起了科学界的关注。本文对胆汁酸在治疗和预防感染性疾病方面的生物活性、潜在作用机制、生产路线和潜在应用进行综述, 比先前的综述更加详细, 并对其作为新型抗感染治疗药剂的潜力进行评价。

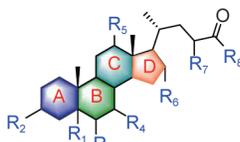
## 2. 胆汁酸的结构和分布

胆汁酸是 24 碳类固醇衍生物, 由三个六元环 (A、B 和 C) 和一个五元环 (D) 组成, 带有羟基取代基和脂肪族侧链[33]。到目前为止, 自然界中已经发现了 100 多种胆汁酸, 常见的胆汁酸的结构如图 1 所示[34–36]。典型的胆汁酸 (蓝色突出显示) 包括 CA、CDCA、UDCA、去氧胆酸 (DCA)、熊果胆酸 (UCA)、猪胆酸 (HCA)、猪去氧胆酸 (HDCA) 和石胆酸 (LCA)。CA 和 CDCA 是在肝脏中由胆固醇产生的两种主要的初级胆汁酸[37]。UDCA 在肝脏中天然生成, 是唯一获批用于治疗原发性胆汁性肝硬化 (PBC) 的药物, 它与甘氨酸和牛磺酸结合, 分别形成 TUDCA 和甘氨酸熊去氧胆酸 (GUDCA) [38]。DCA 和 LCA 分别是细菌从 CA 和 CDCA 脱羟基化而生成的主要次级胆汁酸[39]。在猪体内, HCA 及其衍生物占胆汁酸总量的 76% 左右, HCA 也出现在人类血液中[40]。HDCA 是一种从牛黄中提取的生物活性化合物, 通常在传统中医药中用于治疗中风[41]。UCA (3 $\alpha$ , 7 $\beta$ , 12 $\alpha$ -三羟基-5-胆烷-24-羧酸) 可能是一种适合于治疗胆固醇结石、高脂血症、胆道发育不良、PBC、慢性肝炎和胆汁反流性胃炎的

药物[35]。

结合型胆汁酸包括牛磺胆酸 (TCA)、甘氨酸胆酸 (GCA)、牛磺鹅去氧胆酸 (TCDCA)、甘氨酸鹅去氧胆酸

(GCDCA)、TUDCA、GUDCA、牛磺去氧胆酸 (TDCA)、甘氨酸去氧胆酸 (GDCA)、牛磺熊去氧胆酸 (TUCA) 和甘氨酸熊去氧胆酸 (GUCA)。结合型胆汁酸在水中



| Compound                           | R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub>    | R <sub>4</sub> | R <sub>5</sub> | R <sub>6</sub> | R <sub>7</sub> | R <sub>8</sub> | References |
|------------------------------------|----------------|----------------|-------------------|----------------|----------------|----------------|----------------|----------------|------------|
| CA                                 | β-H            | α-OH           | H                 | α-OH           | α-OH           | H              | H              | OH             | [34,35]    |
| TCA                                | β-H            | α-OH           | H                 | α-OH           | α-OH           | H              | H              | Taurine        | [34,35]    |
| GCA                                | β-H            | α-OH           | H                 | α-OH           | α-OH           | H              | H              | Glycine        | [34,35]    |
| CDCA                               | β-H            | α-OH           | H                 | α-OH           | H              | H              | H              | OH             | [34,35]    |
| TCDCA                              | β-H            | α-OH           | H                 | α-OH           | H              | H              | H              | Taurine        | [34,35]    |
| GCDCA                              | β-H            | α-OH           | H                 | α-OH           | H              | H              | H              | Glycine        | [34,35]    |
| UDCA                               | β-H            | α-OH           | H                 | α-OH           | H              | H              | H              | OH             | [34,35]    |
| TUDCA                              | β-H            | α-OH           | H                 | α-OH           | H              | H              | H              | Taurine        | [34,35]    |
| GUDCA                              | β-H            | α-OH           | H                 | α-OH           | H              | H              | H              | Glycine        | [34,35]    |
| DCA                                | β-H            | α-OH           | H                 | H              | α-OH           | H              | H              | OH             | [34,35]    |
| TDCA                               | β-H            | α-OH           | H                 | H              | α-OH           | H              | H              | Taurine        | [34,35]    |
| GDCA                               | β-H            | α-OH           | H                 | H              | α-OH           | H              | H              | Glycine        | [34,35]    |
| UCA                                | β-H            | α-OH           | H                 | β-OH           | α-OH           | H              | H              | OH             | [34,35]    |
| TUCA                               | β-H            | α-OH           | H                 | β-OH           | α-OH           | H              | H              | Taurine        | [34,35]    |
| GUCA                               | β-H            | α-OH           | H                 | β-OH           | α-OH           | H              | H              | Glycine        | [34,35]    |
| HCA                                | β-H            | α-OH           | α-OH              | α-OH           | H              | H              | H              | OH             | [34,35]    |
| HDCA                               | β-H            | Keto           | H                 | Keto           | Keto           | H              | H              | OH             | [34,35]    |
| LCA                                | β-H            | α-OH           | H                 | H              | H              | H              | H              | OH             | [34,35]    |
| Allocholic acid                    | α-H            | α-OH           | H                 | α-OH           | α-OH           | H              | H              | OH             | [34]       |
| Isolithocholic acid                | β-H            | β-OH           | H                 | H              | H              | H              | H              | OH             | [34]       |
| 5α-Deoxycholic acid                | α-H            | α-OH           | H                 | H              | α-OH           | H              | H              | OH             | [34]       |
| Isochenodeoxycholic acid           | β-H            | β-OH           | H                 | α-OH           | H              | H              | H              | OH             | [34]       |
| 3β,12α-Dihydroxy-5β-cholanoic acid | β-H            | β-OH           | H                 | H              | α-OH           | H              | H              | OH             | [34]       |
| Isoursodeoxycholic acid            | β-H            | β-OH           | H                 | β-OH           | H              | H              | H              | OH             | [34]       |
| 12-Epideoxycholic acid             | β-H            | α-OH           | H                 | H              | β-OH           | H              | H              | OH             | [34]       |
| Murideoxycholic acid               | β-H            | α-OH           | β-CH <sub>3</sub> | H              | H              | H              | H              | OH             | [34]       |
| β-Phocaecholic acid                | β-H            | α-OH           | H                 | α-OH           | H              | H              | α-OH           | OH             | [34]       |
| Vulpecholic acid                   | β-H            | α-OH           | H                 | α-OH           | H              | H              | H              | OH             | [34]       |
| Bitocholic acid                    | β-H            | α-OH           | H                 | H              | α-OH           | H              | α-OH           | OH             | [34]       |
| Avideoxycholic acid                | β-H            | α-OH           | H                 | H              | H              | α-OH           | H              | OH             | [34]       |
| Cygnocholic acid                   | β-H            | α-OH           | H                 | H              | H              | H              | H              | OH             | [34]       |
| Avicholic acid                     | β-H            | α-OH           | H                 | H              | H              | α-OH           | H              | OH             | [34]       |
| Alloavicholic acid                 | α-H            | α-OH           | H                 | α-OH           | H              | α-OH           | H              | OH             | [34]       |
| Hemulcholic acid                   | β-H            | α-OH           | H                 | α-OH           | H              | H              | H              | OH             | [34]       |
| Allochenodeoxycholic acid          | α-H            | α-OH           | H                 | α-OH           | H              | H              | H              | OH             | [34]       |
| Isoallothicholic acid              | α-H            | β-OH           | H                 | H              | H              | H              | H              | OH             | [34]       |
| 3-Oxo-CA                           | β-H            | Keto           | H                 | α-OH           | α-OH           | H              | H              | OH             | [35,36]    |
| 3-Oxo-LCA                          | β-H            | Keto           | H                 | H              | H              | H              | H              | OH             | [35,36]    |
| 7-Oxo-DCA                          | β-H            | α-OH           | H                 | Keto           | α-OH           | H              | H              | OH             | [35,36]    |
| 7-Oxo-LCA                          | β-H            | α-OH           | H                 | Keto           | H              | H              | H              | OH             | [35,36]    |
| 12-Oxo-CDCA                        | β-H            | α-OH           | H                 | α-OH           | Keto           | H              | H              | OH             | [35,36]    |
| 12-Oxo-UDCA                        | β-H            | α-OH           | H                 | β-OH           | Keto           | H              | H              | OH             | [35,36]    |
| 12-Oxo-LCA                         | β-H            | α-OH           | H                 | H              | Keto           | H              | H              | OH             | [35,36]    |
| 7,12-Dioxo-LCA                     | β-H            | α-OH           | H                 | Keto           | Keto           | H              | H              | OH             | [35,36]    |
| α-Muricholic acid                  | β-H            | α-OH           | β-OH              | α-OH           | H              | H              | H              | OH             | [36]       |
| β-Muricholic acid                  | β-H            | α-OH           | β-OH              | β-OH           | H              | H              | H              | OH             | [36]       |
| ω-Muricholic acid                  | β-H            | α-OH           | α-OH              | β-OH           | H              | H              | H              | OH             | [36]       |
| λ-Muricholic acid                  | β-H            | α-OH           | α-OH              | α-OH           | H              | H              | H              | OH             | [36]       |
| Tauro-α-muricholic acid            | β-H            | α-OH           | β-OH              | α-OH           | H              | H              | H              | Taurine        | [36]       |
| Tauro-β-muricholic acid            | β-H            | α-OH           | β-OH              | β-OH           | H              | H              | H              | Taurine        | [36]       |
| Tauro-ω-muricholic acid            | β-H            | α-OH           | α-OH              | β-OH           | H              | H              | H              | Taurine        | [36]       |

