桦褐孔菌化学成分及药理活性研究进展

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摘 要 桦褐孔菌为一种药食两用真菌，在俄罗斯、日本和中国东北民间已有悠久的药用及食用历史。桦褐孔菌含有萜类、甾体、多糖、酚类及生物碱等化合物，具有抗肿瘤、降血糖、抗炎、抗氧化和降脂等药理活性，其中，羊毛甾烷型四环三萜为其特征性成分。本文系统综述了近年从桦褐孔菌中分离鉴定的化学成分及药理活性研究进展，整理并绘制了萜类、甾体及酚类化合物的结构，重点总结了羊毛甾烷型四环三萜的骨架类型和结构特征，为桦褐孔菌的深入研究与综合开发利用提供参考。

关键词 桦褐孔菌；化学成分；羊毛甾烷型三萜；药理活性

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Research progress in chemical constituents and pharmacological activities of *Inonotus obliquus*

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Abstract As a medicinal and edible fungus, *Inonotus obliquus* has a long history of folk application in Russia, Japan, and Northeast China. It is rich in terpenoids, steroids, polysaccharides, phenols, alkaloids, etc, and exhibits pharmacological activities including anti-tumor, hypoglycemic, anti-inflammatory, antioxidant, and lipid-lowering effects. Among these, lanostane-type tetracyclic triterpenes represent its characteristic constituents. This review systematically summarizes the research progress on the chemical components isolated and identified from *I. obliquus* and their pharmacological activities in recent years. The structures of terpenoids, steroids, and phenolic compounds are compiled and illustrated, with a particular focus on the skeletal types and structural characteristics of lanostane-type tetracyclic triterpenes. This work aims to provide some reference for the further investigation and comprehensive development and utilization of *I. obliquus*.

Key words *Inonotus obliquus*; chemical constituents; lanostane-type triterpenoids; pharmacological activity

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桦褐孔菌 (*Inonotus obliquus*) 属担子菌亚门 (Basidiomycotina)、层菌纲 (Hymenomycetes)、锈革孔菌目 (Hymenochaetales)、锈革孔菌科 (Hymenochaetaceae)、纤孔菌属 (*Inonotus*)，是一种常寄生于白桦树、榆树、银桦、赤杨等落叶树的树皮或枝干上的木腐真菌[1−2]。桦褐孔菌主要分布于北半球北纬

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40°−50°地区，如我国黑龙江小兴安岭、吉林长白山和内蒙古等区域，日本北海道、俄罗斯西伯利亚和远东地区、芬兰、波兰等地[3]。早在 16 世纪初期，东欧人民食用桦褐孔菌防治癌症，西伯利亚人以桦褐孔菌水煎剂治疗心脏病、胃病和食管病等[4]。桦褐孔菌次生代谢产物丰富多样，目前已从中分离得到 200 余种化合物，其中萜类和甾体结构类型复杂多变，具有抗肿瘤、降血糖、抗炎等药理活性。本文对桦褐孔菌化学成分、药理作用的研究进行综述，为桦褐孔菌药用植物资源的开发提供依据。

1 桦褐孔菌的化学成分

1.1 萜 类

1.1.1 四环三萜类 羊毛甾烷型四环三萜为桦褐孔菌萜类的主要结构类型，共有 4 种骨架。A 型为经典的羊毛甾烷型三萜，A/B、B/C、C/D 环互为反式结构，C-10 和 C-13 位连 β-CH_3，C-14 位连 α-CH_3，C-17 位为 β 构型侧链，C-20 位连 β-H 且 C-3 常连有羟基、羰基或酯基，环内存在 C-8(9) 双键或 C-7,9(11) 共轭双键，侧链存在双键或 C-21 与 C-24/C-25 成环，也存在少数化合物 H-17 为 β 型，H-20 为 α 型；B 型为 7(8→9) 重排结构，即 C-7、8 断裂，C-7、9 连接形成螺环；C 型特征为 C-4、5 位开环；D 型特征为 C-3、4 开环。各骨架结构类型见图 1，化合物结构如补充材料中表 S1 和图 S1 所示。

