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REVIEW

Progress of Research on *Inonotus Obliquus*

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ABSTRACT *Inonotus obliquus* has high nutritional and medicinal value, especially in treating malignant tumors, diabetes, cardiovascular disease and AIDS, attracting significant attention from scholars in recent years. In this paper, the biological characteristics, chemical composition and pharmacologic effects of *Inonotus obliquus* were summarized. And the applications in medicine and food were introduced. Future research on *Inonotus obliquus* was also discussed in order to make Inonotus obliquus obtain effective exploitation and satisfy people's demands.

KEY WORDS *Inonotus obliquus*, biological characteristics, chemical composition, pharmacologic effect

To date, about 250 thousand species of fungi have been discovered, among which over 300 species are used medicinally in China. Since the 1980s, along with extensive studies on the active ingredients, such as polysaccharides[1], of medicinal fungi, their nutritional and medicinal value have been concerned by more and more people, and it is now becoming one of the more widely developed domains in the health care industry and health care product industry. In recent years, scholars in Russia, Northern Europe, Japan, America and Korea, etc. have further studied *Inonotus obliquus* and tried to determine the active components involved in the prevention and cure of malignant tumors, diabetes mellitus, heart diseases, liver diseases and AIDS. At present, studies on *Inonotus obliquus* by scholars in China are in the initial stages[2-4].

BIOLOGICAL CHARACTERISTICS

Classification and Nomenclature of *Inonotus Obliquus*

Inonotus obliquus belongs to the eumycophyta, basidiomycotina, hymenomycetes, aphyllophorales, polyporaceae, poriahypobrunnea petch families. Its scientific name is Fuscoporia oblique (Pers. Fr.) Aoshi or *Inonotus obliquus* (Fr.). In foreign literature, the preferred scientific name is *Inonotus obliquus* (Fr) Pilat. Its common names include black birch touchwood, malalon mushroom, etc. The Russian name is Chaga.

Distribution

Inonotus obliquus is mainly distributed at latitudes of 45°N-50°N, in North America, Finland, Poland, Russia (Western Siberia, partial regions in the Far East, Kamchatka peninsula), China (Heilongjiang province, Changbai mountain area of Jilin province), Japan (Hokkaido), etc.

Morphological and Bionomic Characteristics

Fruit bodies show a tumor figure (sterility lump) with no stalk, 25-40 cm in diameter, having an outward charcoal grey appearance with an irregular groove trace and deep cleavage, and made of a hard and crisp substance; context is light yellow; foster part is 5 mm in thickness, crustiform, dark brown in color; the tube is 3-10 mm long, in anterior extremity dehiscence; pore is round (spore is egg-shaped), smooth and glossy, 9-10 μm × 5.5-6.5 μm in size with setae. *Inonotus obliquus* is a black parasitic fungus growing on living trunks of the mature birch[3].

Chemical Compositions

The components *Inonotus obliquus* mainly include lanolin alkane triterpenes isolated from, lignin, melanin, etc[4-15].

Lanolin Alkane Triterpenes

Researchers in China and abroad have found lots of triterpene compounds in *Inonotus obliquus*. Fuscoporine[2], lanosterol, 3β-hydroxy-lanosta-8, 24-diene-21-a1, 3β, 21-dihydroxy-lanosta-8,24-diene, 3β-hydroxy-lanosta-8, 24-diene-21-acid, 3β, 22R-dihydroxy-lanosta-8, 24-diene were identified and isolated from *Inonotus obliquus*. Three new lanostane triterpenoids were isolated from the petroleum ether extracts of Fuscoporia oblique and, on the basis of chemical and spectroscopic methods and X-ray crystallographic analysis, their structures have been determined as 25-methoxy-21, 22-cyclolanosta-8-ene-3beta, 21alpha-diol, 3beta, 22alpha-dihydroxy-lanosta-8, 23E-diene-25-peroxide, 3beta, 22alpha, 25-trihydroxy-lanosta-8, 23E-diene.

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Lignin

Boiling water extracts of an edible mushroom, Fuscoporia oblique showed inhibitory activity against the protease of the human immunodeficiency virus type 1 (HIV-1). The active component was identified as a water-soluble lignin derivative with high molecular weight[16].