图1. 自然界中分布的常见胆汁酸的化学结构。R<sub>1</sub>~R<sub>8</sub>: 不同的取代基; TCA: 牛磺胆酸; GCA: 甘氨酸胆酸; TCDCA: 牛磺鹅去氧胆酸; GCDCA: 甘氨酸鹅去氧胆酸; DCA: 去氧胆酸; TDCA: 牛磺去氧胆酸; GDCA: 甘氨酸去氧胆酸; UCA: 熊果胆酸; GUCA: 甘氨酸熊胆酸; TUCA: 牛磺熊胆酸; HCA: 猪胆酸; HDCA: 猪去氧胆酸; LCA: 石胆酸。

的溶解度较高，它们在体内通常以钠盐形式存在，比游离胆汁酸更稳定[42]。

常见的氧代胆汁酸（图1中以橙色突出显示）包括3-氧代胆酸（3-oxo-CA）、3-氧代石胆酸（3-oxo-LCA）、7-氧代去氧胆酸（7-oxo-DCA）、7-氧代石胆酸（7-oxo-LCA）、12-氧代鹅去氧胆酸（12-oxo-CDCA）、12-氧代熊去氧胆酸（12-oxo-UDCA）、12-氧代石胆酸（12-oxo-LCA）、7,12-二氧化石胆酸（7,12-dioxo-LCA），它们都是由多种羟基类固醇脱氢酶（HSDH）催化的氧化产物[35–36]。兔、小鼠和其他啮齿类动物中存在特定的胆汁酸

（如 $\alpha$ -鼠胆酸、 $\beta$ -鼠胆酸、 $\omega$ -鼠胆酸和 $\lambda$ -鼠胆酸），它们的牛磺胆酸盐也在图1中以绿色突出显示[36]。

胆汁酸家族通常包含三类： $C_{24}$ 胆汁酸、 $C_{27}$ 胆汁酸和 $C_{27}$ 胆汁醇[43]，它们在自然界中的分布如图2所示[44–48]。 $C_{24}$ 胆汁酸主要是从人类和熊、牛、猪、狗、羊、鸭、鹅、兔、鸡、鸽子、天鹅、蛇、鱼等动物的胆汁中分离出来的[44]。 $C_{27}$ 胆汁酸在低等原始脊椎动物中更为丰富，已经从卷尾鸟、裸喉钟鸟、犀鸟和短吻鳄的胆汁中分离出多种 $C_{27}$ 胆汁酸[45–47]。例如，从大犀鸟和

