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Bioactive compounds and *in vitro* evaluation of antioxidant capacities, antimicrobial properties, and effectiveness of cytotoxicity of three edible mushrooms from Egypt

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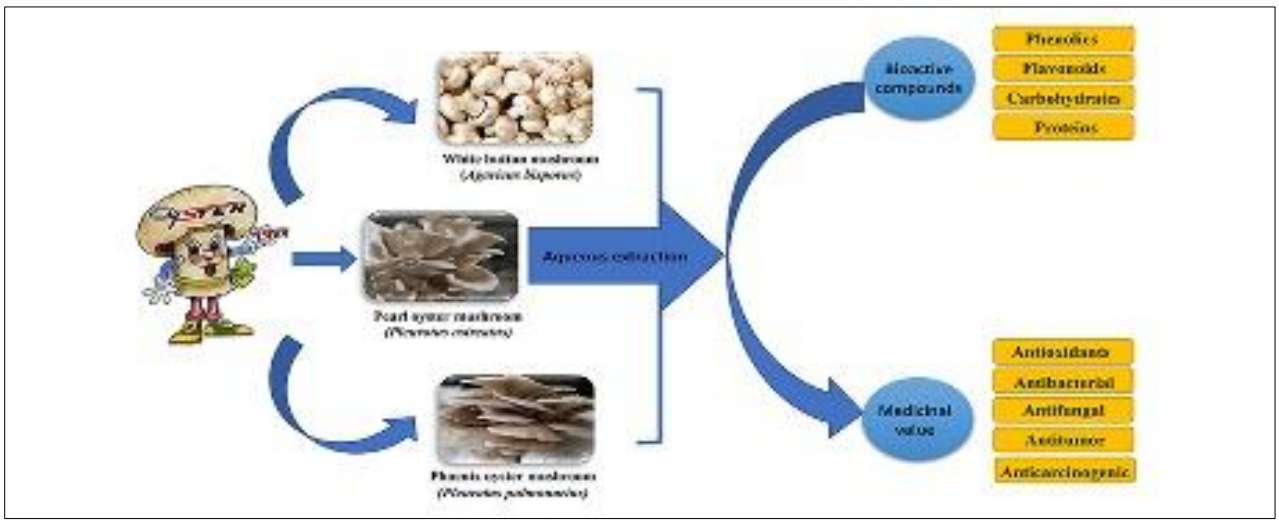
Abstract

Many edible mushrooms have been evaluated as new therapeutic alternatives with various activities. We focused this work to estimate the antioxidant, antimicrobial and cytotoxicity effects of three edible aqueous mushroom extracts: *Agaricus bisporus* (white button mushroom), *Pleurotus ostreatus* (pearl oyster mushroom), and *Pleurotus pulmonarius* (Phoenix mushroom). The biochemical analysis of extracts revealed marked variations for total carbohydrate, protein, phenolic, and flavonoid contents. The three extracts were tested for antioxidant activities using 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) radical scavenging assay. *Pleurotus ostreatus* had a potential antioxidant capacity with lowest IC_{50} value (13.26 µg/mL). Distinct variable degrees of antimicrobial activity were detected against five reference microbial strains, exerting the minimum inhibitory concentration (MIC) ranging from 28 to 89 mg/ml. *Agaricus bisporus* exhibited the highest cytotoxicity against EAC cells with cell viability 68% and showed an evidenced inhibitory action against human breast cancer cell lines (MCF-7) based on Sulforhodamine B (SRB) assay.

Keywords: Mushroom extract; Bioactive; Antioxidant; Antimicrobial; Cytotoxic

Graphical Abstract



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1 Introduction

Edible mushrooms are known from centuries and have a high nutritional value with low calories also, they are cholesterol-free [1, 2]. Besides, mushrooms provide important nutrients, including proteins, fats, volatile oils, cellulolytic enzymes, carotenoids, flavonoids, phenolic compounds, zinc, selenium, iron, sodium, fibers, chitin, minerals, and vitamins such as vitamins B1, B2, B3, C, and the precursor of vitamin D2 [3-8]. Mushrooms are used as natural alternative medicines against pathogens and current life-threatening diseases [9-12]. Nowadays, incrementing use of disinfectants and excessive sanitation procedures against pandemic coronavirus Covid-19 could support the proliferation of multi-drug resistant microorganisms [13, 14]. The anti-inflammatory and antiviral efficiency of medicinal macro fungi reduced the effect of SARs-CoV-2 [15-17]. Therefore, further studies have been proceeded to detect the antimicrobial effect of alternative eco-friendly novel natural sources including mushrooms [18]. These new antimicrobial compounds, mainly secondary metabolites, seem to have an antimicrobial action against both Gram-positive and Gram-negative bacteria and prove potential alternatives to fight against serious infections [19-24].