Melanin

The high-molecular-weight phenolic pigments synthesized by fungus *Inonotus obliquus* (Pers.) Pil. were categorized as melanin according to their physicochemical properties. It has been shown that copper ions (0.008%), pyrocatechol (1.0 mmol/L), and tyrosine (20.0 mmol/L) might stimulate melanogenesis. The melanin production is mutually correlated with the synthesis of o- and p-diphenol oxidases[17]. The physicochemical properties of pigments isolated from the naturally growing sterile form of *Inonotus obliquus* (Fr.) Pil., known as Chaga, which form the major constituents of the medicine "befung in", were different from those of melanin artificially synthesized from this fungus. Studies revealed structural differences in these pigments. The naturally produced melanin is named allomelanin, whereas the cultivated fungus is called eumelanin[18]. P-hydroxybenzoic acid has been identified as among the products of alkaline degradation of melanin by *Inonotus obliquus*[19].

Others

Some scholars reported that *Inonotus obliquus* consisted of a folate derivative, pterolyglutamic acid, and aromatic substances, including aromatic vanillic acid, syringic acid and γ-hydroxybenzoic acid. Moreover, steroids and alkaloid-like chemical compounds were isolated from *Inonotus obliquus* and trametenolic acid was also isolated. *Inonotus obliquus* also contains ergosterol peroxide, sphingoin analogue, mannitol, and demi-tannin compounds[20]. Low molecular weight polyphenols were found in the aqueous extracts of *Inonotus obliquus*.

PHARMACOLOGICAL EFFECT

Anti-cancer Effect

Inonotus obliquus (Chaga mushroom), one of the widely known medicinal mushrooms, has been used to treat various cancers in Russia and most of Baltic countries for many centuries.*Inonotus obliquus* was found to be able to significantly inhibit transplanted tumors in animals *in vivo*[21]. The water extract of *Inonotus obliquus* mushroom exhibited a potential anticancer activity against B16-F10 melanoma cells *in vivo*[22]. The Fuscoporia oblique polysaccharide, made by water extraction and alcohol precipitation, had obvious inhibitory effects on sarcoma S180 in mice was also observed[23]. The most abundant triterpene compound, inotodiol, was investigated for its tumor-inhibitory effect in a two-stage carcinogenesis test on mouse skin, using 7,12-dimethylben (a) anthracene (DMBA) as an initiator and 12-O-tetradecanoylphorbol-13-acetate (TPA) as a promoter, inotodiol was found to have potent anti-tumor promoting activity in the *in vivo* carcinogenesis test[13].

In vitro, the anti-cancer activities of the extracts of Inonotus obliquus against various types of tumor cells were observed[22-27]. Kim, et al[20] reported that the mechanisms of action of polysaccharides from mycelia and sclerote of *Inonotus obliquus* were different. The sclerote polysaccharide exhibited anti-cancer effects directly by inhibiting cancer cells and protein synthesis of tumor cells, whereas the mycelia variety produced an indirect effect through activation of immune cells[24]. Similarly, it was reported that the polysaccharides extracted and fractionated from cultured mycelia of *Inonotus obliquus* had weak inhibitory effects against cdc25 phosphatase[24].

The cytotoxic effect of two aqueous extracts of *Inonotus obliquus* on human cervical uteri cancer cells (Hela S3) *in vitro* was evaluated. The conclusion was that the extracts, at concentrations of 10-2 000 μg/mL, could inhibit cancer cell growth. If cells were cultured in extracts of the fungus, a decrease in the cell proteins and mitotic index was observed. Moreover, the extracts disturbed mitoses by increasing the number of mitotic cells in metaphase. Aqueous extracts of *Inonotus obliquus* influenced not only mitoses but also the cell cycle[26].

The effect of the aqueous extract of *Inonotus obliquus* on the mitotic index and some enzymatic activities in human cervical uteri tumour cells, Hela S3, was evaluated in an *in vitro* study. It was concluded that the Inonotus extract could inhibit the growth of tumor cells and cause a decrease in the amount of cell protein and mitotic index value. Moreover, this extract disturbed metabolism in tumour cells, lowered the activities of lactate dehydrogenase, hydroxybutyrate dehydrogenase, malate dehydrogenase and γ-glutamyltransferase, and enhanced catalase activity[27].