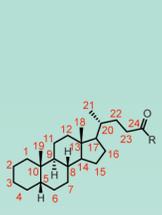
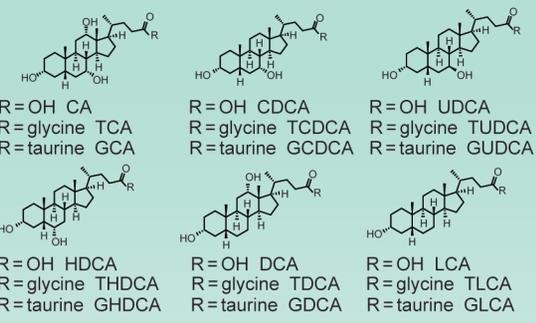
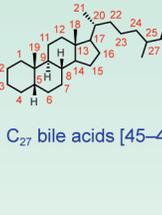
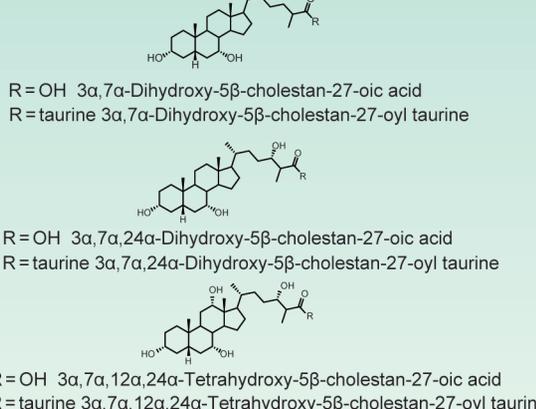
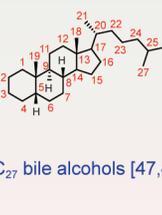
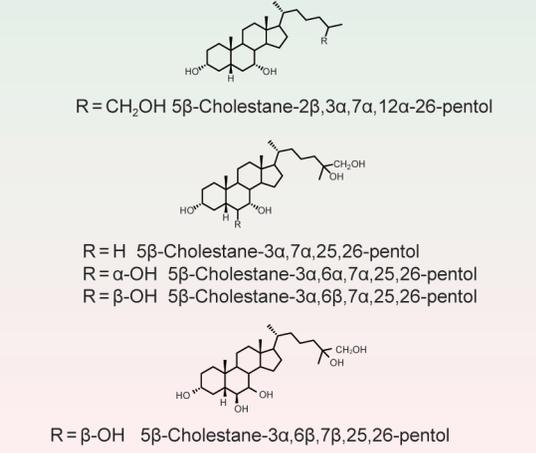
| Skeleton   | Typical bile acids  | Distribution   |
|--|---|--|
|  <p><math>C_{24}</math> bile acids [44]</p>         |  <p>R = OH CA<br/>R = glycine TCA<br/>R = taurine GCA</p> <p>R = OH CDCA<br/>R = glycine TCDCa<br/>R = taurine GCDCA</p> <p>R = OH UDCA<br/>R = glycine TUDCA<br/>R = taurine GUDCA</p> <p>R = OH HDCA<br/>R = glycine THDCA<br/>R = taurine GHDCA</p> <p>R = OH DCA<br/>R = glycine TDCA<br/>R = taurine GDCA</p> <p>R = OH LCA<br/>R = glycine TLCA<br/>R = taurine GLCA</p>   |  <p>Human Pig Bear Cow</p> <p>Sheep Chicken Goose</p> <p>Dog Snake Pigeon</p>        |
|  <p><math>C_{27}</math> bile acids [45–47]</p>    |  <p>R = OH 3<math>\alpha</math>,7<math>\alpha</math>-Dihydroxy-5<math>\beta</math>-cholestan-27-oic acid<br/>R = taurine 3<math>\alpha</math>,7<math>\alpha</math>-Dihydroxy-5<math>\beta</math>-cholestan-27-oyl taurine</p> <p>R = OH 3<math>\alpha</math>,7<math>\alpha</math>,24<math>\alpha</math>-Dihydroxy-5<math>\beta</math>-cholestan-27-oic acid<br/>R = taurine 3<math>\alpha</math>,7<math>\alpha</math>,24<math>\alpha</math>-Dihydroxy-5<math>\beta</math>-cholestan-27-oyl taurine</p> <p>R = OH 3<math>\alpha</math>,7<math>\alpha</math>,12<math>\alpha</math>,24<math>\alpha</math>-Tetrahydroxy-5<math>\beta</math>-cholestan-27-oic acid<br/>R = taurine 3<math>\alpha</math>,7<math>\alpha</math>,12<math>\alpha</math>,24<math>\alpha</math>-Tetrahydroxy-5<math>\beta</math>-cholestan-27-oyl taurine</p> |  <p>Capuchinbird</p> <p>Bare-throated bellbird</p> <p>Hornbill</p> <p>Alligator</p> |
|  <p><math>C_{27}</math> bile alcohols [47,48]</p> |  <p>R = CH<sub>2</sub>OH 5<math>\beta</math>-Cholestane-2<math>\beta</math>,3<math>\alpha</math>,7<math>\alpha</math>,12<math>\alpha</math>-26-pentol</p> <p>R = H 5<math>\beta</math>-Cholestane-3<math>\alpha</math>,7<math>\alpha</math>,25,26-pentol<br/>R = <math>\alpha</math>-OH 5<math>\beta</math>-Cholestane-3<math>\alpha</math>,6<math>\alpha</math>,7<math>\alpha</math>,25,26-pentol<br/>R = <math>\beta</math>-OH 5<math>\beta</math>-Cholestane-3<math>\alpha</math>,6<math>\beta</math>,7<math>\alpha</math>,25,26-pentol</p> <p>R = <math>\beta</math>-OH 5<math>\beta</math>-Cholestane-3<math>\alpha</math>,6<math>\beta</math>,7<math>\beta</math>,25,26-pentol</p>  |  <p>West Indian manatee</p> <p>Arapaima</p> <p>Sunfish</p> <p>Elephant</p>          |

图2. 典型胆汁酸及其在自然界中的分布。R代表不同的取代基。

维萨亚犀鸟中分离得到的两种主要胆汁酸是 $3\alpha,7\alpha,24\alpha$ -二羟基- $5\beta$ -胆甾烷-27-羧酸和 $3\alpha,7\alpha,12\alpha,24\alpha$ -四羟基- $5\beta$ -胆甾烷-27-羧酸与牛磺酸的结合物[46]。一些典型的 $C_{27}$ 胆汁醇如图2所示。 $C_{27}$ 硫酸胆汁盐常常存在于西印度海牛、大象、巨骨舌鱼和太阳鱼中[47–48]。此外,胆汁酸根据其结构可分为两类,即游离胆汁酸和结合胆汁酸,前者与牛磺酸或甘氨酸结合形成后者。

### 3. 胆汁酸的生物活性

胆汁酸是调节碳水化合物和脂质代谢所必需的物质[49]。自20世纪70年代以来,UDCA和CDCA已被证明对胆固醇结石有效。它们可以降低胆固醇饱和度,恢复脂质的微胶体状态,溶解和分解胆结石中的胆固醇;它们也用于治疗PBC、胆管炎、胆囊炎和急性化脓性胆管炎[29, 50]。TUDCA被批准用于治疗PBC [51],此外,已有多项

研究表明,TUDCA具有抗凋亡和神经保护活性,这已在多种疾病模型和临床治疗中得到证实[25,52–53]。不仅如此,由于2型糖尿病与胆汁酸代谢紊乱有关,HCA及其衍生物可以改善葡萄糖稳态,并可能成为2型糖尿病的新型治疗药物[39,54–55]。考虑到胆汁酸的多种药理活性,越来越多的衍生物正在被合成为候选药物。OCA是一种半合成胆汁酸,类似于天然酸CDCA,于2016年被批准作为一种新型药物,用于PBC的临床治疗。OCA是一种有效的法尼醇X受体(FXR)激动剂,能够调节胆汁酸的合成和分泌,以及肝脏和肠道中的脂质和葡萄糖代谢,也被发现是一种有前景的治疗NAFLD的药物[56–57]。

