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Review 综述

中药协同抗真菌药物抗隐球菌的研究进展

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摘　要：隐球菌是一种全球分布的侵袭性真菌，已经引起了严重的公共卫生问题。隐球菌致病菌种主要以新型隐球菌为代表，其在感染人体后可引起死亡率极高的肺隐球菌病及隐球菌脑膜炎等。目前传统抗真菌药物只有多烯类、氟胞嘧啶类、棘白菌素类和唑类四类，在临床中单独用药时存在治疗效果不显著以及导致耐药等情况出现。因此，研究人员把视角转向联合用药，并发现一些中药及天然植物提取物和衍生物与传统抗真菌药物联合使用对治疗隐球菌病具有良好的协同效果，本文就中药联合抗真菌药物研究现状进行总结。

关键词：新型隐球菌；联合治疗；抗真菌药物；中药；抑菌机制

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Research progress in combined application of traditional Chinese medicines and antifungal agents in treating *Cryptococcus* infections

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Abstract: *Cryptococcus*, a genus of invasive fungi with global distribution, have caused serious public health problems. Notably, *Cryptococcus neoformans* (*Cryptococcus neoformans*, *C. neoformans*) represents the main pathogenic species of *Cryptococcus*. The infection of *C. neoformans* can cause pulmonary cryptococcosis and cryptococcal meningitis with high mortality rates. The commonly used antifungal drugs are polyenes, flucytosine, echinocandins, and azoles, which have limited efficacy and may induce resistance when being used alone in clinical practice. Therefore, researchers have studied combined therapy. They have discovered that the combinations of some traditional Chinese medicines and natural plant extracts and derivatives with the commonly used antifungal drugs demonstrate synergistic effects in the treatment of cryptococcosis. This paper reviews the research progress in the combined application of antifungal drugs and traditional Chinese medicines.

Keywords: *Cryptococcus neoformans*; combined therapy; antifungal drugs; traditional Chinese medicine; antifungal mechanism

最新的研究报道，全球每年约 3 亿人罹患严重的真菌感染，且每年死于真菌疾病的总人数已上升至 375 万人[1]。其中，造成患者死亡的真菌主要包括隐球菌、念珠菌、曲霉菌、肺孢子虫、组织胞浆菌等[2-3]。隐球菌属于真菌中的一种经典致病菌，鸽子粪是其天然宿主[4]。目前隐球菌致病菌种主要包括新型隐球菌(*Crytococcus neoformans*)和格特隐球菌(*Crytococcus gatti*)，其中又以新型隐球菌为主[5-6]。在 2022 年，世界卫生组织发布的真菌优先病原体清单上，新型隐球菌被列为关键真菌病原体且位居榜首；同时，新型隐球菌属中的菌种易突变，这导致新型隐球菌病在临床上的致死率极高；常用的临床抗真菌药物对隐球菌病的治疗效果并不理想，且存在耐药性、毒性以及高成本等尚未解决的问题[7]。基于此，越来越多研究人员将视角转向联合用药，并发现一些中药及天然植物提取物和衍生物与传统抗真菌药物联合使用对治疗隐球菌病具有良好的协同效果，本文就中药联合抗真菌药物抗隐球菌的研究现状展开综述，以期为寻找高效、低成本的隐球菌病治疗策略提供参考。

1 隐球菌病现状

1.1 隐球菌病感染现状

新型隐球菌病多见于免疫功能低下的人群，如 HIV 患者、器官移植患者和肿瘤患者等[7-8]。隐球菌最初感染于肺部，随后可以传播到中枢

神经系统和血液中引起隐球菌脑膜炎(cryptococcal meningitis, CM)和隐球菌血症，部分隐球菌侵入中枢神经后还会进一步形成生物膜型隐球菌瘤[9]。此外，临床中医疗器械上黏附的隐球菌也会加大感染几率，这些都为隐球菌病的治疗带来更大挑战[10-11]。最近的研究报道显示，刚果共和国在 1953−2021 年共发现 1 018 例隐球菌病患者，其中 823 例(80.84%)为神经脑膜型，超过一半的患者死于 CM[8]。尽管随着抗逆转录病毒治疗方法的推进，隐球菌相关免疫重建炎症综合征的发病率已经从 2003−2008 年的 30% 左右下降至 2014−2022 年的 3%−20%，但由于全球不同地区和国家的医疗水平有所差异，抗逆转录病毒治疗方法无法得到全面应用，使得许多发展中国家(尤其是撒哈拉以南的地区)仍有很高的 CM 死亡率[7]。目前，全球每年发生约 223 100 例隐球菌脑膜炎，并导致约 181 100 例患者死亡，其中大部分死亡病例来自于医疗水平低下的国家[12-13]。由此可见，抗隐球菌感染已成为当下临床中面临的一个重要难题。