The triterpenes extracted from *Inonotus obliquus*, especially inotodiol, had marked inhibitory effects on Walker-256 carcinosarcoma and MCF-7 breast cancer, as well as on P388 leukemic cells *in vitro*[29]. An Ames test and chromatographic assay of Fuscoporia oblique by Zhao, et al[32] showed that the chemical structure of the active ingredient with anti-mutation activity Ⅲ was 3β,

22 R-dihydroxy-lanosta-8,24-diene (inotodiol).

The *in vitro* effects of the same active ingredient of Fuscoporia oblique on anti-cell proliferation and apoptosis induction in A549 human lung carcinoma cells were also observed by the authors[25]. At present, in China and overseas, more attention has been paid to *Inonotus obliquus*' anti-tumor effects; however, there are not many studies on apoptosis induction.

Hypoglycemic Effect

Polysaccharides in mycelia and sclerote of *Inonotus obliquus* showed hypoglycemic activity in mice with diabetes mellitus[30]. The active components mainly consisted of β-glucan, heteroglycan and proteinum complex. The hypoglycemic effect was maintained for 3-48 h after the mouse was injected with polysaccharides purified from mycelia and sclerote of *Inonotus obliquus*[31]. The mechanism of action needs further investigation.

Anti-virus Effect

Ichimura T, et al[16] reported that inhibitory activity against the protease of HIV-1 was observed in boiling water extracts of an edible mushroom, Fuscoporia oblique. The active component was identified as a water-soluble lignin derivative with high molecular weight. Other polyphenols of low molecular weight and monomeric components of lignin did not inhibit the protease. Lignin alkali (Aldrich), as well as the extract from Fusscoporia. oblique and fraction 23 of the extract, could strongly inhibit HIV-1 protease activity. Fraction 23 contained mostly water-soluble lignin derivatives. The lignin derivative was absorbed on the protease and inhibited HIV reverse transcriptase, thus inhibiting the propagation of HIV-1. Water-soluble lignins isolated from the sclerote of the polypore *Inonotus obliquus*, commonly known as "Chaga", inhibited HIV protease with an IC_{50} value of 2.5 μg/mL[32].

The external dark substance of extracts from *Inonotus obliquus*, at a concentration of 40 μg/mL, demonstrates complete activity against human influenza virus A, B and horse influenza A. The antivirus components mainly consist of betulinol, clerodol and fungisterol, which exist mainly in the outer surface of *Inonotus obliquus*, with lesser amounts inside[33]. The anti-viral mechanisms involved need to be investigated further. Studies on standard high potency extracts from Chaga's inonodiol compounds as treatment against influenza viruses have been conducted in Canada and Finland. The anti-viral mechanisms involved need further study.

Enhancing Immunity

Inonotus obliquus consists of biological response modifier-polysaccharides. Scholars in China also reported that *Inonotus obliquus* polysaccharides has the effect on increasing immunity[34].

Kim, et al[20] reported that the endo-polysaccharide produced by a submerged culture of *Inonotus obliquus* strongly stimulated B lymphocyte- and macrophage-related humoral immunity. In general, high-molecular-weight β-glucans appeared to be more active than low-molecular-weight varieties. The 1 100 kDa endo-polysaccharide seemed to be responsible for the high activities of polysaccharides from *Inonotus obliquus* mycelia. Results showed that the activities of the endo-polysaccharide from mycelia of *Inonotus obliquus* were not changed by proteinase treatment, indicating that the proteins of the endo-polysaccharide complex did not affect the immuno-stimulating activities.

Enhanced proliferation and polyclonal IgM antibody production were observed in B cells treated with purified water-soluble endo-polysaccharide. The expressions of interleukin-β, interleukin-6, tumor necrosis factor-α and inducible nitric oxide synthase in macrophages were also enhanced. However, the endo-polysaccharide did not affect the proliferation of T cells, the interleukin-2 expression in Th1 cells, or the interleukin-4 expression in Th2 cells[20].

Antiplatelet Aggregative Action

It was reported that water and ethanol extracts from mycelium or fruiting bodies in 55 kinds of mushrooms were tested for platelet aggregation inhibitory activities. The maximum platelet aggregation inhibitory activity was found when the mycelia of *Inonotus obliquus* ASI 74006 were extracted with ethanol at 80 ℃ for 12 h. The platelet aggregation inhibitor factor was purified by systematic solvent fractionation, ultrafiltration, sephadex G-10 column chromatography, and reverse-phase HPLC. Ethanol extracts of *Inonotus obliquus* ASI 74006 mycelia showed the highest platelet aggregation inhibitory activity at 81.2%, while water extracts of *Inonotus obliquus* showed 26.2% inhibition. Following further purification of ethanol extracts from the mycelia of *Inonotus obliquus* ASI 74006, the resulting platelet aggregation inhibitor was a novel tripeptide with a molecular weight of 365 Da and a peptide sequence of tryptophan-glycin-cysteine (Trp-Gly-Cys)[35].