1.1.2 五环三萜 桦褐孔菌中五环三萜类型多样(表 1，图 2)，包括羽扇豆烷型(E)、乌苏烷型(F)和齐墩果烷型(G)，但数量较少。

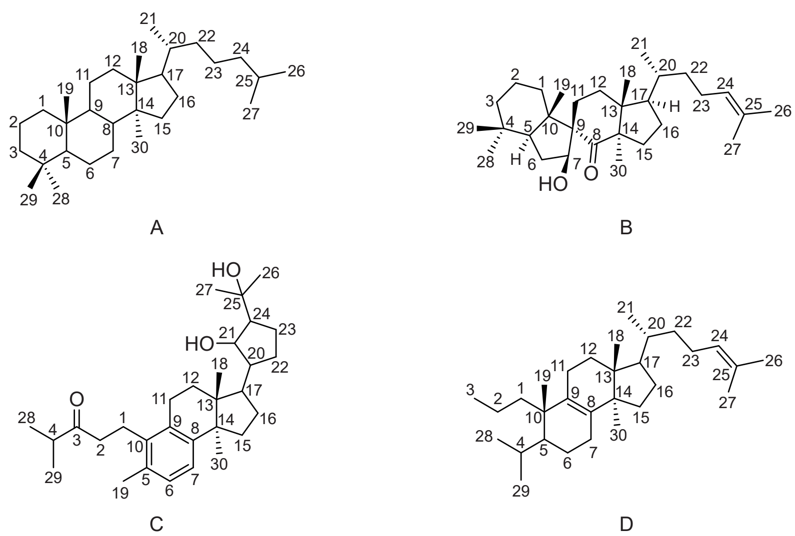

Figure 1 Main framework (A−D) of lanostane-type triterpenes in *I. obliquus*

Table 1 pentacyclic triterpenoids in *I. obliquus*

No.	Compound name	Molecular formula	Skeleton	Ref.
101	Betulin	$C_{30}H_{50}O_2$	E	[10]
102	Betulinic acid	$C_{30}H_{48}O_3$	E	[10]
103	Monogynol A	$C_{30}H_{52}O_2$	E	[33]
104	Ursolic acid	$C_{30}H_{48}O_3$	F	[10]
105	3β-Acetoxy-11α,12α-epoxyoleanan-28,13β-olide	$C_{32}H_{48}O_5$	G	[10]
106	Oleanic acid	$C_{30}H_{48}O_3$	G	[10]

1.1.3 倍半萜及二萜 桦褐孔菌中主要存在 drimane 型倍半萜(DTS)，DTS 为双环倍半萜，含有 4,4,8,9,10-五甲基，其天然产物衍生物来源于 3 种异构体：drimenol，drim-8-ene-11-ol 和 (+)-albicanol，分别具有 $\Delta^{7(8)}$，$\Delta^{8(9)}$ 和 $\Delta^{8(12)}$ 双键，通过焦磷酸金合欢酯(FPP)环化而成[34]。二萜类化合物主要为 abietane(松香烷)型和 labdane(半日花烷)型[35]。倍半萜和二萜成分见表 2，结构见图 3。

1.2 甾体类

甾体也为桦褐孔菌中含量较为丰富的成分，其 A/B、B/C、C/D 环互为反式构型，C-17 位侧链为 β 型 8~10 个碳原子链状取代基，包含麦角甾醇衍生物、豆甾醇衍生物、孕甾烷(新骨架 8,14 开环-4-甲基孕甾烷)衍生物等，见表 3 和图 4。