Bioactive mushroom components: polysaccharides, glycoproteins, proteoglycans, and organic secondary metabolites stimulate immunity and inhibit tumor incidence with an excellent medical therapy [25-29]. Other components have excellent cardiovascular, antiviral, antibacterial, antifungal, antiparasitic, hypoglycemic, immunomodulatory, anti-inflammatory, anticancer, and hypocholesterolemic activities [30-34]. Biologically active β-glucan is the most common metabolite with a broad spectrum of biological potency of different mushroom extracts [35-39].

Therefore, this study focuses on the potentiality of various biological activities (antioxidant, antimicrobial, cytotoxic, and antitumor) of the most popular edible mushrooms in Egypt, namely *Agaricus bisporus, Pleurotus ostreatus*, and *Pleurotus pulmonarius*.

2 Material and methods

2.1 Sample Preparation and Extraction

Fresh *Agaricus bisporus* fruiting bodies were purchased from commercial Egyptian markets. While, *Pleurotus pulmonarius* and *Pleurotus ostreatus* were kindly obtained from the Agriculture Research Center, Giza, Egypt. The mushrooms were well cleaned and kept at 45 °C in hot air oven to get fully dried constant weight, each dried mushroom was ground well to fine powder using an electronic grinder. About 30 g of each powder was dissolved in 300 ml of distilled water, then boiled for 3 h at 90 °C to obtain the aqueous extract. After centrifugation, the supernatant was stored at 4°C for further analysis [40].

2.2 Biochemical Characterization of the Aqueous Mushroom Extracts

2.2.1 Total Carbohydrate and Protein Content

Total Reducing Sugars were estimated by Phenol-sulfuric acid method [41]. Carbohydrates concentration (X) was calculated from the equation (Y=0.003X), where, Y was the absorbance. Protein was assayed based on the Lowry method [42], absorbance was detected at 650 nm. Bovine serum albumin was used to calculate the standard curve (0.03 - 0.15 mg/ml).

2.2.2 Assay for Total Phenolics and Flavonoids

One hundred µl Folin-reagent Ciocalteau and 2 ml of 7.5% Na_2CO_3 were added to 100 µl of mushroom extract, mixed well and after 2 h of incubation at room temperature, the sample absorbance at 750 nm was measured. Total phenolic content was expressed as mg of gallic acid equivalents / ml of extract [43].

Flavonoid content was estimated according to Zou et al. [44]. First, 500 µl of the extract or standard (1 mg/ml) was diluted with 2 ml of distilled water and 0.15 ml of 5% sodium nitrite solution and mix well. About 0.15 ml of 10% aluminum chloride was added and left for 6 min, followed by adding 2 ml of 4% NaOH solution to the mixture. The total volume was adjusted to 5 ml with 70% ethanol and stirred. The intensity of the color was measured at 510 nm after incubation for 15 min. The quantified flavonoid was calculated at mg of quercetin equivalents / ml of extract.

2.3 Antioxidant Potential Assay (DPPH)

DPPH radical scavenging assay was measured according to the method of Brand-Williams et al. [45]. Briefly, 50 mg of each sample and ascorbic acid (standard) were dissolved in 1 ml dimethyl sulfoxide (DMSO). The dissolved sample was

added to 1 ml (6 mg/50 ml) of DPPH/ DMSO solution. The mixture was shaken well and allowed to react for 30 min in dark at room temperature. The EC_{50} (the amount of compound that provides half-maximal scavenging response) of each sample was measured using serial dilutions (5-50 mg/ml). The reduction in DPPH color was measured at 517 nm. Data are represented as means ± SD according to Equation:

$$\text{Radical scavenging \%} = [(A_{DPPH} - A_S)/A_{DPPH}] \times 100,$$

A_S is the average absorbance of the extract solution. The extract concentration yielding 50% inhibition of the free radicals (IC_{50}) was estimated.