1.2 隐球菌病治疗现状

通常，治疗人类侵袭性真菌感染的药物主要有四大类：多烯类、氟胞嘧啶类、棘白菌素类和唑类，其具体抑菌机制如表 1、图 1 所示[7]。

遗憾的是，由于隐球菌属的固有特性以及相关药物的局限性，目前关于隐球菌感染的治疗具有极大的挑战性[12]。唑类药物只能抑制隐球菌生长却无法杀死隐球菌，并且会影响其他药物的作用，隐球菌属对棘白菌素类药物具有天然抗性，并且多烯类、氟胞嘧啶类药物存在毒性大、成本高、治疗成功率低等多方面问题[21-24]。需要注意的是，当两性霉素 B (多烯类)与一些药物同时使用时会造成一些严重的不良反应，如与利尿剂、糖皮质激素或泻药等合用时，通常会造成低钾血症进而引起心律失常[19]。

表1 常见抗隐球菌药物的抑菌机制和耐药机制

Table 1 Mechanisms of inhibition and resistance of common anti-*Cryptococcus* drugs

Drug class	Representative drug	Mechanism of inhibition	Mechanism of resistance
Polyene	Amphotericin B (AMB)	Binds to ergosterol and directly damages cell membranes to produce bactericidal activity	Altering the amount of ergosterol in the cell membrane[14]
Flucytosine	5-fluorocytosine (5-FC)	As a precursor that enters cells *via* the cytosine permease FCY2 and is converted to toxic 5-fluorouracil by the cytosine deaminase FCY, affecting nucleic acid metabolism[15-16]	Mutations in the FUR1 and FCY2 genes that result in deficiencies in enzymes required for cellular uptake or metabolism of fluorocytosine (cytosine permease and deaminase) and increase the synthesis of pyrimidines that compete with fluorinated anti-metabolites of fluorocytosine[16-17]
Echinocandins	Micafungin (MIF)	Noncompetitive binding of the Fks1p subunit of β-(1,3)-D-glucan synthetase leads to structural abnormalities in fungal cell walls[18]	Mutations in the Fks1 subunit gene[18]
Azole	Fluconazole (FLC)	Inhibition of ERG11, which inhibits the conversion of lanosterol to ergosterol[19] Influence on beta microtubule protein distribution[20]	Upregulation of the ERG11 gene due to mutations in ERG11 and UPC2, and overexpression of drug efflux pumps (Mdr1p and Cdr1p/Cdr2p) due to mutations in transcription factor genes (MRR1, TAC1, and PDR1)[15]