有趣的是,除了上述药理活性外,胆汁酸还表现出广泛的生物活性谱,包括抗病毒、抗菌、抗炎和免疫调节活性,这些活性正逐渐被揭示和阐明(图3)。

#### 3.1. 胆汁酸的抗病毒作用

血管紧张素转化酶2(ACE2)已被鉴定为SARS-

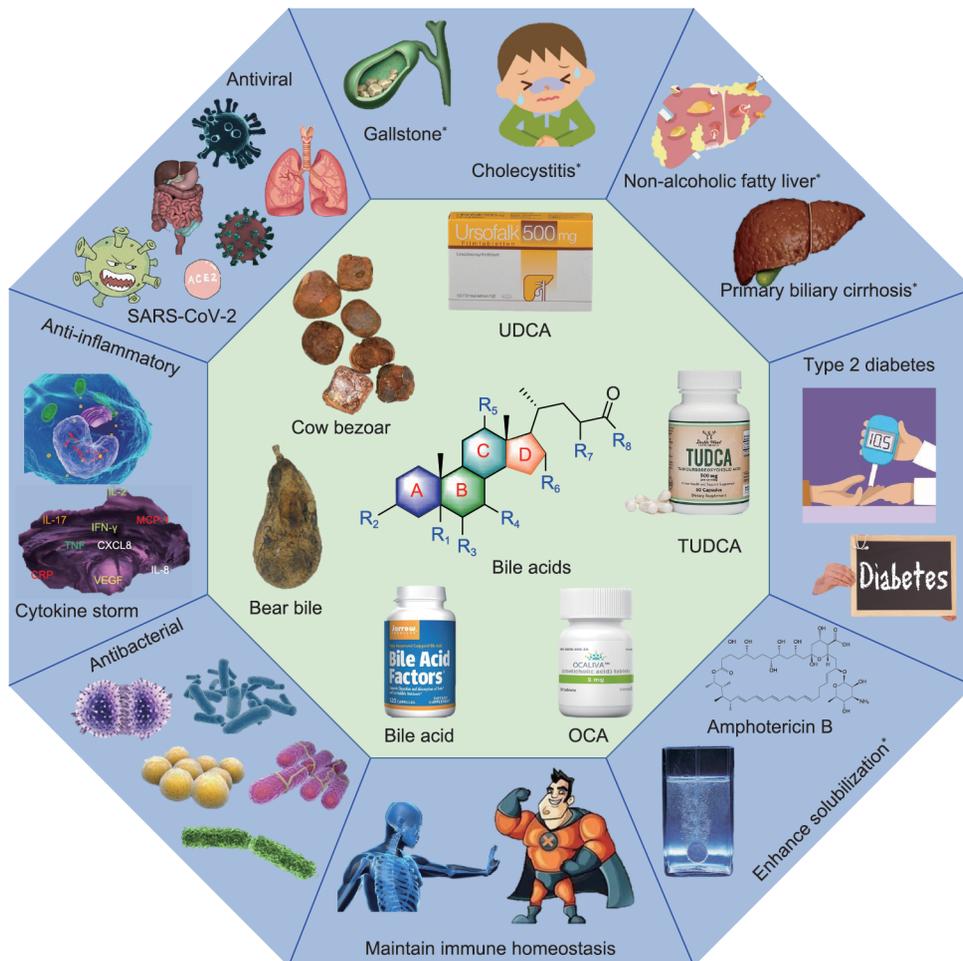


图3. 胆汁酸的生物活性、临床和潜在应用。上标\*表示基于临床证据的发现,而其他发现则是基于体内和体外试验的结果。IL-2: 白细胞介素-2; IL-8: 白细胞介素-8; IL-17: 白细胞介素-17; TNF: 肿瘤坏死因子; MCP-1: 单核细胞趋化蛋白-1; IFN: 免疫干扰素; CXCL8: 趋化因子(C-X-C基序)配体8; CRP: C反应蛋白; VEGF: 血管内皮生长因子。

CoV-2进入细胞的受体和进入点。G蛋白偶联胆汁酸受体1 (GPBAR1) 和FXR是两个主要的胆汁酸受体, 以GPBAR1/FXR配体为靶标是COVID-19富有前景的新型治疗方法[58]。据报道, 天然GPBAR1配体, 如GUDCA, 可以抑制尖突蛋白的受体结合域(RBD)与ACE2的结合, 结合率下降约20%。UDCA、TUDCA、BAR501和BAR502也可以轻微减少RBD与ACE2的结合[58]。胆汁酸受体GPBAR1促进胰高血糖素样肽(GLP)-1的释放, 并作为ACE2的正向调节剂发挥作用[59]。

在呼吸系统中, FXR是ACE2表达的直接调节剂, 而且FXR激动剂(如UDCA)可以减少人类鼻黏膜中的FXR信号传导和ACE2表达, 从而减少对SARS-CoV-2的易感性[60–62]。UDCA还可以抑制呼吸道上皮细胞的异常迁移, 防止SARS-CoV-2引起的损伤, 并增强上皮基底的修复[63]。最近, 熊胆(其中总胆汁酸含有高达40%~50% UDCA)被推荐作为一种冠状病毒治疗药剂[64]。CDCA和GCDCA也被证明可以将SARS-CoV-2/ACE2相互作用减少45%~50%, 而其他半合成衍生物均为FXR受体激动剂(BAR704和OCA), 分别导致RBD/ACE2结合减少40%和20%[58]。另外, OCA被证实具有显著的抗病毒和抗炎属性, 可以控制ACE2的表达并减轻COVID-19的症状[61]。

流感是一种高死亡率的急性呼吸道感染, 流感病毒直接侵入呼吸道并引起病毒性肺炎、急性呼吸窘迫综合征、休克和其他严重危及生命的并发症[65]。1918年流感大流行造成约2100万人死亡, 而1920年以来流感造成的总死亡人数, 可能已经超过了1918年流感大流行。甲型流感病毒引起的流感仍然对全球人群的健康构成严重威胁, 而且有病毒产生耐药性的风险[60]。CDCA和TUDCA虽然机制不同, 但都有可能被开发为潜在的抗甲型流感药物。CDCA已被证明可通过阻断病毒核糖核蛋白(vRNP)的核输出来抑制甲型流感病毒的复制[66]。TUDCA于2007年在中国以某商品名批准上市, 作为基质蛋白2(M2)质子通道抑制剂, 它可以破坏M2质子通道的寡聚状态, 从而消除或诱导低效病毒感染[67]。另一项研究结果表明, TUDCA通过内质网(ER)应激途径抑制1型单纯疱疹病毒(HSV-1)的复制[68]。

CDCA、HDCA和UDCA可以减轻A549和MDCK细胞培养中的三种甲型流感病毒亚型的复制, 半数最大抑制浓度(IC<sub>50</sub>)分别为5.5~11.5、31.0~73.7和34.2~58.7 μmol·L<sup>-1</sup>。遗憾的是, 本研究中未使用标准抗病毒药物作为阳性对照[66]。然而, 另一项研究报道称, 奥司他韦、扎那米韦和帕拉米韦对甲型流感病毒的IC<sub>50</sub>值分别为

0.04~748.14、0.15~50.97和0.05~178.23 nmol·L<sup>-1</sup> [69]。猪病毒性胃肠炎通常由猪丁型冠状病毒(PDCoV)引起, 目前尚无针对该病毒的疫苗或抗病毒药物。CDCA和LCA均可通过肠上皮细胞系(IPEC-J2)中的GPCR-IFN-λ3-ISG15信号传导轴抑制PDCoV的复制[70]。胆汁酸的抗病毒效果如表1所示[58,60–62,66–68,70]。

### 3.2. 胆汁酸的抗菌作用

胆管炎和胆囊炎往往同时发生, 最常见的是由于胆汁淤积引起的继发性细菌感染[71]。对来自急性梗阻性化脓性胆管炎患者的胆汁进行细菌培养, 显示存在大肠杆菌、产气荚膜梭菌、肺炎克雷伯菌、绿脓杆菌和粪肠球菌。有证据表明, UDCA可能对消化道感染具有治疗效果。艰难梭菌是引起腹泻和结肠炎的主要病原体, 是一种威胁生命的院内病原菌, 而且当正常的结肠微生物群新陈代谢失调时, 就会发生艰难梭菌感染。在体外试验中, UDCA治疗可以使艰难梭菌的孢子萌发、营养生长和毒素活性显著下降, 患者服用UDCA之后十个月以上未再发生感染[71–72]。不管是在体内还是体外, UDCA都能阻断超广谱β-内酰胺酶(ESBL)-肠聚集性大肠杆菌(EAEC)的生长和入侵, 并缓解结肠炎症状[73]。

我们最近的研究表明, CDCA和UDCA可以显著抑制对甲氧西林敏感的金黄色葡萄球菌(MSSA)和耐甲氧西林金黄色葡萄球菌(MRSA)的活性。CDCA的最低抑制浓度(MIC)值是320 μg·mL<sup>-1</sup>。CDCA与氨基糖苷类药物有协同作用, 或可增强对MSSA和MRSA的杀伤性。CDCA和阿米卡星(AMK)联合使用可以显著减少生物膜形成, 并对感染金黄色葡萄球菌的小鼠模型具有保护作用[23]。这种协同作用机制的基础是, CDCA能够消散质子动力(PMF)的化学势(ΔpH), 而且可以通过抑制MSSA和MRSA中的超氧化物歧化酶(SOD)的活性来增强活性氧(ROS)的生成。此外, CDCA与碳青霉烯类在对抗MRSA方面具有协同作用, 这一点已经在25个临床菌株中得以证实。不仅如此, 我们发现UDCA对MSSA和MRSA菌株均表现出显著活性(MIC = 1280 μg·mL<sup>-1</sup>) [24]。

