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·综述·

天然产物抗病原真菌的研究进展

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摘　要:目前,侵袭性真菌感染的发病率逐年上升,但现有抗真菌药物匮乏且新药研发相对缓慢,因此亟须发现和开发新的抗真菌药物。天然产物具有来源广、不良反应少等特点,是开发抗真菌药物的来源之一。大量研究证明,从植物和中药中分离的许多化合物具有抗真菌活性,且抗真菌机制多样。本文综述了天然产物抗真菌药物研发的最新进展,调查了具有潜在抗真菌活性的天然产物,并展望了新型抗真菌候选药物的开发前景。

关键词:侵袭性真菌感染;抗真菌药物;天然产物;中药;抗真菌机制

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Research on antifungal activity of natural products

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Abstract: The incidence of invasive fungal infections has increased year by year. However, the current antifungal drugs are scarce and the development of new drugs is relatively slow. Therefore, it is urgent to develop new antifungal drugs. Natural products have the characteristics of wide sources and low side effects. They are one of the sources of antifungal drugs. A large number of studies have proved that many compounds isolated from plants and traditional Chinese medicine have antifungal activities, and the antifungal mechanisms are different. The present paper reviews the latest progress on the development of antifungal drugs obtained from natural products, investigates the natural products with potential antifungal activity, and prospects the development of new antifungal candidates.

Keywords: Invasive fungal infection; Antifungal drug; Natural product; Traditional Chinese medicine; Antifungal mechanism

近年来,随着医学技术(如移植医学)的进步,越来越多的疾病可被治愈,但其导致的免疫抑制人群数量也迅速增加[1-2],促进了侵袭性真菌感染(invasive fungal infection, IFI)的发病[3],给临床真菌感染治疗带来了巨大挑战。真菌感染可分为浅表/皮下感染(皮肤癣病、花斑癣和孢子丝菌病)和侵

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袭性真菌感染[假丝酵母(也称念珠菌)病、曲霉病和隐球菌病],可累及任何类型的组织或器官,导致骨骼、肺和神经等损伤[3-4]。侵袭性真菌感染在免疫受损患者中尤其常见,如感染人类免疫缺陷病毒(human immunodeficiency virus,HIV)的患者,以及器官或骨髓移植和癌症患者等[4-5]。侵袭性真菌能引起可能导致死亡的全身感染,死亡率高达90%,每年造成约150万人死亡,严重威胁人类公共卫生健康[5]。

抗真菌药物可控制和治疗真菌感染,改变真菌的自然进化,其研发取得了重大进展。目前,临床上主要使用多烯类、唑类、烯丙胺类、棘白菌素类和氟胞嘧啶类5类抗真菌药物,包括两性霉素B、特比萘芬、氟康唑、5-氟胞嘧啶和卡泊芬净等[6]。然而,最近的流行病学数据显示,由于抗真菌药物的滥用及免疫抑制人群数量的增加,耐药和多重耐药菌株的临床检出率显著升高[7],特别是念珠菌属和曲霉属,对唑类药物耐药的非白念珠菌和烟曲霉的临床检出率正不断升高[8]。近年来获得极大关注的"超级真菌"——耳道念珠菌,其高达90%的临床分离株对氟康唑耐药[9]。因此,人们亟须发现和开发新的抗真菌药物,更新药物库,以应对新的耐药菌株的出现。

抗真菌药物的缺乏及真菌耐药性的出现,使得从化学合成产物或天然产物中发现和筛选新的抗真菌药物成为一项紧迫的任务。与化学合成产物相比,天然产物具有来源广、结构多样、毒性相对较低等优点[10],无论是以其原有形式还是作为结构优化的原始模板来获得高效安全的衍生物,天然产物都是抗真菌药物库的潜在来源。中药是天然产物的资源库,从中草药中分离得到的许多化合物被证明具有多种药理活性,如抗细菌、抗肿瘤、抗病毒和抗真菌活性[11]。鉴于目前抗真菌药物的缺乏和中药的有效性,从天然产物中开发抗真菌药物具有良好的前景。本文简要回顾了抗真菌天然产物的研究现状。