1.3 酚 类

桦褐孔菌中含有多种酚类化合物，包括褐孔菌内酯、酚醛、酚酸、联苯及异香豆素片段等带有一

Table 2 Sesquiterpenes and diterpenes in *I. obliquus*

No.	Compound name	Molecular formula	Ref.
107	Inonotusic acid	$C_{20}H_{26}O_3$	[28]
108	4-[(5,5,8a-Trimethyl-2-methylene-1-naphthylenyl)methyl]-2,5-dihydroxybenzaldehyde	$C_{22}H_{32}O_3$	[36]
109	Inotolactone C	$C_{15}H_{24}O_3$	[31]
110	Inotolactone E	$C_{15}H_{22}O_3$	[37]
111	Inotolactone F	$C_{15}H_{20}O_3$	[37]
112	Inotolactone G	$C_{15}H_{20}O_3$	[37]
113	6*α*-Hydroxycinnamolide	$C_{15}H_{22}O_3$	[37]
114	Inotolactone H	$C_{15}H_{20}O_4$	[37]

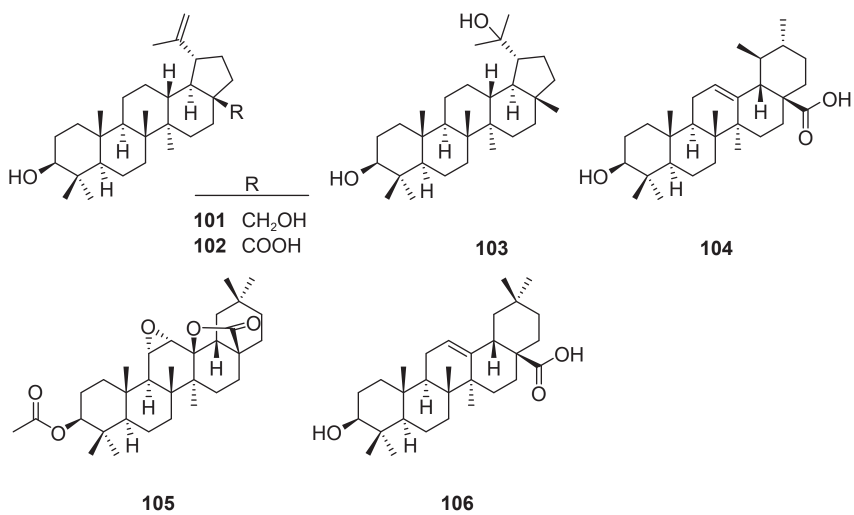

Figure 2 Structures of pentacyclic triterpenoids from *I. obliquus*

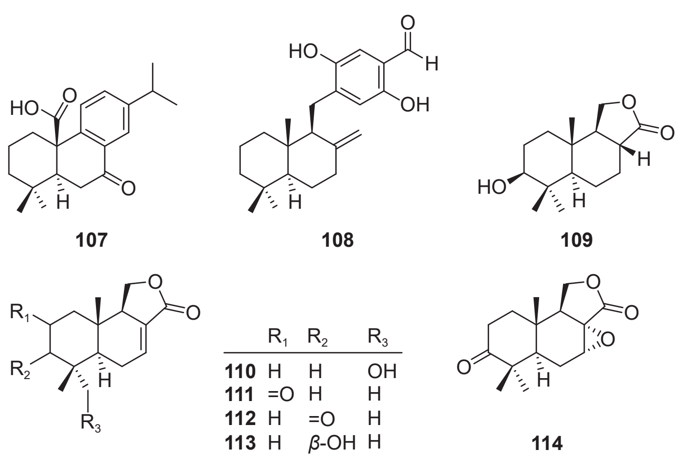

Figure 3 Structures of sesquiterpenes and diterpenes from *I. obliquus*

个或多个苯环的高度氧化的结构。化合物结构如补充材料中表 S2 和图 S2 所示。

1.4　多　糖

葡聚糖、甘露聚糖、杂多糖、糖蛋白及多糖肽是桦褐孔菌多糖的主要组成成分[58]。Xuan 等[59]利用 PMP 柱前衍生化 HPLC 法分析桦褐孔菌多糖成分，发现桦褐孔菌多糖主要由甘露糖、葡萄糖、鼠李糖、木糖、半乳糖和阿拉伯糖组成，摩尔比为 2.13∶7.01∶1.36∶1∶2.98∶1.78。Wu 等[60]采用加热水提法和柱色谱从桦褐孔菌中得到低聚糖 IOP-2A，相对分子质量约 1 000 D，单糖组成及摩尔比为葡萄糖-木糖-半乳糖-甘露糖（5.41∶1.36∶1.32∶0.67），另