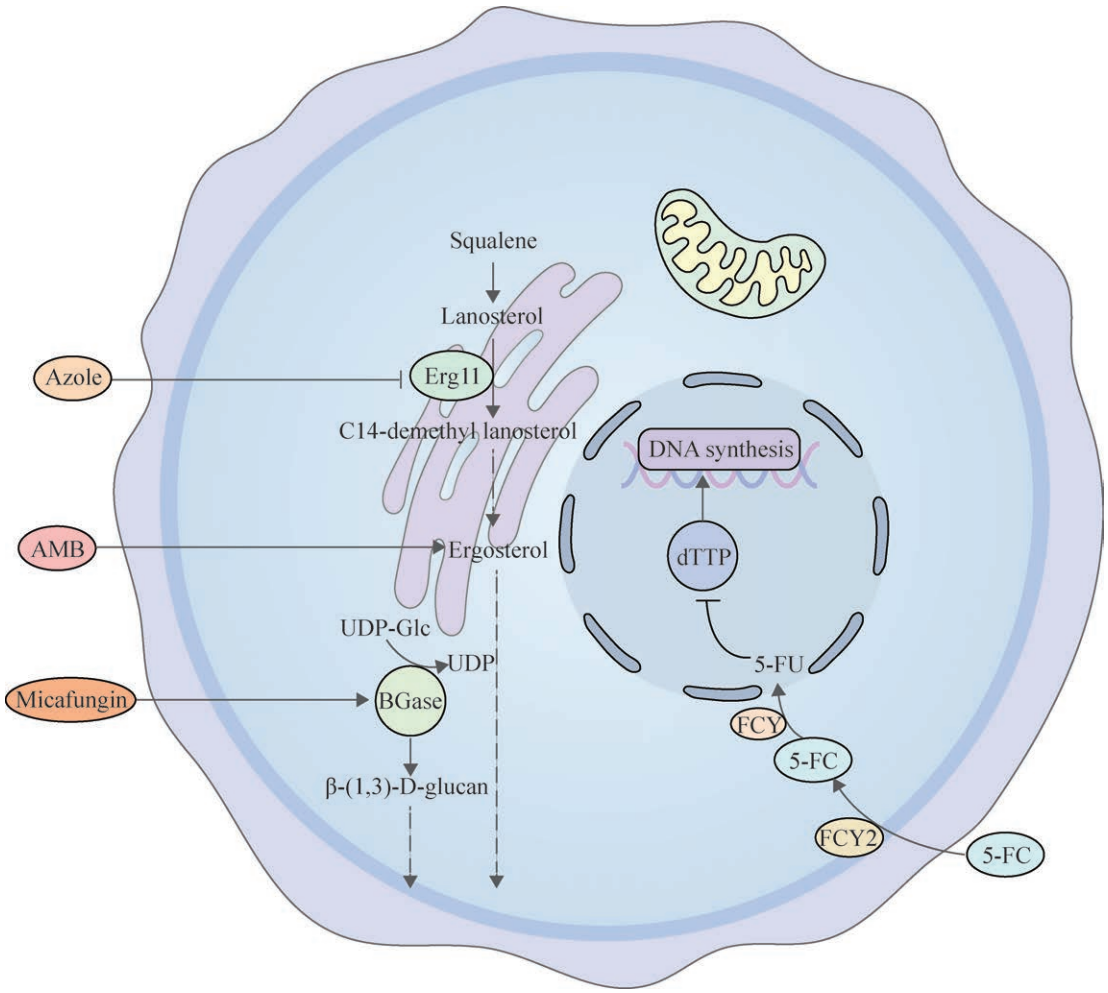

图1　常见抗隐球菌药物的抑菌机制图。唑类药物通过抑制Erg11酶进而抑制羊毛甾醇转化为麦角甾醇；多烯类药物(如两性霉素B)通过直接与麦角甾醇结合进而破坏细胞膜；棘白菌素类药物(米卡芬净)通过结合BGase的Fks1p亚基进而抑制β-(1,3)-D-葡聚糖合成；氟胞嘧啶类药物5-氟胞嘧啶(5-fluorocytosine, 5-FC)通过转化为5-氟尿嘧啶(5-fluorouracil, 5-FU)以抑制dTTP合成，进而破坏真菌DNA合成。

Figure 1　Diagram of Common anti-*Cryptococcus* drugs' inhibition mechanisms. Azole drugs inhibit the Erg11 enzyme, thereby blocking the conversion of lanosterol to ergosterol; Polyene drugs (AMB) bind directly to ergosterol, disrupting the cell membrane; Echinocandin drugs (micafungin) inhibit β-(1,3)-D-glucan synthesis by binding to the Fks1p subunit of BGase; Flucytosine (5-FC) is converted to 5-FU, which inhibits dTTP synthesis and ultimately disrupts fungal DNA synthesis.