1 天然产物的抗真菌机制

目前,临床上用于治疗真菌感染的药物主要是多烯类、唑类、烯丙胺类、氟嘧啶类和棘白菌素,如两性霉素B、特比萘芬、氟康唑、5-氟胞嘧啶和卡泊芬净等[5],它们的作用靶点各不相同。与此类似,天然产物的抗真菌机制也不尽相同。明确天然产物的抗真菌机制有利于人们针对性地开发新一代抗真菌药物,本文从以下几个方面阐述天然产物的抗真菌靶点。

1.1 靶向细胞膜

细胞膜是许多代谢过程发生的场所,同时它能将细胞内容物与周围环境分隔开,以维持细胞内部稳态。因此,细胞膜的完整性和流动性对真菌细胞的生存和生长至关重要。提取自接骨木的松脂醇能破坏白念珠菌的细胞膜,且对人红细胞没有溶血活性,具有潜在的抗真菌活性[12-13]。麦角甾醇是真菌细胞膜的重要成分,能调节真菌细胞膜的流动性和细胞分裂[5]。厚朴酚是厚朴的主要单体之一,研究显示其可显著降低白念珠菌中麦角甾醇的含量,还可减少细胞膜上的转运蛋白对氟康唑的外排,从而增强氟康唑的抗真菌作用[14]。薄荷精油中的化合物,如薄荷醇、薄荷酮和香芹酮,可通过降低细胞膜中麦角甾醇的含量来抑制白色念珠菌的生长[15]。香芹酚和百里酚也可降低麦角甾醇的水平,影响抗氧化防御系统,增加膜通透性,阻断外排泵,从而恢复唑类的抗真菌敏感性[14,16]。

1.2 靶向细胞壁

真菌细胞壁具有较高的机械强度,能为细胞提供保护性屏障,抵抗各种环境压力,如冷、热、渗透压力等[17]。真菌细胞壁主要由葡聚糖、甘露糖和几丁质等组成,其中几丁质维持真菌细胞壁的机械强度,保持细胞壁的完整性。从地钱科提取出来的羽苔素E能抑制几丁质合成酶1(chitin synthase 1,CHS1)基因的表达,阻止真菌合成几丁质,从而达到破坏真菌细胞壁的目的[18]。真菌细胞壁的另一组分葡聚糖是宿主识别的病原相关分子模式,而棘白菌素能抑制真菌β-1,3-葡聚糖的合成,获得杀菌效果[19]。最近一项研究显示,鱼腥草素钠可能通过干扰β-1,3-葡聚糖的合成和运输而与氟康唑联用发挥协同作用[20]。

1.3 靶向线粒体

能量供应和代谢产物对于真菌的生存和生长及主要细胞事件(如白念珠菌从酵母态到菌丝态的转变)不可或缺。小檗碱能诱导真菌线粒体功能障碍和增加活性氧(reactive oxygen species, ROS)生成,与氟康唑联用具有协同作用[10,21]。此外,小檗碱能破坏白念珠菌细胞壁的完整性[22],还可抑制白念珠菌耐药基因 *CDR*1 的过度表达[23]。从姜黄中提取的姜黄素对许多真菌具有抗真菌活性[24-25],且其可单独或与唑类和多烯类药物联用发挥协同作用,增加白念珠菌细胞的活性氧生成并促使其凋

亡[26-27]。有报道称，从水飞蓟中分离的最著名和最有效的化合物——水飞蓟宾，可诱导白念珠菌细胞中与线粒体 Ca^{2+} 内流相关的凋亡[28]，且其安全性已通过临床试验证明，水飞蓟宾成为抗真菌感染的一个非常有希望的候选药物。

1.4 靶向真菌毒力因子

真菌通过众多毒力因子来帮助其对宿主的定植和感染[29]。白念珠菌从酵母态向菌丝态的转化是主要毒力因子之一，是其在宿主组织中定植、入侵/渗透、毒力释放、免疫逃避和存活的主要影响因素[19]。厚朴酚可诱导白念珠菌 Ras1-cAMP-Efg1 信号通路的成分（如 *RAS*1、*EFG*1、*TEC*1 和 *CDC*35）下调，以及菌丝特异性基因 *ECE*1、*HWP*1 和 *ALS*3 的表达水平下降，进而抑制白色念珠菌从酵母态向菌丝态的转化[30-31]。姜黄素可通过靶向转录抑制因子 TUP1 而抑制白念珠菌从酵母态向菌丝态的转化[32]。

