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RESEARCH ARTICLE

The potential anticancer compounds from the button mushroom *Agaricus bisporus*

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Abstract

Thus far, very limited compounds of *A. bisporus* have been identified to exert in vitro or in vivo anticancer activity; including lectin, unsaturated fatty acids, and crude polysaccharides. Therefore, further research would be warranted to identify additional bioactive compounds that possess significant anticancer activity in *A. bisporus*. In this mini-review, an overview of anticancer properties of compounds obtained from the button mushroom has been presented. This mini-review may encourage more research on various fields, including investigation of discovery and characterization of anticancer compounds, anticancer capabilities of wild sources of *A. bisporus*, exploring mechanism of action of anticancer compounds obtained from *A. bisporus*, and the potential inhibitory effect of *A. bisporus*-derived compounds in animal models.

1. Introduction

So far, drugs approved by US Food and Drug Administration have played an undeniable role in cancer therapy; however, few ones have been approved as cancer chemopreventive agents (Patterson et al., 2013). This fact warrants more research into naturally occurred compounds for development or discovery of potential cancer preventive agents. Amongst other dietary-sourced compounds, edible mushrooms have been considered a noteworthy potential for their cancer preventive abilities (Chen et al., 2006). Accordingly, a number of anti-tumor compounds from a range of edible mushrooms have been isolated and reported (Patel and Goyal, 2012).

The button mushroom, *Agaricus bisporus* is the most important cultivated mushroom in the world (Masoumi et al., 2015). However, studies into the anticancer properties of *A. bisporus* are obviously limited, as compared to other important cultivated mushrooms. Particularly, very limited studies have been undertaken to identify anticancer compounds from this mushroom. So far, very limited review articles have outlined achievements on anticancer activities reported in several species of edible mushrooms, including *A. bisporus* (Patel and Goyal, 2012; Xu et al., 2012). However, recent developments in the research into anticancer properties of *A. bisporus* have not been reviewed. Furthermore, the anticancer potential of wild populations of *A. bisporus* has not yet been evaluated. Hence, this mini-review tries to present research studies undertaken on anticancer potential of cultivated and wild *A. bisporus*. The focus of this mini-review will be largely given to possible anticancer compounds reported in *A. bisporus*. In vitro studies that have investigated anticancer properties of crude extracts of *A. bisporus* are not included in this review. In addition, it discusses possibilities, limitations, and further research related to the anticancer potential of *A. bisporus.*

2. An overview on anticancer compounds from mushrooms:-

Mushrooms are considered functional foods that possess bioactive compounds with a broad range of pharmacological and medicinal properties, including antimicrobial, anticancer, antioxidant, antiviral,

immunomodulatory, immunosuppressive, anti-allergic, anti-inflammatory, and anti-cholesterol activities (Rathee et al., 2012).

A number of mushrooms species have been investigated for their anticancer properties, including species belonging to *Phelinnus, Pleurotus, Agaricus, Ganoderma, Clitocybe, Russula, Antrodia,Lentinula, Flammulina, Trametes, Grifola, Hericium, Cordyceps, Boletus, Calvatia, Schizophyllum, Suillus, Inonotus, Inocybe, Coprinus, Funlia, Lactarius, Albatrellus, Fomes, Piptoporus,* and *Polyozellus* (Patel and Goyal, 2012). Some of these species have been recognized as commercially cultivated mushrooms including *Agaricus* and *Pleurotus*, while some of them are well-known as medicinally important inedible mushrooms such as *Ganoderma*.

So far, several major compounds obtained from mushrooms have been reported to possess anticancer activities. Some of the most frequently reported compounds that have shown anticancer activities include lentinan, krestin, hispolon, lectin,calcaelin, illudin S, psilocybin, hericium polysaccharideAandB (HPA and HPB), ganoderic acid, schizophyllan, and laccase (Patel and Goyal, 2012).

3. Anticancer compounds obtained from *A. bisporus*:

3.1. Lectin

Lectins are carbohydrate-binding proteins that have been isolated and purified from a wide variety of sources. Binding of lectins to cell surface carbohydrates may affect the behavior of the cell. Accordingly, lectins such as peanut agglutinin and *Agaricus bisporus* Lectin (ABL) are able to bind to the carbohydrate structure galactosyl β-1,3-N-acetyl-galactosamine and modulate the proliferation of malignant epithelial cells. However, peanut agglutinin increases colonic carcinoma cell division, while ABL inhibits proliferation of these cells (Yu et al., 1993). Thus, over the past two decades, much of the research on anticancer properties of *A. bisporus* has focused on lectin isolated from this species.

So far, several cancerous cell lines have been shown to be affected by anti-proliferative activity of ABL. For the first time, Yu et al. (1993) showed that ABL at 25 µg/mL could inhibit the growth of several epithelial cancerous cell lines through inhibition of incorporation of [3H]-thymidine into DNA of the tested cells. However, ABL caused no cytotoxicity and its anti-proliferative effects were seen to be reversible after removal of the lectin. Research has shown that ABL inhibits proliferation of a range of cancerous cells including HT-29 colon cancer cells, primary human sub-conjunctival fibroblasts (Yu et al., 1993), retinal pigment epithelial (RPE) cells (Yu et al., 1993; Wenkel et al., 1999), and Tenon's capsule fibroblasts (Batterbury et al., 2002).