研究表明, CDCA还具有抑制其他致病菌的作用。CDCA可以有效抑制人畜共患感染性病原体鼠伤寒沙门氏菌侵入上皮细胞。值得注意的是, 我们发现CDCA直接抑制转录调节因子HilD, 这与毒力和发病机制密切相关[74]。DCA和CDCA对淋病的病原体淋病奈瑟菌具有极快的杀菌作用[75–76]。虽然β-内酰胺类抗生素是最重要的抗菌剂, 但它们对β-内酰胺酶出现的防控效果大大降低。研究发现, CA是多重耐药菌株产生的针对β-内酰胺酶的

表1 胆汁酸的抗病毒作用

| Bile acid | Target      | Mechanism   | References |
|-----------|-------------|---|------------|
| UDCA      | SARS-CoV-2  | Reduce the RBD/ACE2 binding through GPBAR1                                    | [58]       |
|           | SARS-CoV-2  | Reduce the RBD/ACE2 binding through FXR                                       | [60–62]    |
|           | Influenza A | attenuated virus replication  | [66]       |
| GUDCA     | SARS-CoV-2  | Reduce the RBD/ACE2 binding through GPBAR1                                    | [58]       |
| TUDCA     | SARS-CoV-2  | Reduce the RBD/ACE2 binding through GPBAR1                                    | [58]       |
|           | Influenza A | Disrupt oligomeric states of M2 proton channel                                | [58]       |
|           | Influenza A | Induce inefficient viral infection  | [67]       |
|           | HSV-1       | Inhibit virus replication through the ER stress pathway                       | [68]       |
| BAR501    | SARS-CoV-2  | Reduce the RBD/ACE2 binding through GPBAR1                                    | [58]       |
| BAR502    | SARS-CoV-2  | Reduce the RBD/ACE2 binding through GPBAR1                                    | [58]       |
| CDCA      | SARS-CoV-2  | Reduce the RBD/ACE2 binding through FXR                                       | [58]       |
|           | Influenza A | Inhibit virus replication through block nuclear export of vRNP                | [66]       |
|           | PDCoV       | Inhibit virus replication through GPCR-IFN- $\lambda$ 3-ISG15 signaling axis  | [70]       |
| GCDCA     | SARS-CoV-2  | Reduce the RBD/ACE2 binding through FXR                                       | [58]       |
| BAR704    | SARS-CoV-2  | Reduce the RBD/ACE2 binding through FXR                                       | [58]       |
| OCA       | SARS-CoV-2  | Reduce the RBD/ACE2 binding through FXR                                       | [58]       |
| LCA       | PDCoV       | Restrict virus replication through GPCR-IFN- $\lambda$ 3-ISG15 signaling axis | [70]       |
| HDCA      | Influenza A | Attenuate virus replication   | [66]       |

抑制剂，CA与氨苄西林的组合对七种生产 $\beta$ -内酰胺酶的菌株均表现出显著的抗菌活性和协同作用，其分数抑菌浓度（FIC）小于或等于0.5 [77]。异别石胆酸（Isoallo-LCA）由肠道 *Odoribacteraceae* 菌株生成，对耐多药艰难梭菌和屎肠球菌具有强效抗菌作用，并且可能对维持肠道稳态也有潜在作用[78]。此外，IsoalloLCA可强烈抑制其他革兰氏阳性病原体的生长和扩散，包括耐万古霉素屎肠球菌（VRE）、MRSA、停乳链球菌似马亚种（SDSE）、产气荚膜梭菌、化脓性链球菌、血链球菌、蜡芽芽孢杆菌和单核细胞增多性李斯特氏菌。IsoalloLCA在形态变化中表现出强效抗菌活性，包括艰难梭菌和VRE的塌陷、肿胀和形成多个横壁，已通过扫描和透射电子显微镜观察到上述变化[78–80]。DCA和LCA也可以抑制艰难梭菌的生长[79–82]。Theriot等[83]报道称，霍乱、阿米巴痢疾和艰难梭菌结肠炎等肠道感染都受到胆汁酸代谢的影响。胆汁酸的抗菌作用如表2所示[23,71–82]。

### 3.3. 胆汁酸的抗炎作用

感染性疾病是一种病原体种类繁多、感染途径多样、症状和体征存在个体差异的临床疾病，而参与炎症反应的相关常见炎症因子是由多种感染引起的。由于某些感染引发的炎症反应常常是组织损伤和死亡的原因，因此，以减轻炎症为目的策略可能有助于评估新型抗感染药物[84]。

众所周知，胆汁酸通过激活GPBAR1和FXR受体介导的信号通路来调节脂质、葡萄糖和能量的代谢，而GP-

BAR1和FXR受体是胆汁酸治疗代谢性疾病的两种主要受体。有趣的是，越来越多的证据表明，胆汁酸可以直接和间接地通过GPBAR1和FXR受体来缓解和抑制炎症反应，这表明胆汁酸的抗炎机制与某些代谢性疾病的治疗密切相关，如胆结石、胆囊炎、2型糖尿病和非酒精性脂肪肝。

UDCA是一种现有的减轻炎症和防止细胞死亡的药物，对以细胞因子风暴综合征为特征的COVID-19患者具有治疗潜力[64]。据报道，在艰难梭菌感染期间，UDCA降低了炎症介质NO的释放，同时降低了肿瘤坏死因子- $\alpha$ （TNF- $\alpha$ ）、白细胞介素-1 $\alpha$ （IL-1 $\alpha$ ）、白细胞介素-1 $\beta$ （IL-1 $\beta$ ）和白细胞介素-6（IL-6）的表达水平。此外，UDCA增加了白细胞介素-10（IL-10）的表达水平并减弱了宿主的炎症反应[72,85]。不仅如此，据报道，UDCA和LCA通过激活G蛋白胆汁酸偶联受体5（TGR5，也称为GPBAR1）来改善肠道屏障完整性，并减轻小鼠结肠炎的症状[86–87]。UDCA对体内结肠炎症的发展有保护作用，而UDCA的主要代谢产物LCA可能是肠道炎症的强效抑制剂[88]。

眼部碱烧伤（OAB）常伴有炎症，据报道，TUDCA可抑制炎症反应并保护角膜和视网膜免受损伤，这表明TUDCA可能是OAB的潜在治疗或干预药剂[89]。多项研究揭示了3-oxo-LCA和IsoalloLCA的抗炎作用。更具体地说，3-oxo-LCA和IsoalloLCA抑制T辅助细胞17（TH17）细胞分化，异硫胆酸增强调节性T细胞（Treg）细胞分