真菌生物膜是黏附在固体表面的由不同类型细胞和细胞外基质组成的群落，是真菌抵抗化学和物理损伤的重要毒力因子[33]。真菌生物膜通常形成于植入的医疗设备（如导管、起搏器等）上以及宿主表面。许多植物的提取物具有抑制白念珠菌生物膜形成的能力，如茶多酚[34]、桂皮醇提物[35]、芫荽和罗勒属植物精油[36-38]等。小檗碱、百里酚、黄芩素等许多天然产物活性单体都可单独或与氟康唑等抗真菌药物协同抑制真菌生物膜的形成[10, 39-41]。

1.5 与现有抗真菌药物的协同作用

由于耐药和多重耐药真菌的出现，现有抗真菌药物的治疗效果有限，而增加药物浓度则会导致毒副作用加重和治疗成本升高[42]。鉴于目前新的抗真菌药物研发进展缓慢，现有抗真菌药物联用成为有效且实用的替代方法。许多研究报道了天然产物与现有抗真菌药物具有协同效应，包括植物精油（薄荷属、天竺葵属、葱属、牛至属、百里香属等）[43]，以及天然产物单体（小檗碱、姜黄素、百里酚、丁香酚、厚朴酚、大蒜素等），它们与唑类、多烯类药物联用具有协同作用[44]。最近一项研究探讨了 5 种天然产物单体（鱼腥草素钠、肉桂醛、小檗碱、药根碱和巴马汀）联用对白念珠菌和耳道念珠菌的抑制作用[22]。其结果显示，鱼腥草素钠 + 巴马汀、肉桂醛 + 小檗碱、肉桂醛 + 药根碱组合对白念珠菌的协同效果最好，肉桂醛 + 巴马汀、肉桂醛 + 药根碱组合对耳道念珠菌的协同效果最好，这种抗真菌协同作用可能是由于组合内的药物针对不同的药物靶标而获得的。还有研究发现，血根碱和白屈菜红碱联用能抑制白念珠菌和新生隐球菌的生长，且具有协同作用[45]。两者联用能破坏真菌细胞膜的完整性，抑制生物膜的形成，因此具有开发为抗真菌药物的潜能。

2 天然产物单体成分

目前，从天然产物中提取了 20 多种结构新颖、活性强、不良反应小的活性单体成分，包括醌类、黄酮类、萜类和生物碱等，这些单体成分经过实验证明具有体内或体外抑制真菌生长或杀菌的能力（见表 1）。体外实验评估抑菌效果大多采用微量稀释法，实验对象大多为白念珠菌或临床分离的耐氟康唑白念珠菌，少数为新生隐球菌或曲霉。体外研究大多聚焦于天然产物单体成分对真菌毒力因子的影响，如：大黄素、姜黄素、厚朴酚、小檗碱、苦参碱等能抑制白念珠菌从酵母态到菌丝态的转换；红紫素、丁香酚、土荆皮乙酸、百里酚、薄荷醇等能抑制真菌生物膜的形成；香芹酚、薄荷醇、芳樟醇、血根碱、没食子酸等能破坏细胞膜等。然而，评估天然产物单体成分体内抑菌效果的报道相对较少。有研究使用秀丽隐杆线虫模型来测试天然产物单体成分的潜在抗真菌活性，结果显示 2 种皂苷能提高被白念珠菌感染的线虫的存活率，具有体内抗真菌活性[46]。大部分活性单体成分提取自中药药用植物，如提取自姜黄的姜黄素[47]和提取自水飞蓟的水飞蓟宾[48]等，提示传统中药依然是开发抗真菌感染药物的巨大宝库。

值得一提的是，随着抗真菌药物研发的深入，海洋来源的天然产物活性单体作为新的抗真菌候选药物获得了极大关注[4]。其中，海绵被认为是具有抗真菌特性的次级代谢产物的主要来源。从斐济海绵 *Hippospongia* sp. 中分离出的一种倍半萜醌 epi-ilimaquinone，能抑制耐两性霉素 B 的白念珠菌的生长[49]，从隋氏蒂壳海绵（*Theonella swinhoei*）中分离的多肽 Aurantoside 则对白念珠菌和新生隐球菌都有抑制作用，具有良好的广谱抗真菌活性[4]。