2.4 Antimicrobial Efficacy

Antimicrobial potency of the three mushroom extracts was evaluated by the agar well diffusion method and minimum inhibitory concentration (MIC) technique *in vitro* against five microbial pathogens kindly donated from the Microbiological lab at Departement of Microbiology, Faculty of Science, Helwan University, Egypt. The tested microorganisms viz., Gram +ve bacteria: *Staphylococcus aureus* ATCC 25923 and *Streptococcus pneumoniae* ATCC 49619, Gram -ve bacteria: *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 7853, grown in Mueller Hinton Agar (MHA) at 35 °C for 1 day *Candida albicans* ATCC 20231 as a unicellular fungal species was grown in potato dextrose agar at 27 °C for 3 days. MHA plates were swabbed with 100 µl of each strain (0.5 McFarland standards). Approximately 5-mm diameter of wells aseptically were made in the agar plates [46]. 100 µl of each sample (extract) was injected into the wells. Negative controls were employed with DMSO, while positive controls were gentamicin (10 µg/mL) for bacteria and nystatin (100 U) for fungi. Evaluation of the antimicrobial efficiency was detected by monitoring the mean diameter of the growth inhibition zones (mm) in triplicate.

Minimum inhibitory concentration (MIC) was detected by dilutions technique [47]. Serial two-fold dilutions of each mushroom extract were adjusted 6.25, 12.5, 25, 50, and 100 mg/ml. Negative control was zero concentration. Half ml of bacterial suspension (0.5 McFarland standards) was mixed well with 9.5 ml of each concentration in sterile tubes. After that, the seeded tubes incubated at 35 °C for 24 h. The experiment was tested three times. The optical density of growth was measured spectrophotometrically at 600 nm (Optima SP-300, Japan). The minimum inhibitory concentration (MIC) of each mushroom extract was considered the lowest concentration without growth [48].

2.5 Assessment of Cytotoxicity

2.5.1 Cytotoxic Activity toward Ehrlich Ascites Carcinoma (EAC)

The anticancer efficiency of mushroom extracts was investigated on tissue culture of EAC that kindly provided from National Cancer Institute, Cairo University, Egypt. Tumor cell suspensions ($2.5x10^5$ cells/ ml) were prepared in phosphate buffer [49]. About, 1 mg/ml from each extract was added and kept in rotating water bath for 2 h at 37 °C. Ten µl of sample was mixed with trypan blue stain (10 µl of 0.4%), the number of total, dead and live cells were counted immediately within 5 min using hemocytometer [50]. Morphological investigation of the cells was observed, viable cells had bright centers and dark edges whereas nonviable cells showed signs of staining.

2.5.2 Cytotoxic Effect against Human Breast Cancer Cell Lines (MCF-7)

MCF-7 were obtained from the American Type Culture Collection (ATCC, Minisota, USA) and maintained by routine sub-culturing in 75 cm^2 tissue culture flasks at the National Cancer Institute, Cairo, Egypt. The inhibitory action of mushroom extracts on MCF-7 cells growth was evaluated calorimetrically by sulforhodamine B (SRB) [51]. Stock solution (1:1) of mushroom extracts in DMSO was prepared and stored at 20 °C. Doxorubicin was the positive standard. Serial concentrations of both extract and doxorubicin (5, 12.5, 25, 50 µg/ml) were applied and the cell viability was detected.

2.6 Statistical Analysis

Experimental analyses were performed at least three parallel times and the statistical analyses of results were calculated as mean ± SD. The difference between mean values was estimated using ANOVA test and values of $p < 0.05$ was significantly observed.

3 Results

3.1 Biochemical Analysis of Aqueous Mushroom Extracts

Comparative analyses of total carbohydrate, protein, phenols, and flavonoids were estimated (Table 1). This study revealed an evidenced variations among the test mushroom extracts. The phenolic content of the tested extracts ranged between 5.11 and 8.35 GAE mg/ml. *P. ostreatus* extract showed the greatest content of carbohydrate, protein, flavonoid and relatively low phenolic content. *A. bisporus* extract exceeded the other species in its total phenolics (8.35 mg/ml).