Table 3 Steroids in *I. obliquus*

No.	Compound name	Molecular formula	Ref.
115	Ergosta-4,6,8(14),22-tetraene-3-one	$C_{28}H_{40}O$	[10]
116	Inonotoide E	$C_{28}H_{38}O_4$	[38]
117	Ergosterol	$C_{28}H_{44}O$	[10]
118	Lawsaritol	$C_{29}H_{50}O$	[39]
119	Stigmast-4-en-3-one	$C_{29}H_{48}O$	[40]
120	Ergosta-7-en-3*β*-ol	$C_{28}H_{48}O$	[28]
121	Ergosta-7,22-dien-3*β*-ol	$C_{28}H_{46}O$	[28]
122	Ergost-6,8,22-trien-3*β*-ol	$C_{28}H_{44}O$	[41]
123	Ergosta-7,22-dien-3-one	$C_{28}H_{44}O$	[42]
124	3*β*,5*α*-Dihydroxy-(22*E*,24*R*)-ergosta-7,22-dien-6-one	$C_{28}H_{44}O_3$	[21]
125	(3*β*,5*α*,6*β*,22*E*)-6-Methoxyergosta-7,22-diene-3,5-diol	$C_{29}H_{48}O_3$	[33]
126	Inonotoide D	$C_{22}H_{30}O_5$	[38]
127	Inonotoide C	$C_{22}H_{30}O_4$	[38]
128	Inonotoide A	$C_{22}H_{32}O_4$	[38]
129	Inonotoide B	$C_{22}H_{30}O_5$	[38]
130	Ergosterol peroxide	$C_{28}H_{44}O_3$	[42]
131	3*β*-Hydroxy-5*α*,8*α*-epidioxyergosta-6,9,22-triene	$C_{28}H_{42}O_3$	[43]
132	Inonotoide F	$C_{21}H_{32}O_4$	[38]