3 天然产物提取物

采用植物制备粗提取物是发现抗真菌药物的第一步，一般通过水提或醇提的方式获得，也可通过蒸馏从植物中分离精油[50]。国内外均报道了一些在植物不同部位经水提或乙醇提取的粗提物具有抗真菌活性[51]（见表 2）。吴晶[52]采用 75% 乙醇超声提取中药有效成分，筛查了 1 557味中药的粗提物对

表 1　天然产物活性单体成分对病原真菌的抑制作用

Tab. 1　Inhibitory effect of monomers of natural products on pathogenic fungi

化学分类	单体名称	来源	MIC（μg/mL）	实验对象	抑菌机制
醌类	大黄[53-54]	大黄	64～128	新生隐球菌	抑制生物膜和菌丝发育
			12.5	白念珠菌	
	红紫素[55]	茜草根	2.56～5.12	白念珠菌	抑制生物膜形成
			2.56	光滑念珠菌	
	紫草[56]	紫草	8	白念珠菌	诱导 ROS 产生，降低线粒体膜电位
			8	光滑念珠菌	
			8	新生隐球菌	
			＞64	烟曲霉	
	epi-ilimaquinone[49]	海绵 *Hippospongia* sp.	125	白念珠菌	-
萜类	厚朴酚[57-58]	厚朴	64	白念珠菌	抑制酵母态到菌丝态的转化；抑制生物膜形成；抑制药物外排泵的表达
			16	光滑念珠菌	
			＞200	新生隐球菌	
	丁香酚[59]	丁香	82.68～1 325	白念珠菌	抑制生物膜形成
			331.25～1 325	光滑念珠菌	
	土槿皮乙酸[60-61]	土槿皮	8～16	热带念珠菌	抑制生物膜形成
			32～128	白念珠菌	
	香芹酚[62]	百里香	128	白念珠菌	降低麦角甾醇含量，破坏细胞膜
			16～512	光滑念珠菌	
	百里酚[62-63]	百里香	32～256	白念珠菌	降低麦角甾醇含量，破坏细胞膜；抑制生物膜形成
			32～128	光滑念珠菌	
			20～51	新生隐球菌	
	薄荷醇[64]	薄荷	1.42～45.6	白念珠菌	降低麦角甾醇含量，破坏细胞膜；抑制生物膜形成
			0.17～2.85	光滑念珠菌	
	芳樟醇[65]	天竺葵	8～32	白念珠菌	降低麦角甾醇含量，破坏细胞膜；抑制生物膜形成
			16	光滑念珠菌	
	紫苏醇[66]	薄荷	350	白念珠菌	抑制乙醛酸循环
黄酮类	姜黄[47,67]	姜黄	4～32	白念珠菌	诱导 ROS 产生；抑制酵母态到菌丝态的转化；抑制生物膜形成
			64	烟曲霉	
			4～64	格特隐球菌	

（续表 1）

化学分类	单体名称	来源	MIC（μg/mL）	实验对象	抑菌机制
黄酮类	姜黄	姜黄	32～64	光滑念珠菌	
			64	耳道念珠菌	
	黄芩苷[68]	黄芩	500	白念珠菌	诱导细胞凋亡
	水飞蓟宾[48]	水飞蓟	30～1 200	白念珠菌	诱导细胞凋亡
	甘草查尔酮 A[41]	甘草	62.5～150	白念珠菌	抑制酵母态到菌丝的转化
	芹菜[69]	欧芹	5	白念珠菌	抑制乙醛酸循环；抑制菌丝生长；抑制生物膜形成
	槲皮[47]	槲皮	16～32	白念珠菌	抑制生物膜形成；诱导法尼醇产生
			64	烟曲霉	
			64	光滑念珠菌	
			64	耳道念珠菌	
生物碱	汉防己甲素[70]	汉防己	16～64	白念珠菌	抑制药物外排泵；下调 *MDR*1、*FLU*1、*CDR*1 和 *CDR*2 基因表达
	小檗碱[71-73]	小檗属	4～256	烟曲霉	抑制菌丝形态转换；抑制生物膜形成；破坏细胞壁完整性
			8～16	新生隐球菌	
			17.75	白念珠菌	
	苦参碱[74]	苦参、山豆根	1 000	白念珠菌	抑制菌丝形态转换
	血根碱[45]	博落回	4	白念珠菌	抑制生物膜形成；破坏细胞膜
			64	新生隐球菌	
	白屈菜红碱[45]	白屈菜	4	白念珠菌	抑制生物膜形成；破坏细胞膜
			64	新生隐球菌	
多酚类	没食子酸[75]	五倍子	12.5	白念珠菌	抑制麦角甾醇合成
			100	光滑念珠菌	
醛类	肉桂醛[56，59，62]	肉桂	20.48～163.80	白念珠菌	抑制生物膜形成；抑制菌丝形态转换
			40.95～163.80	光滑念珠菌	
			1.37	新生隐球菌	
	鱼腥草素钠[22]	鱼腥草	128	白念珠菌	干扰 β-1，3-葡聚糖合成与运输
			64	耳道念珠菌	
多肽	Aurantoside[4]	海绵 *Theonella swinhoei*	0.125～0.5	白念珠菌	-
			14	新生隐球菌	
大环内酯	羽苔素 E[76]	地钱科	16～32	白念珠菌	抑制 CHS1 表达；诱导 ROS 产生