Table 1 Bioactive component analysis of different mushroom extracts

Mushroom extract	Total carbohydrate content (mg/ml)	Total protein content (mg/ml)	Total phenolic content (mg/ml)	Total flavonoid content (mg/ml)
Agaricus bisporus	355.21 ± 4.99	0.86 ± 0.02	8.35 ± 0.62	10.22 ± 0.41
Pleurotus ostreatus	1510.99 ± 16.25	0.90 ± 0.01	5.11± 0.88	16.44 ± 0.48
Pleurotus pulmonarius	1267.55 ± 13.35	0.81 ± 0.01	5.74 ± 0.37	12.02 ± 0.60

Each result is presented as mean ± SD of three replicates (n = 3)

3.2 Antioxidant Activity

As shown (Table 2, Figure 1), *P. ostreatus* exhibited a significant antioxidant capacity (75.04%) and was relatively close to that of standard (81.57%). *A. bisporus* was a considerably less effective radical scavenger. Higher efficiency for antioxidant properties recommends the lower IC_{50}.

Table 2 DPPH radical scavenging abilities (IC_{50} µg/ml) of different mushroom extracts

Mushroom extract	Decrease in absorbance %	IC_{50} (µg/ml)
Agaricus bisporus	52.29 ± 1.24	36.54
Pleurotus ostreatus	75.04 ± 1.50	13.26
Pleurotus pulmonarius	71.65 ± 1.51	16.35
Ascorbic acid (standard)	81.57 ± 0.54	9.14

Each result is presented as mean ± SD of three replicates (n = 3)

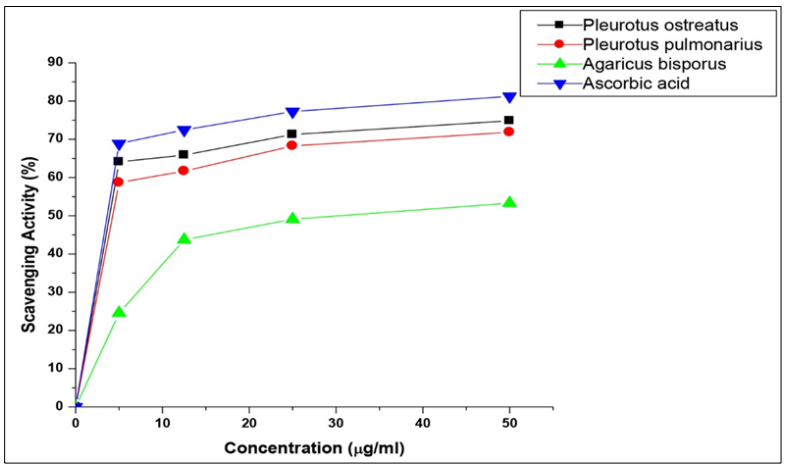

Figure 1 Antioxidant effectiveness of different mushroom extracts on DPPH free radicals in comparison to ascorbic acid (standard)

3.3 Antimicrobial Activity

Maximum antibacterial activity against *S. aureus* ATCC 25923 (12.00 ± 0.7mm) was exhibited by *A. bisporus* extract (Table 3), followed by *P. ostreatus* and *P. pulmonarius* (10.00 ± 0.6 and 9.0 ± 0.5 mm), respectively. *P. ostreatus* extract had the most potent inhibitory efficiency toward *C. albicans* ATCC 20231.

The MIC technique was performed for the highly sensitive bacterial strains based on the former results. The MIC values varied from 28 to 89 mg/ml (Table 4). The *P. ostreatus* and *P. pulmonarius* extracts represented higher MIC values than *A. bisporus*. The maximum MIC values were revealed against *S. aureus* ATCC 25923, *S. pneumoniae* ATCC 49619, and *E. coli* ATCC 25922 at 12.5, 12.5, and 25 mg/ml, respectively.