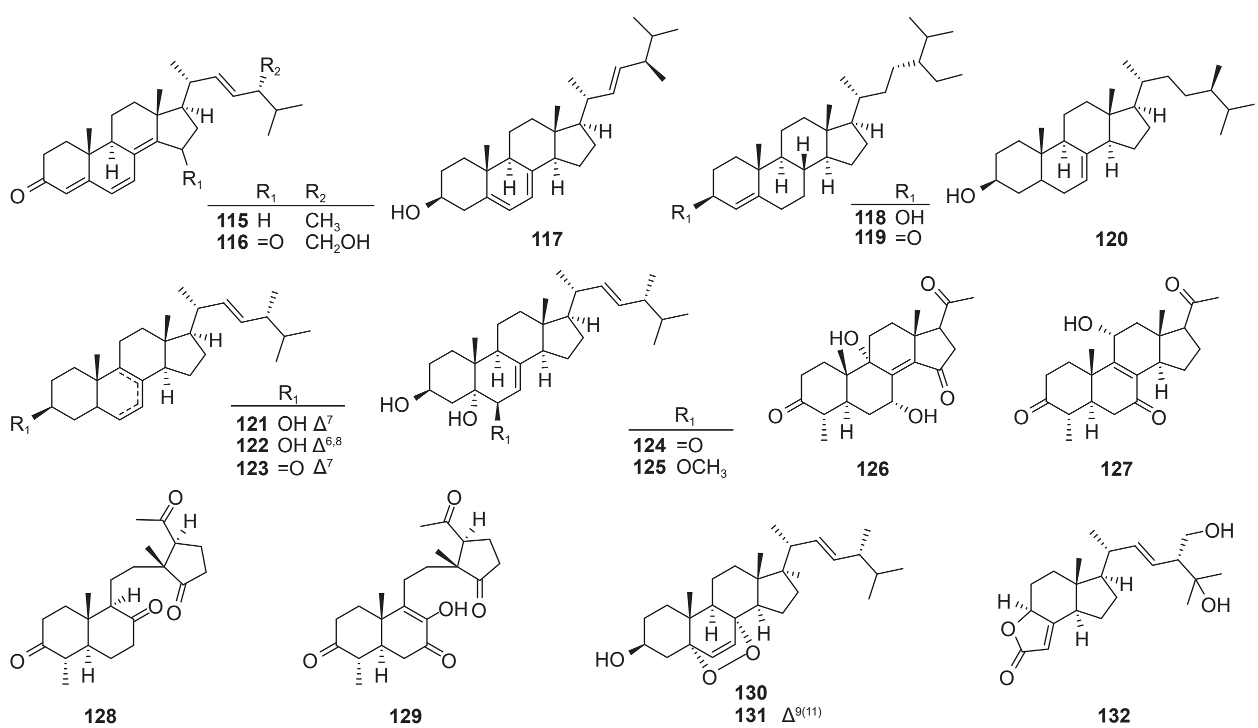

Figure 4 Structures of steroids from *I. obliquus*

含有少量半乳糖、葡萄糖酸、鼠李糖和岩藻糖，主要含有 *β*-糖苷键，1,4-糖苷键占比 9.1%，1,6-糖苷键占比 85.1%。Dai 等[61] 从桦褐孔菌中醇沉及多次纯化得到多糖 IOP-2S，其相对分子质量为 26 760 D，单糖组成及摩尔比为甘露糖-鼠李糖-葡萄糖-半乳糖-木糖-阿拉伯糖（5.21∶5.11∶15.51∶7.93∶5.67∶2.32）。

1.5 其 他

除上述成分外，桦褐孔菌中还存在吡咯型生物碱、脂肪族化合物、单糖及其衍生物、氨基酸、核苷及微量元素等。Yan 等[62] 首次从桦褐孔菌中

分离得到烟酸 (Nicotinic acid); Zhang 等[63] 首次分离得到灵芝碱甲 (Inotopyrrole); Shan 等[64] 从桦褐孔菌中分离得到吡咯型生物碱 Inotopyrrole B 和 5-(Hydroxymethyl)-1*H*-pyrrole-2-carboxaldehyde。Liu[21] 从桦褐孔菌中分离出棕榈酸 (Palmitic acid)、甘油单油酸酯 (Monoolein)、单棕榈酸甘油酯 (Monopalmitin) 等脂肪族化合物以及核苷类化合物腺苷和鸟苷。Zhang 等[65] 从桦褐孔菌水提物中分离出 *L*-苯丙氨酸、*α*-D-葡萄糖、*β*-D-葡萄糖、半乳糖醇、甘露醇等成分。Qi 等[66] 利用原子吸收光谱法对桦褐孔菌中的微量元素进行分析, 发现桦褐孔菌含 Mn、Ca、Zn、Fe、Pb、Cu、Cr 等无机元素, 金属元素 Ca 总质量比最高。