然而，开发新型抗真菌药物是一个昂贵且耗时极长的过程，其最终的结果往往也不尽如人意。当研究方向转向中药时，我们发现，相较于西药单一的作用靶点而言，大部分中药都具有多种药理作用，它们既可以抗炎又可以增强机体免疫力，这种多作用靶点使得中药在感染性疾病中的治疗应用可能更为全面有效[25]。同时，由于大部分中药源于天然植物，其副作用通常比一些西药更小，并且中药相关的复方配方也能够在一定程度上减轻药物的毒性，进而减少

对器官的损害风险[26]。此外，中药本身具有多种活性成分，包括黄酮类、生物碱、酚类和醌类，这些成分不仅可以抑制微生物的生长，还能与多种抗菌药物协同作用，共同应对各种微生物感染性疾病的治疗[27]。例如，黄芩素与四环素和β-内酰胺类抗生素的联合用药显著降低了耐甲氧西林金黄色葡萄球菌的最低抑菌浓度(minimum inhibitory concentration, MIC)，使其发挥更有效的抗菌作用[28]；黄芩素和青霉素的联合应用可以抵抗产生青霉素酶的耐甲氧西林金黄色葡萄球菌或金黄色葡萄球菌感染[29]；槲皮素联合妥布霉素和阿米卡星对多重耐药铜绿假单胞菌具有潜在的抗菌活性[30]；丁香酚与头孢噻肟和环丙沙星联合使用可抵抗产生超广谱β-内酰胺酶的喹诺酮类耐药病原肠杆菌感染[31]。诸如此类，中药联合一些常见抗菌药物来抵抗微生物感染的临床实例已非常多见，而在抗隐球菌方面同样也可以采用联合用药组合。已有研究指出，中药与西药联合用药策略是一个比较理想的治疗方案，其可以有效避免当前隐球菌感染治疗中常见的耐药性强、毒性大及成本高等问题[32-33]。因此，下文将介绍在抗隐球菌中一些中药与常见抗真菌药物联合使用的抑菌疗效与机制。

2 中药协同抗真菌药物抗隐球菌的作用影响

在探讨中药与抗真菌药物联合抗新型隐球菌的策略时，理解其毒力因子与药物的相互作用至关重要。新型隐球菌通过毒力因子和细胞膜形成强大的致病与耐药屏障，这些毒力因子不仅帮助隐球菌抵御宿主免疫，还推动耐药性的发展。以下将通过分析荚膜、黑色素等毒力因子和细胞膜的作用及其与药物的交互，以深入理解抗新型隐球菌的治疗机制。

2.1 毒力因子

新型隐球菌公认的3个毒力因子分别是荚膜、黑色素和耐热性。此外，还有一些酶类也与其毒性有关。

2.1.1 荚膜

新型隐球菌的多糖荚膜由葡萄糖醛酸木糖甘露聚糖(glucuronoxylomannan, GXM)、半乳糖木糖甘露聚糖(galactoxylomannan, GalXM)和甘露糖蛋白(mannoproteins, MPS)组成，其中GXM含量高达88%[34]。这种主要由GXM组成的可以抗吞噬的多糖荚膜是隐球菌属所特有的，其对宿主免疫具有多种作用，并且可以随着暴露于身体组织和体液的多少而改变大小[35-36]。Lee等[37]通过对小鼠进行鼻内外源性GXM药物处理，发现≥62.5 μg/mL的GXM剂量可降低脑组织中紧密连接蛋白如Claudin-5、ZO-1和JAM-A (P<0.05)的表达，在10 μg/mL的浓度下可以上调细胞骨架调节因子RhoA的表达，研究还发现GXM可以破坏跨内皮电阻进而损坏血脑屏障，促进隐球菌向中枢神经系统转移。此外，王甜甜[38]的研究表明，当厚朴酚浓度为16 μg/mL时可完全抑制新型隐球菌荚膜生长；徐佳龙等[39]研究发现，小檗碱(1×MIC和4×MIC)可显著抑制新型隐球菌的胞体和荚膜生长。

2.1.2 黑色素

黑色素是一种抗氧化多酚色素，通过漆酶诱导合成，由2个基因LAC1和LAC2编码，LAC1是参与这种色素生产的主要蛋白质，黑色素可以结合并降低抗真菌药物的敏感性[40]。黑色素还可以保护新型隐球菌免受紫外线或极端电离辐射、氧化损伤、极端温度以及感染期间巨噬细胞的吞噬作用，是隐球菌难以治疗的一个重要因素[34,41-43]。目前，研究发现它的合成有环AMP/蛋白激酶A (cAMP/PKA)和高渗透压甘油反应2条通路[43]。徐佳龙等[39]研究也发现，