Table 3 Screening of antimicrobial efficacy of mushroom extracts against the tested pathogenic microbes

Microbial strain	**Mean diameter of growth inhibition zones (mm)**					
	Mushroom extract			**+ve control**		**-ve control**
	P. ostreatus	***A. bisporus***	***P. pulmonarius***	**Gentamicin for bacteria (10 µg/mL)**	**Nystain for fungi (100 U)**	**DMSO**
C. albicans ATCC 20231	9.50 ± 0.3	7.00 ± 0.1	6.50 ± 0.1	ND	20 ± 0.6	00.00
P. aeruginosa ATCC 7853	4.00 ± 0.2	6.00 ± 0.3	5.50 ± 0.2	14 ± 0.4	ND	00.00
E. coli ATCC 25922	6.00 ± 0.4	7.00 ± 0.4	5.50 ± 0.1	17 ± 0.5	ND	00.00
S. aureus ATCC 25923	10.00 ± 0.6	12.00 ± 0.7	9.00 ± 0.5	21 ± 0.7	ND	00.00
S. pneumoniae ATCC 49619	7.00 ± 0.5	7.50 ± 0.3	9.00 ± 0.5	19 ± 0.8	ND	00.00

Each result is presented as mean ± SD of three replicates (n = 3); ND: not detected

Table 4 Mean minimum inhibitory concentration (mg/ml) of mushroom extracts against the tested pathogenic microbes

Mushroom	**MIC (mg/ml)**	**MIC (mg/ml)**		
		***E. coli* ATCC 25922**	***S. aureus* ATCC 25923**	***S. pneumonia* ATCC 49619**
	0.0	100	100	100
P. ostreatus	6.25	82	63	74
	12.5	65	29	30
	25	31	30	29
	50	29	29	29
	100	30	28	28
A. bisporus	6.25	87	61	73
	12.5	72	55	49
	25	41	29	32
	50	30	30	31
	100	29	29	32
P. pulmonarius	6.25	89	66	74
	12.5	70	29	28
	25	38	30	29
	50	35	30	28
	100	33	29	28

3.4 Assessment of Cytotoxic Effect against Ehrlich Ascites Carcinoma (EAC) Cells

The antitumor efficiency was assessed by counting the total, live and dead EAC cells. Distinct results were recorded for all aqueous extracts (Table 5, Figure 2). *A. bisporus* exhibited the highest cytotoxicity against EAC cells and reduced the viability to 68%.

Table 5 Cell viability of the three mushrooms extracts against Ehrlich (EAC) cells

Mushroom extract	Live	Dead	Total	Viability (%)
Agaricus bisporus	$1.9*10^6$	$8.7*10^5$	$2.7*10^6$	68%
Pleurotus ostreatus	$1.8*10^6$	$3*10^5$	$2*10^6$	86%
Pleurotus pulmonarius	$1.6*10^6$	$4.1*10^5$	$2*10^6$	80%

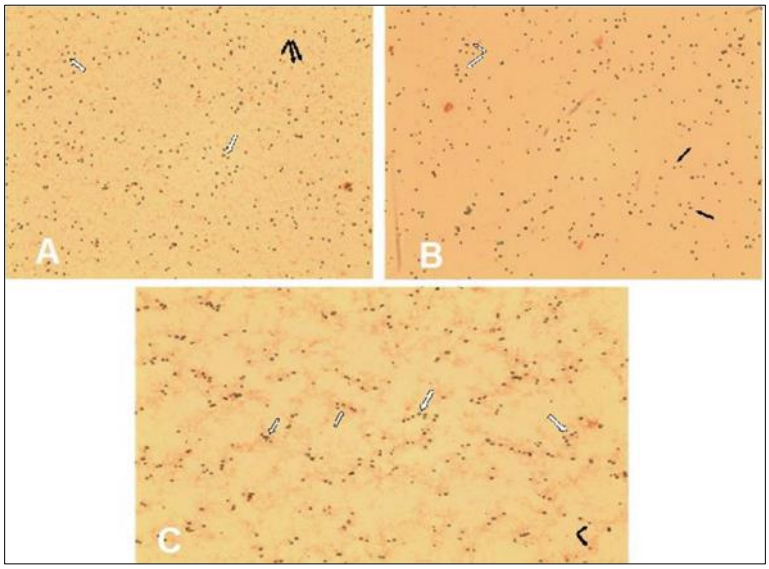

Figure 2 Morphological study of Ehrlich (EAC) cells showing the cytotoxic effect of different mushroom extracts on EAC cells. Where, white arrows represent live cells and black arrows represent dead cells. A) *Agaricus bisporus* extract (live cells 68% and dead cells 32%). B) *Pleurotus ostreatus* extract (live cells 86% and dead cells 14%). C) *Pleurotus pulmonarius* extract (live cells 80% and dead cells 20%)

3.5 Inhibitory Effects of Mushroom Extracts on Human Breast Cancer Cell Lines (MCF-7)

Table 6, Figure 3 showed the cytotoxicity of *A. bisporus* extract that exhibited a remarkable anti-breast cancer activity (IC_{50} 16.40± 1.2 µg/ml) higher than that of the reference doxorubicin (IC_{50} 3.53± 0.2 µg/ml).