2　桦褐孔菌的药理活性

桦褐孔菌化学成分结构类型多样且复杂多变, 现代药理研究表明, 其次生代谢产物具有抗肿瘤、抗氧化、抗炎、降糖、降脂等药理作用。

2.1　抗肿瘤作用

桦褐孔菌多糖和三萜类化合物具有抗肿瘤活性, 通过多途径多机制发挥作用。

桦褐孔菌三萜对肿瘤细胞具有细胞毒作用, Wang 等[17] 发现 Inonotsutriol C (**77**)、(23*E*)-Lanosta-8,23-diene-3*β*,25-dihydroxy-21-al (**32**) 和 (20*R*,21*S*,24*S*)-21,24-Cyclopenta-3*β*,21,25-trihydroxy-lanosta-8-ene (**53**) 对乳腺癌细胞 (4T1 和 MDA-MB231)、肺癌 (A549) 和胃癌细胞 (BGC-823) 具有显著的抑制作用, MTS 实验表明 Inonotsutriol C 可剂量依赖性降低 4T1 细胞的活力。

桦褐孔菌三萜和甾体可通过调控凋亡相关蛋白和干预细胞信号传导通路促进细胞凋亡。Zhang 等[67] 研究发现桦褐孔菌醇 (**12**) 通过激活 HeLa 细胞中促凋亡基因 Bax 的蛋白表达和阻断抗凋亡基因 Bcl-2 蛋白表达, 提高 Cleaved PARP 和 Cleaved Caspase-3 蛋白表达水平来调控细胞凋亡。Kang 等[68] 实验发现过氧麦角甾醇 (**130**) 可抑制 *β*-连环蛋白 (*β*-catenin) 的核水平, 下调 *β*-catenin 信号转导, 导致转录调节因子 c-Myc、细胞周期蛋白 D1 (cyclin D1) 和细胞周期蛋白依赖性激酶 8 (CDK-8) 转录减少, 从而促进结直肠癌细胞凋亡。Shan 等[69] 从桦褐孔菌中分离得到的 Inonotsutriol E (**37**), 可显著抑制白细胞介素 6 (IL-6) 诱导的 STAT3 (signal transducer and activator of transcription 3) 核积聚和 STAT3 下游蛋白的表达, 通过阻断 JAK2/STAT3 信号通路抑制乳腺癌 (BC) 细胞的生长和迁移。Shao 等[70] 等利用网络药理学和分子对接技术及体内实验验证桦褐孔菌三萜可通过抑制 PI3K/Akt 通路抑制 HeLa 裸鼠肿瘤组织的生长。

桦褐孔菌三萜成分可阻滞细胞周期, Jin 等[71] 从桦褐孔菌中分离得到的三萜类成分对卵巢癌细胞 ES2、SKOV3 和肺癌细胞 A549、PC9 具有显著的抑制作用, 细胞周期实验表明阻滞发生在 G_0/G_1 期, 能有效诱导细胞凋亡。

桦褐孔菌多糖和三萜可抑制肿瘤细胞侵袭和迁移, Zhang 等[58] 从桦褐孔菌种分离得到的多糖 IOP-5 可有效抑制已移植 4T-1 乳腺癌细胞的小鼠中乳腺肿瘤的生长, 其作用机制是上调 NFKBI (NFKB 抑制因子) 抑制 NFKB 通路, 并下调受体酪氨酸激酶 FLT3, Spi-B 转录因子 (SPIB), 肾上腺素受体 1 (ADRB1) 的表达以改变免疫微环境, 从而抑制肿瘤迁移。Zhang 等[67] 研究发现桦褐孔菌醇 (**12**) 通过提高 p53 蛋白的表达调控 HeLa 细胞的迁移和浸润。