小檗碱(4×MIC)可显著抑制新型隐球菌黑色素的产生。

2.1.3 其他

Hassanpour 等[44]研究发现，在尿素培养基培养物中添加丁香酚(125 μg/mL)和氟康唑(8 μg/mL)可降低新型隐球菌的脲酶活性。菌类来源的脲酶与人类和动物的一些发病机制密切相关，脲酶可以催化水解尿素生成二氧化碳和氨，可能会影响体内尿素的正常代谢，造成氮的过量积累，进而影响身体的酸碱平衡[45]。这表明，丁香酚与氟康唑联合使用可以有效减小新型隐球菌感染对人体的影响。

2.2 细胞膜

Nóbrega 等[46]针对 *C. neoformans* LM-22 菌株进行测试，发现香芹酚的 MIC 在麦角甾醇浓度为 100 μg/mL 和 200 μg/mL 时增加 4 倍，在 400 μg/mL 浓度下增加 8 倍，其 MIC 与培养基中麦角甾醇的浓度成比例增加。这表明香芹酚可能通过与外源性麦角甾醇结合使膜渗透性增加，进而导致细胞内容物如 Ca^{2+}、K^{+}、自由基和蛋白质的渗出而发挥作用[47]。Cardoso 等[48]研究指出，罗勒的乙醇粗提取物(312 μg/mL)、己烷馏分(78 μg/mL)、乙醇粗提取物(19.5 μg/mL)+罗勒精油(78 μg/mL)以及己烷馏分(10 μg/mL)+罗勒精油(39.36 μg/mL)对新型隐球菌麦角甾醇合成的抑制率分别为 9.09%、27.27%、62.46% 和 68.28%。研究还发现，即使在非常低的浓度下，罗勒的各提取物也能显著降低麦角固醇的含量，这表明它们可能抑制麦角固醇的生物合成[48]。

3 中药联合抗真菌药物抗隐球菌的具体机制

3.1 作用于生物膜

Kumari 等[49]通过研究百里香、牛至提取物百里酚(thymol, THY)和香芹酚(carvacrol, CARV)对新型隐球菌生物膜的抑菌机制，结果发现，当加入麦角甾醇后，百里酚和香芹酚的 MIC_{80} 和 BIC_{80} (biofilm inhibition concentration, BIC)显著增加(在 100−400 μg/mL 麦角甾醇中，THY 和 CARV 的 MIC_{80} 值增加 2−8 倍，其 BIC_{80} 值增加 4−16 倍)，这表明 THY 和 CARV 可以结合麦角甾醇并抑制其生物合成，进而导致生物膜形成孔洞；此外，THY 和 CARY 还能影响生物膜上脂质的分布，使饱和脂肪酸/不饱和脂肪酸值升高，从而降低细胞膜流动性(膜脂质变化如表 2 所示)；最后，他们发现 THY 和 CARY 可引起 K^{+}外流和线粒体膜去极化进而破坏离子稳态并激活氧化应激等系统，触发活性氧(reactive oxygen species, ROS)生成，使细胞外聚合基质和荚膜糖(甘露糖、木糖和葡萄糖醛酸)的数量显著下降，破坏菌体荚膜。

3.2 抑制酶的合成

Bang 等[50]基于 DNA 微阵列的转录组分析，通过监测 1 mg/L 小柴碱衍生物 KR-72 处理 *C. neoformans* H99 的转录组谱，结果发现 KR-72 与抗生素他克莫司 FK506 的联合处理在 37 ℃可

表2 药物处理后膜脂质成分百分比的变化

Table 2 Changes in the percentage of membrane lipid composition after drug treatment

Drug treatment	Saturated fatty acid			Unsaturated fatty acid	
	Palmitic acid (%)	Stearic acid (%)	Heptadecanoic acid (%)	Oleic acid (%)	Linoleic acid (%)
Control	26	6.3	2.9	36.65	27.75
THY	43	14.1	4.2	2.40	35.59
CARV	41	16.5	1.2	7.80	33.06

以抑制新型隐球菌中钙调磷酸酶活性，其比每种药物的单独治疗更能有效杀死新型隐球菌。王甜甜[38]研究发现厚朴酚可以通过下调相关基因表达使谷胱甘肽转移酶、醌氧化还原酶和谷氨酸转氨基酶的含量明显下降，进而影响菌体的氧化还原过程。