表2 胆汁酸的抗菌作用

| Bile acid  | Target                      | Mechanism  | References   |         |
|------------|-----------------------------|--|--|---------|
| UDCA       | <i>C. difficile</i>         | Reduces spore germination, vegetative growth, and toxin activity | [71–72]  |         |
|            | ESBL-EAEC                   | Blocks growth and invasion                                       | [73]   |         |
|            | MSSA                        | Represses viability, synergistic effect with aminoglycosides     | [23]   |         |
|            | MRSA                        | Represses viability, synergistic effect with aminoglycosides     | [23]   |         |
| CDCA       | MSSA                        | Repress viability  | [23]   |         |
|            | MSSA                        | Represses viability, synergistic effect with aminoglycosides     | [23]   |         |
|            | MSSA                        | Reduces biofilm formation  | [23]   |         |
|            | MSSA                        | Protective effect on mouse model                                 | [23]   |         |
|            | MSSA                        | Dissipates the $\Delta$ pH of the PMF                            | [23]   |         |
|            | MSSA                        | Enhances ROS generation by inhibiting SOD activity               | [23]   |         |
|            | MRSA                        | Represses viability  | [23]   |         |
|            | MRSA                        | Represses viability, synergistic effect with aminoglycosides     | [23]   |         |
|            | MRSA                        | Reduces biofilm formation  | [23]   |         |
|            | MRSA                        | Protective effect on mouse model                                 | [23]   |         |
|            | MRSA                        | Dissipates the $\Delta$ pH of the PMF                            | [23]   |         |
|            | MRSA                        | Enhances ROS generation by inhibiting SOD activity               | [23]   |         |
|            |                             | <i>S. typhimurium</i>  | Inhibits transcriptional regulator HilD of virulence | [74]    |
|            |                             | <i>N. gonorrhoeae</i>  | Rapid bactericidal effect                            | [75–76] |
| DCA        | <i>N. gonorrhoeae</i>       | Rapid bactericidal effect  | [75–76]  |         |
|            | <i>C. difficile</i>         | Inhibits growth  | [79–82]  |         |
| CA         | Multidrug-resistant strains | Inhibits $\beta$ -lactamases                                     | [77]   |         |
| IsoalloLCA | <i>C. difficile</i>         | Anti-microbial effects in morphological changes                  | [78–80]  |         |
|            | <i>E. faecium</i>           | Anti-microbial effects in morphological changes                  | [78–80]  |         |
|            | Gram-positive pathogens     | Inhibits growth and spread                                       | [78–80]  |         |
| LCA        | <i>C. difficile</i>         | Inhibits growth  | [79–82]  |         |

*S. typhimurium*: *Salmonella typhimurium*; *N. gonorrhoeae*: *Neisseria gonorrhoeae*.

化，这可能与炎症疾病有关[90–91]。在治疗类风湿性关节炎方面，LCA、DCA、IsoalloLCA和3-oxo-LCA与狄氏副拟杆菌表现出相似性和协同作用[92]。

体内和体外研究表明，UCA具有良好的抗炎作用，使其成为有前景的抗炎治疗药剂。UCA的抗炎机制已得到广泛研究，包括其对组胺释放、脂氧合酶、环氧合酶、磷脂酶和弹性蛋白酶活性的抑制作用[93]。已发现CDCA可抑制多种促炎脂肪因子和关键炎症调节因子[94]。OCA是一种有效的FXR激动剂，具有显著的抗炎作用，可抑制核因子 $\kappa$ B (NF- $\kappa$ B)的表达[62]。Sinha等[95]发现，补充次级胆汁酸可减轻三种小鼠结肠炎模型中的肠道炎症。

在动物实验中，某些胆汁酸可有效对抗革兰氏阳性菌[96–98]。研究发现，DCA通过调节TGR5/蛋白激酶A (PKA)/NF- $\kappa$ B信号通路来抑制金黄色葡萄球菌诱发的子宫内膜炎[96]。由肠道菌群介导的次级胆汁酸，通过小鼠的TGR5-环磷酸腺苷(cAMP)-PKA-NF- $\kappa$ B/含有NACHT、LRR和PYD结构域的蛋白3 (NLRP3)通路来

缓解金黄色葡萄球菌诱发的乳腺炎[97]。此外，DCA和LCA可减轻肺炎克雷伯菌感染引起的小鼠肝损伤和炎症[98]。总之，胆汁酸的抗炎活性因其保护肝脏、促进胆汁分泌和控制肠道炎症的能力而备受关注。胆汁酸的抗炎作用如表3所示[62,72,85–98]。

### 3.4. 维持免疫稳态

免疫稳态是免疫系统的一种生理功能，在正常情况下通过识别和清除衰老和受损细胞来维持内环境的稳定。免疫稳态的紊乱会导致免疫疾病的发生。胆汁酸在维持免疫和稳态方面起着重要作用，促进CD4+ T细胞分化为各种T细胞亚群。据报道，IsoalloLCA可能在维持免疫稳态中起关键作用，IsoalloLCA水平可能是炎症性肠病患者的生物标志物[99]。

胆汁酸在调节肠道免疫反应中起着关键作用，它们通过与受体的化学通信来调节对肠道微生物抗原的免疫反应。FXR和GPBAR1在肠上皮细胞中高表达，抑制炎症小体组装并降低促炎细胞因子水平[100–102]。FXR由初

表3 胆汁酸的抗炎作用

| Bile acid            | Target  | Mechanism  | References |
|----------------------|---|--|------------|
| UDCA                 | Inflammatory mediator NO                            | Decreases release  | [72,85]    |
|                      | TNF- $\alpha$ , IL-1 $\alpha$ , IL-1 $\beta$ , IL-6 | Decreases expression levels                                | [72,85]    |
|                      | IL-10   | Decreases expression levels                                | [72,85]    |
|                      | <i>C. difficile</i> infection                       | Attenuates the host inflammatory response                  | [72,85]    |
|                      | GPBAR1  | Improves gut-barrier integrity                             | [86–87]    |
|                      | GPBAR1  | Reduces inflammation in murine colitis                     | [86–87]    |
|                      | Colonic inflammation                                | Protective effect  | [89]       |
| TUDCA                | Inflammation response                               | Inhibits ocular inflammation                               | [89]       |
| 3-oxoLCA             | TH17 cell   | Suppresses cell differentiation                            | [90–91]    |
|                      | Rheumatoid arthritis                                | Synergistic effects with <i>Parabacteroides distasonis</i> | [90–91]    |
| IsoalloLCA           | TH17 cell   | Suppresses cell differentiation                            | [90–91]    |
|                      | Rheumatoid arthritis                                | Synergistic effects with <i>Parabacteroides distasonis</i> | [90–91]    |
| LCA                  | GPBAR1  | Improves gut-barrier integrity                             | [86–87]    |
|                      | GPBAR1  | Reduces inflammation in murine colitis                     | [86–87]    |
|                      | Rheumatoid arthritis                                | Synergistic effects with <i>Parabacteroides distasonis</i> | [92]       |
| DCA                  | Rheumatoid arthritis                                | Synergistic effects with <i>Parabacteroides distasonis</i> | [92]       |
| UCA                  | Histamine   | Inhibits release   | [93]       |
|                      | Lipoxygenase  | Inhibits activity  | [93]       |
|                      | Cyclooxygenase                                      | Inhibits activity  | [93]       |
|                      | Phospholipase                                       | Inhibits activity  | [93]       |
|                      | Elastase  | Inhibits activity  | [93]       |
| CDCA                 | Pro-inflammatory factors                            | Suppresses expression                                      | [94]       |
|                      | Inflammatory regulators                             | Suppresses expression                                      | [94]       |
| OCA                  | NF- $\kappa$ B                                      | Suppresses expression                                      | [62]       |
| Secondary bile acids | Murine colitis                                      | Reduces intestinal inflammation                            | [95]       |
| DCA                  | <i>S. aureus</i> -induced endometritis              | TGR5/PKA/NF- $\kappa$ B                                    | [96]       |
| Secondary bile acids | <i>S. aureus</i> -induced mastitis                  | TGR5-cAMP-PKA-NF- $\kappa$ B/NLRP3                         | [97]       |
| DCA                  | Liver abscess and bacteremia                        | Targets <i>K. pneumoniae</i> -induced inflammation         | [98]       |
| LCA                  | Liver abscess and bacteremia                        | Targets <i>K. pneumoniae</i> -induced inflammation         | [98]       |

NO: nitric oxide.