2.2　降血糖作用

α-葡萄糖苷酶位于小肠刷状缘, 可将寡糖末端非还原性 *α*-1→4 糖苷键分解为单糖, 故抑制 *α*-葡萄糖苷酶活性可降低餐后血糖, Liu 等[72] 从桦褐孔菌中分离得到多糖 HIOP2-S, 对 *α*-葡萄糖苷酶抑制作用的 IC_{50} 值为 3.84 μg/mL, 给药 21 d 可显著降低链脲佐菌素 (STZ) 诱导的糖尿病小鼠的血糖水平。Ying 等[31] 从桦褐孔菌中分离得到 2 个新化合物 Inotolactone A (**90**)、Inotolactone B (**89**), 与阳性对照阿卡波糖相比具有更强的 *α*-葡萄糖苷酶抑制活性, IC_{50} 均为 (0.24 ± 0.01) mmol/L。Chen 等[5] 实验发现 Inonotusol F (**88**) 具有显著的 *α*-葡萄糖苷酶抑制活性, IC_{50} 为 (11.5 ± 0.4) μmol/L, 分子对接表明 Inonotusol F 与 *α*-葡萄糖苷酶结合主要由范德华力实现, 分子动力学模拟揭示了 Inonotusol F 与蛋白相互作用的关键氨基酸残基。Ye 等[73] 研究发现桦褐孔菌能有效改变 db/db 小鼠肠道菌群组成, 降低变形菌门 (Proteobacteria) 和理研菌科 RC9 肠道群 (*Rikenellaceae_RC9_gut_group*) 等潜在危险细菌的数量, 增加文肯菌属 (*Rikenella*) 和臭气杆菌属 (*Odoribacter*) 等有益菌的数量, 改善肠道微生态紊乱, 维护肠道菌群的动态平衡从而控制炎症, 缓解

T2DM 相关症状。

2.3　抗炎作用

Kou 等[24]从桦褐孔菌中分离得到 Inonotusol H-N 等单体化合物，检测其对脂多糖 (LPS) 诱导的 BV-2 小胶质细胞 NO 生成的抑制作用，发现 Inonotusol I (**65**) 和 Inonotusol L (**68**) 具有显著的抑制活性，IC_{50} 分别为（4.07 ± 0.03）和（2.32 ± 0.02）μmol/L，Western Blot 实验和分子对接结果表明化合物可能通过与诱导型一氧化氮合酶 (iNOS) 的活性腔结合显示抗炎作用。Qian 等[74]实验发现 Inotodiol (**12**) 能显著减轻促炎细胞因子 IL-1β 诱导的软骨细胞损伤，并抑制炎症因子的释放；体内实验表明 Inotodiol 可明显增加软骨厚度，减少纤维软骨数量，减少软骨破坏面积，有效改善小鼠关节损伤症状。Kim 等[75]研究发现桦褐孔菌 70% 乙醇提取物可剂量依赖性抑制 LPS 诱导的巨噬细胞人核因子 κB 抑制蛋白 α (IκBα)、蛋白激酶 B (Akt) 和丝裂原活化蛋白激酶 (MAPKs) 的磷酸化及 iNOS 和环氧化酶 2 (COX-2) 蛋白的表达，作用机制可能是通过磷脂酰肌醇 3-激酶 (PI3K) /Akt/IκB 途径抑制核因子 κB (NF-κB) 和应激活化蛋白激酶 (JNK) 的活化。

2.4　抗氧化作用

Zhao 等[76]从桦褐孔菌中分离得到的桦褐孔菌醇 (**12**)、栓菌酸 (**13**) 和羊毛甾醇 (**10**) 可剂量依赖性增强超氧化物歧化酶 (SOD)、过氧化氢酶 (CAT) 和谷胱甘肽过氧化物酶 (GSH-PX) 活性，对四氯化碳 (CCl_4) 所致的小鼠氧化应激损伤具有显著的保护作用。Wang 等[77]从桦褐孔菌中分离得到 3 种均一的蛋白质结合酸性多糖组分 (IOPS 1-3)，其中 IOPS 2 具有最高的酶抑制活性和对 H_2O_2 所致肝细胞氧化损伤的保护作用，可能与多糖比相对分子质量、蛋白质和糖醛酸含量有关。Nakajima 等[46]从桦褐孔菌菌核中分离得到芳香化合物 3,4-Dihydroxybenzaldehyde (**133**) 和 2,5-Dihydroxyterephthalic acid (**142**)，具有显著的抗氧化作用，其 DPPH 清除活性 IC_{50} 为(18.06 ± 0.18)和(24.84 ± 0.48) μmol/L。