3.3 影响核酸合成代谢活动

王甜甜[38]研究表明，与对照组相比，厚朴酚联合氟康唑处理组可通过下调相关基因影响DNA复制相关蛋白的表达(如微小染色体维持蛋白/DNA聚合酶ε)，进而干扰DNA的复制过程。Bang等[50]研究还发现，小柴碱衍生物KR-72可引起MGE1基因过表达，MGE1通过影响DNA损伤修复和遗传毒性应激反应，进而引起细胞周期紊乱。

3.4 破坏信号通路

Li等[51]将大蒜素与两性霉素B (amphotericin B, AMB)联合作用于*C. neoformans* H99，发现其分数抑菌浓度(fractional inhibitory concentration index, FICI)可达0.375，提示大蒜素与AMB在抗隐球菌作用上具有协同效应($FICI=MIC_{A+B}/MIC_A+MIC_{A+B}/MIC_B$，当$FICI\leq0.5$表示两药物联合作用具有协同效应；当$0.5<FICI<4$，表示两药物为相加作用；$FICI\geq4$提示两药物为拮抗作用)。同时，Li等[51]发现大蒜素可以抑制隐球菌菌丝形成，处理的机制主要涉及以下几个方面：破坏菌体核苷酸错配修复、糖基磷脂酰肌醇(glycosylphosphatidyli-nositol, GPI)锚定蛋白生物合成、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路-酵母和磷脂酰肌醇信号系统等的相关基因，其中GPI锚定蛋白对真菌黏附、形态转化和细胞壁合成有重要作用。MAPK信号通路由信息素激活，并通过一系列激酶的顺序磷酸化来协调信号转导，包括Ste20α/a (p21-激活激酶，PAK)、Ste11α/a (MAPK激酶激酶)、Ste7 (MAPK激酶)和Cpk1 (MAPK激酶)[52-53]。Nrf2/HO-1/NQO1信号通路及其下游产物可调节氧化应激，抗炎、抗氧化和抗细胞凋亡[54-56]。王甜甜[38]研究发现厚朴酚可能通过该信号通路对新型隐球菌产生抗真菌作用。

综上所述，中药与抗真菌药物的协同作用能够通过多种分子介导的相关信号通路，有效地对抗隐球菌，关于联合用药的具体药物组合、药物作用浓度及其作用机制如表3和表4所示。

4 抗隐球菌药物的研发方向

尽管抗真菌药物通过不同机制抑制隐球菌的生长与繁殖，但有时隐球菌仍然能够通过免疫逃逸成功躲避宿主防御。因此，抗隐球菌药物的研发应重点关注如何削弱其免疫逃逸能力，同时增强宿主免疫反应，以进一步提高治疗效果。

4.1 减少免疫逃逸

通常情况下，细胞表面成分的改变会影响人体对新型隐球菌的免疫力；隐球菌的荚膜和黑色素可以通过参与隐球菌免疫逃逸的过程，从而增强了隐球菌感染宿主的能力。反之，如果破坏这些结构，则可以抑制隐球菌的免疫逃逸[68]。研究发现，隐球菌荚膜的主要成分GXM可以诱导Fas/FasL通路介导的巨噬细胞凋亡从而抑制宿主免疫系统的激活[69]，同时，GXM还可以降低趋化因子受体的表达，抑制血管中白细胞流出，减少细胞因子产生并阻碍树突状细胞的成熟和抗原呈递过程[70-71]。此外，隐球菌荚膜的另一成分GalXM通过诱导T细胞凋亡，抑制巨噬细胞吞噬作用和抗原呈递细胞的抗原呈递能力，下调炎性细胞因子水平，消耗补体成分从而形成免疫逃逸[72]。参与荚膜合成需要

表3　中药协同抗真菌药物抗隐球菌的作用浓度

Table 3　The concentration of traditional Chinese medicine in synergy with antifungal drugs against *Cryptococcus*