表 2　不同植物来源提取物的抗真菌研究

Tab. 2　Antifungal effects of extracts from different plants

实验对象	粗提物	提取方法
白念珠菌	丁香、牛至、百里香、茴香、迷迭香、芫荽、柴桂、香绵菊[25，77-81]	精油
	大蒜、芫荽、骆驼蓬[82-84]	甲醇提取
	肉桂[85-86]	水提物
		乙醚提取
	芫荽[84]	乙醇水提取
	辣椒[87]	正己烷提取
	嘉兰百合[86]	正丁醇提取
	月桂[89]	水提物
新生隐球菌	丁香、小茴香、天竺葵、薰衣草、香蜂叶、牛至、松树、鼠尾草、百里香[77]	精油

白念珠菌、新生隐球菌和烟曲霉等常见侵袭性真菌的抑制作用，共发现 453 味中药的粗提物具有抗真菌活性，并发现重楼、粉萆薢、白薇、穿山龙、藜芦、羌活等提取物在低浓度下即能完全抑制白念珠菌的菌丝生长，具有很强的抗真菌作用。宫毓静等[90]采用半固体药基混合法测试了 164 种单味药的 95%乙醇提取物的抗真菌活性，结果显示牡丹皮、土荆皮等 9 种单味药的粗提物对白念珠菌具有明显的抑制作用。

通过蒸馏分离的植物精油具有更强的抗真菌活性，有学者对其组成和抗真菌活性进行了深入研究[91]。从丁香、牛至、百里香和肉桂中提取的精油对真菌具有显著的抑制作用，这些植物精油中的酚类化合物（香芹酚和百里香酚）能破坏真菌的细胞膜，抑制真菌生长[25]。植物精油可能通过破坏真菌细胞壁和质膜来达到杀菌效果，有研究表明精油可用来治疗浅表真菌感染，但对侵袭性真菌感染疗效不佳，这可能是由植物精油在人体肠道中吸收较差导致的[92]。因此，将植物精油与现有抗真菌药物联用以治疗侵袭性真菌感染可能有更好的治疗效果。

通过天然产物提取物筛选抗真菌药物是经济、简便的初步方法，对进一步的研究工作具有一定的指导意义。然而，由于粗提取物中的化学成分不同，提取物的生物活性可能无法在实验中重现。此外，获得提取物的溶剂和提取方法也可能导致某些化合物的损失。

4　结语

综上所述，许多天然化合物可通过不同的机制发挥抗真菌活性，成为开发抗真菌药物的巨大资源库。尽管针对天然产物活性单体成分已有众多深入的研究，但针对天然产物粗提物的研究大多只局限于用体外药敏试验来检测抗真菌活性，未深入研究其抗真菌机制，且大多数研究仅有体外实验数据，动物实验和临床研究较少，已开展的临床研究主要为治疗浅部真菌病，研究范围小，周期较短。因此，基于天然产物的抗真菌药物研发须更加深入。相信随着技术的进步和人们不断的关注，基于天然产物开发新型抗真菌药物的进程会越来越快。

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