2.5　降脂作用

Zhang 等[78]研究发现桦褐孔菌提取物可剂量依赖性降低 HepG2 细胞中甘油三酯 (TG) 水平，在 0.60 g/L 质量浓度下 TG 清除率可达 32.33%，可改善细胞中的脂质堆积现象。Wu 等[60]发现桦褐孔菌低聚糖具有预防小鼠高脂血症的作用，通过改善小鼠肠道菌群平衡，减少脂肪酸等营养素的摄入量实现。Lin 等[79]实验发现桦褐孔菌多糖通过调节脂质代谢中胆固醇 7α-羟化酶 (CYP7A1) 和固醇调节元件结合蛋白 1 (SREBP-1C) 的表达和纠正高脂饮食所致的肠道菌群结构失衡以治疗大鼠高脂血症。

2.6　其他作用

Zhao 等[80]通过 Ames 实验证明了桦褐孔菌三萜 Inotodiol (**12**) 具有显著的抗突变活性。Zhang 等[49]利用 ESI-MS^n 鉴定出紫萁酮 (**147**) 和原儿茶醛 (**133**)，探究其对尿酸钠 (MSU) 诱导的 RAW264.7 细胞保护机制，结果表明原儿茶醛和紫萁酮通过减少细胞中炎症因子 (IL-1β、ICAM-1) 的基因表达水平发挥抗痛风作用。Yong 等[81]发现从桦褐孔菌中得到的白桦脂醇 (**101**) 可能通过抑制黄嘌呤氧化酶 (XOD) 活性发挥抗高尿酸血症的作用，IC_{50} 为（121.10 ± 4.57）μmol/L，低于别嘌醇 (IC_{50} 148.10 ± 5.27 μmol/L)。Nakata 等[25]研究发现 Inonotsuoxide A (**72**)、Inotodiol (**12**)、Trametenolic acid (**13**) 和 Lanosterol (**10**) 对 TPA 诱导的 EB 病毒早期抗原 (EBV-EA) 的活性有显著的抑制作用。Zou 等[14]从桦褐孔菌中分离得到 Inonotsutriol A (**51**) 测试其对 H_2O_2 诱导的人神经母细胞瘤 (SH-SY5Y) 细胞损伤的神经保护作用，结果表明，Inonotsutriol A 具有中等保护活性，通过抑制细胞凋亡实现。Basal 等[82]发现 Betulinic acid (**102**) 与 Inonotusane C (**4**) 对接在 SARS-CoV-2 刺突蛋白受体结合区域 (RBD) 与血管紧张素转换酶 2 (ACE2) 最接近的结合部位，具有良好的结合亲和力，或可用于新冠肺炎的抗病毒治疗。

3　结　语

桦褐孔菌为寄生菌，生长周期长，且对生长环境要求较高，野生资源匮乏，如何开发人工栽培技术，得到品质及药效均一、产量稳定的人工栽培桦褐孔菌是桦褐孔菌综合开发利用的一大挑战。此外，桦褐孔菌作为一种珍贵的药食两用真菌，结构类型复杂多样，具有多种药理活性，但对其药理研究多集中在多糖、桦褐孔菌醇、栓菌酸和羊毛甾醇等成分，对结构新颖的众多化合物未进行系统的活性研究。人工智能 (artificial intelligence, AI) 可快速进行靶点识别，预测候选化合物的疗效与毒性，

未来通过 AI 技术预测桦褐孔菌化合物库的分子靶标及生物活性, 进一步通过细胞及动物实验验证潜在药物靶点及药效活性, 有望加速天然产物药物发现进程[83−84]。本文对近年从桦褐孔菌中分离鉴定的化学成分及药理活性研究进展进行概述, 以期为阐明其药效物质基础提供科学依据, 为其进一步综合开发利用提供参考。

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