Anti-inflammatory and Analgesic Effects

Park YM, et al[36] revealed the mechanism of action of the anti-inflammatory effect due to methanol extracts from *Inonotus obliquus* (MEIO). The effect

on lipopolysaccharide (LPS)-induced responses was examined in a murine macrophage cell line RAW 264.7. It was found that MEIO could significantly inhibit the production of nitric oxide and the release of prostaglandin E_2 and TNF-α in LPS-stimulated RAW 264.7 macrophages. Consistent with these observations, MEIO could potentially inhibit the protein and mRNA expression of iNOS cyclooxygenase-2 (COX-2). Furthermore, MEIO could inhibit the LPS-induced DNA binding activity of nuclear factor-kappaB (NF-kappaB), which was associated with the prevention of inhibitor kappaB degradation and the reduction in nuclear p65 protein level. Taken together, the data indicated that the anti-inflammatory and analgesic properties of MEIO may be due to the inhibition of iNOS and COX-2 expression via the down-regulation of NF-kappaB binding activity[36].

Antioxidant Effect

The Chaga mushroom has been known to exhibit potent antioxidant activity and the extraction from *Inonotus obliquus* has strong antioxidant stability[37]. Several fungal extracts were evaluated for their antioxidant activities by Cui Y, et al[38]. The polyphenol extract had a strong antioxidant activity, and the extract containing triterpenoids and steroids presented a relatively strong antioxidant effect. The polysaccharide extract, however, was the most inactive extract. Phenolic compounds produced by sclerotia of *Inonotus obliquus* are the active constituents responsible for antioxidant activities[39]. It was also reported that the polyphenolic extract of *Inonotus obliquus* has strong antioxidant activity because the polyphenolic extract may contain a strong antioxidant melanin complex or a related polyphenol[17].

Furthermore, daily oral administration of the Inonotus water extract to BALB-line mice with long-term (two months) external gamma-irradiation at the power dose of 0.025 sGr/min had a positive effect on the extension of average lifespan, and kept the oxygenation of lipid peroxidation in the blood and main tissues, and the serum R-protein levels approaching those in the control group with no irradiation treatment[40]. Park YK, et al[41] demonstrated that the Chaga mushroom extract could inhibit oxidative DNA damage in human lymphocytes as assessed by Comet assay.

In much literature, it has been reported that the antioxidant activities of Inonotus obliquus were responsible for the therapeutic effects against cancer, cardiovascular diseases and diabetes mellitus. It is believed that the antioxidants are related to the capcity of scavenge superoxide anion and DPPH radicals[37,39,42].

Folk and Clinical Application

In Olynet, Siberia, the Baltics of Russia, and in Finland, *Inonotus obliquus* has been taken as an anticancer medicine among the people. *Inonotus obliquus* is used as a medicinal fungus in treating cancer patients incapable of accepting operation as a home remedy in Russia, including patients with breast cancer, gastric cancer, lung cancer, skin cancer, rectal cancer and Hopkins lymphoma. Moreover, ulcer, gastritis, hyperplasia of the reproductive organs and glandular organs, and colon carcinoma are treated with *Inonotus obliquus* by the Russians. The Tartars of West Siberia traditionally used *Inonotus obliquus* to treat tuberculosis, gastrosia, liver diseases, heart diseases and ascariasis.

CONCLUSIONS

Inonotus obliquus is utilized widely within various societies, but systematic studies on *Inonotus obliquus* are not thorough enough. Overall systematic studies should be comprehensive, multi-disciplinary, developmental, and applicable, not only focusing on its anti-cancer effects, but also systematically focusing on its anti-atherosclerosis, anti-viral and anti-fibrosis effects. Focus should also not only be on pathological studies but also on synergistic and comprehensive studies in biochemistry, pharmacology, immunology, and clinical medicine; not only on basic theory studies, but also on its clinical applications as well as the development of health products.

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