级胆汁酸（如CA和CDCA）激活，而GPBAR1主要由次级胆汁酸激活。FXR和GPBAR1受体是位于宿主免疫系统与肠道微生物群界面的信号分子，由胆汁酸激活[103–105]。此外，常见的胆汁酸受体包括孕烷X受体（PXR）和维生素D受体（VDR）。LCA、3-酮LCA、CDCA、DCA和CA可通过PXR调节肠上皮细胞的多种炎症因子，并加速伤口修复[106–110]。VDR可被3-oxo-LCA、IsoalloLCA和LCA激活，从而抑制Th17分化，并增加Treg分化[111–112]。胆汁酸维持肠道免疫稳态，相关机制与抗炎作用部分重叠。因此，胆汁酸受体可能是干预肠道疾病的有前景的靶点。

### 3.5. 增强抗真菌药物的溶解

两性霉素B是一种广谱抗真菌药物，是临床一线用

药，已成为治疗真菌感染的黄金标准。该药物用于治疗真菌引起的深部真菌感染，如败血症、心内膜炎、脑膜炎、腹腔感染、肺部感染、尿路感染和眼内炎。由于两性霉素B的溶解度有限，临床上用脱氧胆酸钠（SDCA）进行溶解，以便增强两性霉素B的溶解度[113]。

## 4. 胆汁酸的生产策略

### 4.1. 从原材料提取胆汁酸

胆固醇在肝脏内形成初级胆汁酸，CDCA和CA的形成需要多个关键酶。在哺乳动物中，胆汁酸在经过甘氨酸或牛磺酸修饰后，形成结合型胆汁酸盐。这些胆汁酸随后被肠道细菌代谢，生成DCA、LCA、HDCA和UDCA（图4）[114]。CDCA、CA、DCA和HDCA是鸡、猪、

牛、羊和家禽胆汁中的初级胆汁酸，可以通过树脂法、超临界萃取法、有机溶剂萃取法和沉淀法来获得这些初级胆汁酸[115–119]。然而，这些过程都比较复杂，制备周期长，而且来源有限，因此无法满足工业化生产的需求。UDCA是一种安全的治疗PBC的一线药物[37]，但是，其生物活性成分主要采用一种无管引流技术从熊胆汁中提取，价格非常昂贵。在中国，熊属于国家二级保护动物，因此，由于资源有限以及动物保护法的限制，现有的无管引流技术已经被人工合成的UDCA生产方式所取代[120–121]。

#### 4.2. 胆汁酸的人工合成

胆汁酸是熊胆和牛黄的主要成分，熊胆和牛黄在中国都属于珍稀药用动物原料。由于资源有限，人们正在考虑化学催化、生物催化和化学-酶法合成作为替代方法来生产胆汁酸。自20世纪50年代以来，化学合成方法已经广泛用于合成UDCA，该过程主要包括氧化（Jones氧化）和还原（Wolff-Kishner）反应[35]。由于CA在牛和羊的胆汁中含量丰富，因此曾使用CA作为UDCA化学催化的前体。但是，从CDCA合成UDCA的过程更加简单，而

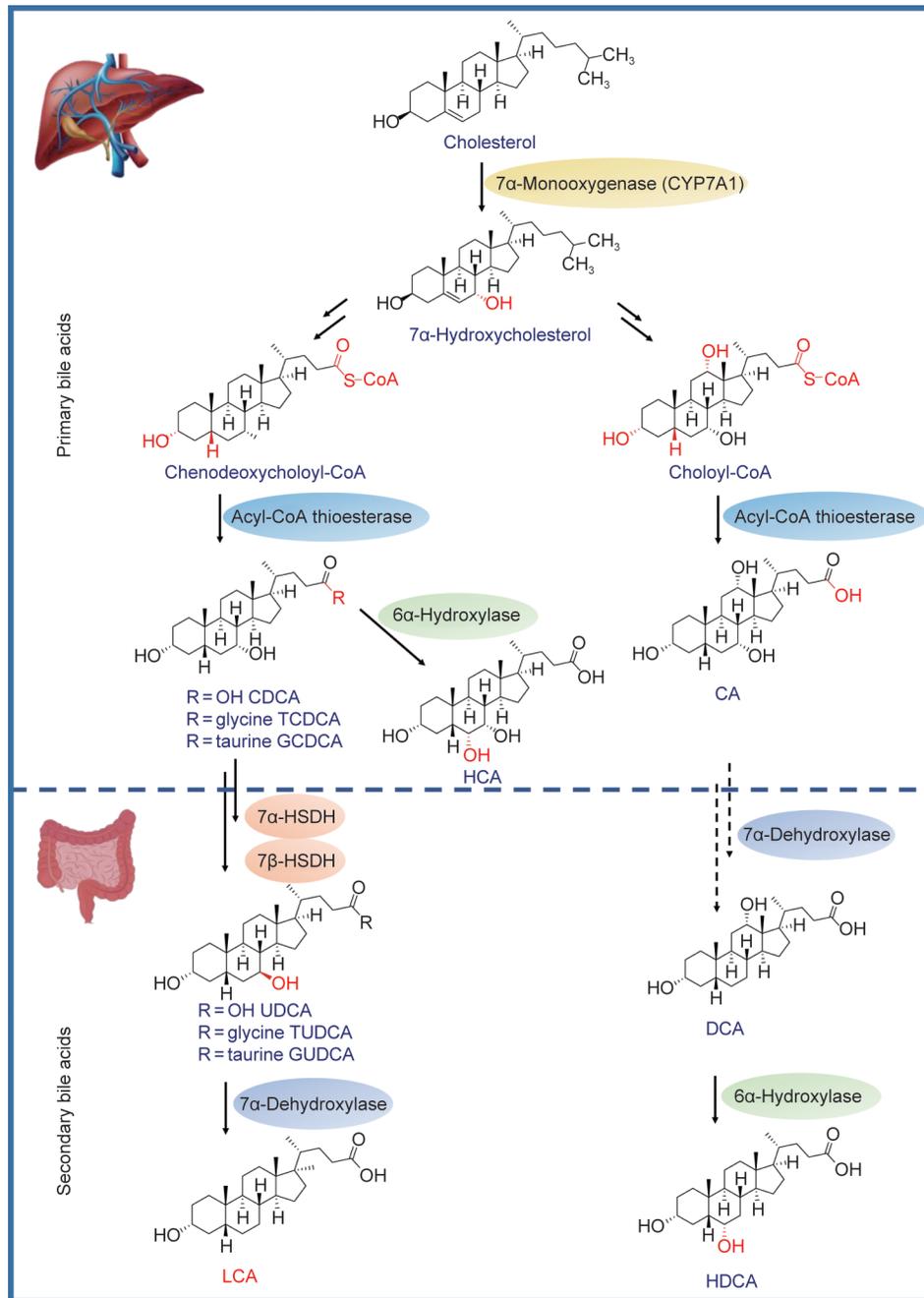


图4. 胆汁酸的生物合成途径。CoA：辅酶A。

且生产成本比CA合成更低,因此,随着提取工艺的成熟和大规模生产,CDCA已经逐渐取代CA用于合成UDCA。目前,CA、UCA、DCA和HDCA都作为CDCA和UDCA化学合成的原材料。由于复杂的反应过程、低选择性、苛刻的反应条件、高能耗、高污染等问题,胆汁酸的化学合成仍然面临各种挑战,限制了该工艺的工业化发展。