Drug combination	MIC of drugs used alone (μg/mL)		Combination therapy MIC (μg/mL)		FICI
	Chinese medicine	Antifungal drugs	Chinese medicine	Antifungal drugs	
Oxidized resveratrol+itraconazole (ITC)/MIF[57]	2.5×10^5–1×10^6	31–250/250–1 000	1.5×10^4–2.5×10^5/1.5×10^4–1.25×10^5	15–125/63–250	≤0.5
Li Shen Pills+AMB[58]	128	0.25	32	0.125	0.625
Chaparraline+FLC/AMB[39]	8–16	0.25–4.00			0.625/1.000
Acteoside+AMB[59]	>12.5	1.0	<0.195	0.015 6	0.031 2
Magnolo+FLC[38]	4–32	4–32	0.5–2	0.5–2	≤0.5
Ocimum basilicum+AMB[48]	625–2 500	1.56	39–157.2	0.099–0.396	0.188
Eugenol+AMB/FLC/ITC[44]	8	125	0.75	4	0.75
Pedalitin+AMB[60]	3 900	125	100	30	0.49
Pinus sylvestris/*Origanum vulgare*/*Thymus vulgaris*+ITC[61]	300/140/560	0.5			0.375/0.375/0.375
Allicin+AMB[51]	2	0.25	0.25	0.062 5	0.375
Aloe emodin/barbaloin/hrysophanol+AMB[62]	64–128/64–128/≥256	1.00		0.25/0.03/0.25	≤0.5

多种糖基转移酶，目前隐球菌木糖基转移酶 1 (cryptococcal xylosyltransferase 1, Cxt1p)是已知的唯一直接参与隐球菌荚膜合成的糖基转移酶，通过破坏 Cxt1p 的功能，可以有效地阻断隐球菌的免疫逃逸过程[73]。综上所述，多种中药与抗真菌药物联合使用可以有效抑制隐球菌荚膜的生长，但具体机制目前尚不清楚。因此，未来可以针对荚膜合成所需的其他糖基转移酶进行抗隐球菌药物的开发研究。

研究发现，隐球菌的黑色素可降低宿主的细胞因子反应性，减弱吞噬作用，中和炎症细胞释放的氧化物质(如 ROS)，并抑制抗真菌药物活性，从而起到保护隐球菌和逃避宿主免疫功能的作用[74-75]。因此抑制隐球菌黑色素合成也是抗隐球菌的一个重要思路。黑色素受核心转录因子的合成网络调节，包括 Bzp4、Usv101、Hob1 和 Mbs1，以及核心激酶 Gsk3 和 Kic1，这些都为开发抑制黑色素合成的临床药物提供了潜在作用靶点[69]。

4.2　增强宿主免疫反应

尽管隐球菌荚膜抑制了宿主的吞噬作用，但补体蛋白和循环抗体等调理素可以协助巨噬细胞吞噬隐球菌[76]。研究发现，缺乏补体的动物比补体充足的动物更容易感染新型隐球菌，并且感染隐球菌的患者可能会出现补体耗竭的情况[77]。特异性抗荚膜抗体、甘露糖结合凝集素分别可以通过经典途径、凝集素途径激活补体[78-79]。目前，已经有各种研究集中在隐球菌抗原(即 GXM、细胞壁多糖和隐球菌蛋白)的获得性抗体上。因此，开发增强补体和抗体的临床药物也是一条抗隐球菌的新途径。

值得一提的是，在巨噬细胞内，隐球菌可以通过抑制吞噬溶酶体的完全酸化、抵抗吞噬溶酶体产生的自由基等途径在巨噬细胞内存活并繁殖[80-81]。这分别依托于隐球菌的脲酶活性和荚膜的抗氧化特性[81-82]。因此，任何能够抑

表4 中药协同抗真菌药物抗隐球菌的分子机制

Table 4 Molecular mechanisms of synergistic antifungal drugs against *Cryptococcus* in traditional Chinese medicine