Very few studies have also tried to gain insight into possible mechanisms of action of ABL towards proliferation of cancerous cells. A more recent study conducted by Cheung et al. (2012) confirmed the previous findings, where ABL suppressed RPE cell proliferation in a dose-dependent manner without cell toxicity. The further flowcytometry studies confirmed the absence of sub-G1 (apoptotic) population. Also, ABL was shown to specifically suppressed the amount of cells present in S phase. This suggested that cells were less able to transit into S phase from G1 phase when ABL was present (Cheung et al., 2012).

3.2. Unsaturated fatty acids

The findings of several studies conducted by a research team in the US demonstrated that unsaturated fatty acids of *A. bisporus* possess outstanding anticancer properties both *in vitro* and *in vivo*. Firstly, it was shown that the heat-stable extract of *A. bisporus* could inhibit aromatase activity and proliferation of breast cancer cell line in MCF-7aro, an aromatase-transfected breast cancer cell line (Grube et al., 2001). Further investigations showed that major active compounds present in the ethyl acetate fraction of *A. bisporus* were unsaturated fatty acids (Chen et al., 2006). These findings revealed that unsaturated fatty acids inhibited aromatase higher than saturated fatty acids. In addition, unsaturated fatty acids that had more than one double bond (e.g., linoleic acid, conjugated linoleic acid, and linolenic acid) inhibited the tested cancerous cells greater than those with only one double bond (e.g., oleic acid).Linoleic acid is an essential fatty acid in humans and is present in many foods including vegetables. The in vivo investigations of these researchers also showed that the *A. bisporus* heat-stable extract inhibited the growth of hormone-dependent breast tumors in mice, indicating the myco-constituents present in the extract were orally active (Chen et al., 2006).

Further studies were also undertaken to assess *in vitro* and *in vivo* anticancer potentials of the *A. bisporus* extract towards prostate cancer. The in vitro assays were performed in both androgen sensitive LNCaP and androgen insensitive PC3 and DU145 prostate cancer cell lines. The findings showed that conjugated linoleic acid inhibited

proliferation of the prostate cancer cell lines. In addition, the mushroom extract decreased DU145 and PC3 prostate tumor size and proliferation in mice (Adams et al., 2008).

3.3. Polysaccharides

As the literature shows, the majority of research studies on biological effects of *A. bisporus* have focused on the white strains of this mushroom. Furthermore, it is well- known that polysaccharides are the main bioactive component of *A. bisporus*, particularly (1→6)-β-D-glucans; however, very limited dada is available regarding possible anticancer activity of these polysaccharides in *A. bisporus*. Based on the afore-mentioned knowledge gaps, Zhang et al. (2014) studied the anticancer potential of the polysaccharide extract of a brown strain of *A. bisporus*. Their findings showed that the polysaccharide extract significantly inhibited proliferation of HeLa cells. It also, increased spleen index, thymus index and carbon clearance ability of mice (Zhang et al., 2014). However, the crude polysaccharide studied by Zhang et al. (2014) was not further analyzed to investigate its major active components. Therefore, further studies might be warranted to determine potent anticancer component(s) present in the crude polysaccharide of *A. bisporus.*

As opposed to the findings of Zhang et al. (2014) with the brown strain of *A. bisporus*, we showed that methanol-dichloromethane (1:1) extracts of a brown strain of *A. bisporus* could not inhibit proliferation of two cancerous cell lines, PC3 and MCF-7. By contrast, the extract of commercially cultivated *A. bisporus* (white strain) and its ethyl acetate-petroleum ether fraction exhibited potent anti-proliferative activities, as well as cytotoxicity against PC3 and MCF-7 cells (Pourianfar et al., 2015). However, this contradiction might be due to differences in methodology, extraction, cancerous cell lines, and mushroom strain. Therefore, further investigations would be warranted to determine the potency of wild *A. bisporus* strains (crude extract and fractions/compounds) in anticancer research.

4. Conclusions and further research:-

Thus far, few compounds of *A. bisporus* have been identified to exert anti-proliferative or cytotoxicity; including lectin, unsaturated fatty acids (such as linoleic, linoleic conjugate, and linolenic), and polysaccharides, warranting further research to identify additional bioactive compounds in this important commercial mushroom. Discovery and characterization of anticancer myco-compounds present in *A. bisporus* are essential to better understand their mode of action and facilitate future studies using purified compounds.

Furthermore, wild populations of *A. bisporus* may provide a great source of nutritional and medicinal bioactive compounds. At the present, there is a shortage of information in the literature regarding anticancer potency of wild *A. bisporus* in different countries. In this regard, it is required to determine differences between wild and cultivated strains of *A. bisporus* in chemical composition and biochemical properties.

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Declaration of interest:

There is no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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