生物催化在高效环保的合成中发挥着越来越重要的作用,全细胞转化和酶催化都已用于胆汁酸生产的生物催化。一些微生物,如梭状芽孢杆菌、产气柯林斯菌、大肠杆菌和脆弱拟杆菌,已用于全细胞转化,生产UDCA、UCA和12-oxo-UDCA [35]。真菌菌株,包括双极霉属、赤霉菌属、小克银汉霉菌属和弯孢菌属、假诺卡氏菌属、糖丝菌属、拟无枝菌酸菌属、伦茨菌属、糖多孢菌属和诺卡氏菌属,可生产UDCA,一些菌株还可生产CDCA、DCA、CA、7-酮DCA和3-酮DCA [122]。需要注意的是,全细胞转化也存在生长条件苛刻、微生物致病性强、催化产物复杂等缺点。

随后,全细胞转化逐渐被酶催化系统所取代。 $3\alpha$ -HSDH、 $7\alpha$ -HSDH、 $7\beta$ -HSDH和 $12\alpha$ -HSDH是参与胆汁酸生物合成的关键酶。 $3\alpha$ -HSDH催化C3-羟基基团的氧化,已用于临床定量检测血清中的总胆汁酸[123]。 $7\alpha$ -HSDH和 $7\beta$ -HSDH是从CDCA合成UDCA的两种关键生物催化剂,已引起越来越多的关注,它们催化类固醇底物中C-7位羟基的氧化或还原反应[124]。CA、UCA和DCA的12-OH基团可被 $12\alpha$ -HSDH氧化,分别生成12-oxo-CDCA、12-oxo-UDCA和12-oxo-UDCA。这些酶能够进行高区域选择性和立体选择性的羟基化和脱羟基反应。P450单加氧酶、 $6\alpha$ -羟化酶、 $7\alpha$ -脱羟基酶和脂肪酶也已被表征。CYP107D1 (OleP)是一种高度区域和立体选择性的P450单加氧酶,它可以羟基化LCA形成鼠脱氧胆酸(MDCA)作为唯一产物[125]。随后,Grobe等[126]改造了CYP107D (OleP)、S240A变体和三重突变体(F84Q/S240A/V291G)作为生物催化剂,对LCA进行区域和立体选择性 $7\beta$ -羟基化,以生成UDCA。 $6\alpha$ -羟化酶(CYP4A21)催化CDCA的 $6\alpha$ -羟基化,产生猪的主要胆汁酸HCA,它也用于从DCA生产HDCA [127]。 $7\alpha$ -脱羟基酶负责CA和UDCA的 $7\alpha$ -脱羟基化,分别形成DCA和LCA [128]。脂肪酶可催化HDCA,产生各种HDCA衍生物[129]。这些序列大部分已上传到美国国家生物技术信息中心(NCBI) GenBank数据库,已经开展许多研究,基于序列-结构-功能分析进行了合理设计,以提高酶活性。

但是,生物催化法生产的UDCA和CDCA成本较高,

市场竞争力不强。化学-酶法合成兼具化学合成和生物合成的优点,立体选择性高、产率高、毒性低,是一种具有广阔工业前景的潜在方案。总体而言,目前已开发出多种廉价易得的胆汁酸作为化学-酶法合成胆汁酸的原料,包括CA、DCA、HDCA、UCA、脱氢胆酸(DHCA)、磷酸胆酸(PCA)(图5)。

## 5. 结论和未来展望

根据致病源的不同,感染性疾病可以分为病毒性、细菌性、真菌性和寄生虫感染几种类型。药物疗效是药物与病原体之间一场由来已久且不断升级的“军备竞赛”。目前,耐药性的出现已成为全球性难题,因此,控制其发展恶化刻不容缓。特别是在细菌引起的感染性疾病中,细菌耐药性加强是后抗生素时代的严峻现实。抗生素长期以来被用于对抗致病细菌,而细菌对越来越多的抗生素逐渐产生长期耐药性。虽然真菌耐药性还不如细菌耐药性普遍,但有资料显示,光滑念珠菌对棘白菌素的耐药性以及烟曲霉对唑类药物的耐药性正在增加[130–133]。由于抗真菌药物数量有限以及耐药性的出现,可用的药物非常有限。病毒和寄生虫也存在类似的情况,乙肝病毒(HBV)和人类免疫缺陷病毒(HIV)对拉米夫定的耐药性正在成为临床治疗的瓶颈[134–135]。近年来,疟原虫被发现对奎宁和氯喹具有耐药性,而这两种药物都是一线抗疟药物[136]。为了解决这个问题,世界各地的科学家一直在寻找新的方法来消灭病原体,同时不产生耐药性。数百年来,研究人员获得了大量的抗感染药物,其中大多数针对病原体。与细菌对这些药物的反应相比,细菌不易对胆汁酸产生耐药性,这使得胆汁酸成为药物开发中有吸引力的候选药物。

随着天然产物的枯竭和耐药性的增加,新型抗菌药物的开发变得越来越困难。近年来,针对上市药物的病理生理学机制进行药物再利用一直是新药研发的热点。例如,瑞德西韦是吉利德公司开发的一种广谱抗病毒药物,最初研究用于治疗埃博拉病毒感染,2020年,瑞德西韦成为首个用于治疗COVID-19患者的药物[137]。沙利度胺是一种镇静镇痛药,最初用于治疗妊娠期早孕反应,但后来发现它会导致严重的出生缺陷。后来,沙利度胺被发现具有抗血管生成和免疫调节的活性,具有独特的抗骨髓瘤作用,因此它目前是治疗多发性骨髓瘤的常用药物之一[138–139]。我们期望用于治疗肝胆疾病的胆汁酸药物可以在未来重新利用,成为新型抗感染药物,为预防和治疗传染性疾病、减少耐药性、缩短药物研发周期、降低成本和安全



用, 成为未来有前途的抗感染药物。然而, 研究人员对感染性疾病的病理机制和过程了解不足, 这严重限制了该领域的发展, 因此, 需要对胆汁酸在预防和治疗传染性疾病方面的基础研究和临床疗效进行更全面的研究。我们认为, 胆汁酸可以通过靶向作用特定的受体或通路来治疗相关疾病, 从而提供更精准的治疗方案。由于胆汁酸对免疫反应有影响, 因此可用于治疗其他以免疫异常为特征的疾病。胆汁酸在维持肠道菌群平衡和肠道健康方面也具有广阔的应用前景。

迄今为止, 抗感染药物的发展还没有跟上微生物进化的步伐。相比之下, 中医药已被广泛使用了数千年, 没有出现耐药性, 其安全性和有效性也得到了证实。中医的基本原理是“扶正祛邪”, 而不是直接杀死病原体。因此, 我们推测中药不会刺激病原体发生变异, 不太可能使它们产生耐药性。中医术语的定义列于附录 A 表 S1 中。中药可以被视为药物发现的生物活性化合物宝库。将中药与抗生素相结合的新型治疗策略已显示出对抗各种感染的独特优势。

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## Compliance with ethics guidelines

Shuang Liu, Shuo Yang, Biljana Blazekovic, Lu Li, Jidan Zhang, and Yi Wang declare that they have no conflict of interest or financial conflicts to disclose.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eng.2023.11.017>.

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