Drug combinations	Research strains	Synergistic inhibitory mechanism
Oxidized resveratrol+itraconazole (ITC)/MIF[57]	*C. gatti* and *C. neoformans*	Binds to DNA causing it to cleave, stalling the G2/M phase[63]
Li Shen Pills+AMB[58]	*C. neoformans*	
Chaparraline+FLC/AMB[39]	*C. neoformans* H99 and *C. neoformans* N99a	Inhibition of podophyllotoxin and melanin production Up-regulation of the NRG1 gene inhibits sexual reproduction[64]
Cryptocephalus analgesic soup+AMB[65]	Patients with novel CM	Reduces cerebrospinal fluid pressure, white blood cell count, and cryptococcal count and reduces inflammatory response
Acteoside+AMB[59]	*C. neoformans* ATCC 204092	Inhibits biofilm synthesis; increases cell membrane permeability while decreasing cell viability
Magnolol+FLC[38]	*C. neoformans* BNCC 225501 and clinical isolates	Inhibition of podogenesis and urease synthesis Affects histidine metabolism, arginine biosynthesis, and sphingomyelin metabolism
Ocimum basilicum+AMB[48]	*C. neoformans* T-444, *C. neoformans* H99A, and *C. gattii* WM779	Reduces hyperpigmentation, pod size and ergosterol synthesis
Eugenol+AMB/FLC/ITC[44]	*C. neoformans* PFCC 93-589	Reduced Cxt1p gene expression results in decreased β-1,2-xylosyltransferase synthesis
Thapsia villosa+FLC[66]	*C. neoformans* CECT 1078	Hydrophobicity of limonene promotes the solubilization of lipids aggregated in microbial plasma membranes, leading to loss of membrane integrity
Pedalitin+AMB[60]	*C. neoformans* ATCC 90112	
Allicin+AMB[51]	*C. neoformans* H99	Penetrates cell and organelle membranes (mitochondria), leading to organelle destruction and cell death
Curcumin+FLC[67]	*C. neoformans* ATCC 24065 and *C. neoformans* ATCC 32608	
Aloe emodin/barbaloin/chrysophanol+AMB[62]	*C. neoformans* ATCC 90113, human, and animal isolates	Anthraquinones may interrupt the cross-linking of β-glucan, making it easier for AMB to enter cells

制脲酶合成和荚膜生长的物质都具备成为抗隐球菌药物的潜力。同时，这也再次证明隐球菌荚膜是抗隐球菌药物开发的重要靶点。

4.3 中药抗隐球菌感染的应用前景

目前，已有多个研究指出，中药可以通过调节宿主免疫功能进而发挥其抗感染活性。如将莲花清瘟与常见抗病毒药物(奥司他韦)联合使用可抑制病毒诱导的核因子 κB (nuclear factor-κ-gene binding, NF-κB)活化，并减轻病毒诱导的 IL-6、IL-8、肿瘤坏死因子(tumor necrosis factor, TNF)-α、IP-10 和单核细胞趋化蛋白 1 的基因表达[83]。金花清感颗粒的核心活性成分可以和冠状病毒 3-胰凝乳蛋白酶样蛋白酶结合，进而抑制病毒复制和与靶细胞的结合，减少宿主炎症并激活抗病毒免疫[84]。化湿败毒颗粒通过抑制脂多糖、ROS 和干扰素-γ 介导的信号通路及 AGE-RAGE、TNF、NF-κB 和 RIG-I 样受体信号通路从而发挥其抗炎、抗病毒和免疫调节的作用[85]。甘草酸通过作用于 NOD 样和 Toll 样信号通路从而有效调节免疫反应，以促进干扰素的

产生，激活和平衡 T 细胞，并可防止过度的炎症反应发生[86]。研究发现，血必净通过防止细胞因子风暴、抑制炎症和调节 Tregs 及 Th17 细胞的平衡，提高了多种微生物败血症模型中感染性休克小鼠的存活率[87]。

总之，以上研究均表明中药能够调节宿主的免疫功能，这为抗隐球菌的药物研发提供了新思路，并为研发以中药为主的疫苗提供新方向。

5 结语

研发一种高效、价格低廉的抗隐球菌治疗方案迫在眉睫，中药文化源远流长，众多中药古典记录着中国古代医疗的发展，记载了大量的草药及其详细功效。一些中药本身就具有抗菌或抑菌活性，其与抗真菌药物联合使用后能更好地发挥抗隐球菌病的治疗效果。此外，一些中药还能为抗真菌药物提供进入细胞的“钥匙”，从而使抗真菌药物更好地发挥功效。因此，中药与抗真菌药联合抗隐球菌治疗将是大势所趋，这不仅可以极大减少探索研发新药的成本，并对现存药物的二次开发利用具有重要意义。

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