Table 6 Cytotoxicity (IC_{50}) of the tested *Agaricus bisporus* extract on breast cancer cell lines (MCF-7)

Extract	IC50 (µg/ml)
Agaricus bisporus	16.40 ± 1.2
Reference drug (DOX-MCF7)	3.53 ± 0.2

Each result is presented as mean ± SD of three replicates (n = 3)

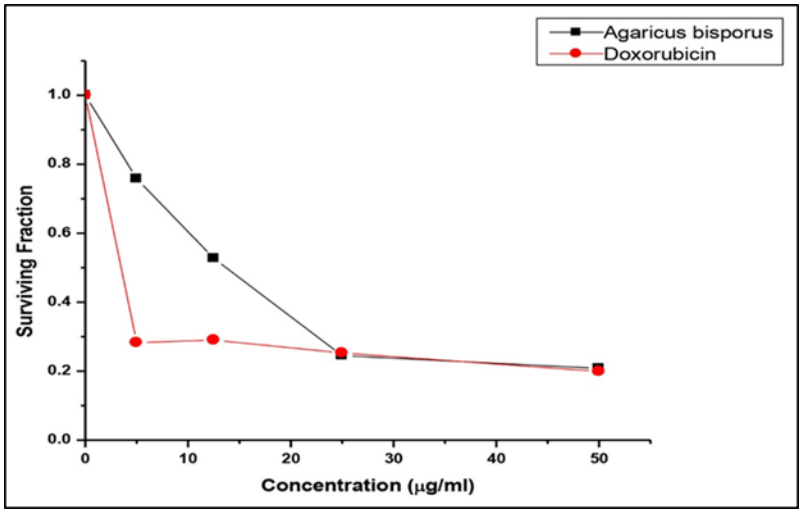

Figure 3 IC_{50} of *Agaricus bisporus* extract on breast cancer cell lines (MCF-7) in comparison with doxorubicin

4 Discussion

In this study, we reported the potentiality of different biological activities (antioxidant, antimicrobial, cytotoxic, and antitumor) of the three edible aqueous mushroom extracts.

Edible fruiting bodies are a greatly rich source of immunomodulatory proteins [1,3,52]. According to the obtained results, *P. ostreatus* recorded a higher level of protein than that of *A. bisporus* and *P. pulmonarius* which had close values. Braaksma and Schaap [53] indicated that the crude amount of protein of *A. bisporus* mushroom has been estimated to be 19-38% / dry weight, but complications of the assay has been established by the presence of nonproteinic nitrogenous compounds. Goyal et al. [54] reported both total protein and nitrogen were remarkably richer in *Pleurotus* sp. than *Agaricus* sp. The greatest protein contents of the mushrooms do not seem to be related to the highest protein contents found in the respective cultivation substrates [55].

P. ostreatus and *P. pulmonarius* extracts had higher carbohydrate content which increased than that found in *A. bisporus* by about 4.25 and 3.50 folds, respectively. These results agree with those detected by Abou-Raya et al. [56] who reported the total carbohydrates content of *P. ostreatus* (57.05%) higher than that of *A. bisporus* (42.56%). It may be due to the growth of hyphal mycelium of *A. bisporus* consuming a diversity of monosaccharides during the vegetative stage. This indicates that sugars other than hexoses may provide energy for growth and reproduction of the vegetative mycelium [57].

Our findings regard to total phenolic and flavonoid compounds indicated that *A. bisporus* had a higher content of total phenolic compounds than that of both *Pleurotus* spp. These data are in line with that achieved by Alispahić et al. [58]. Abou-Raya et al. [56] estimated that total phenols in *A. bisporus* was higher than that in *P. ostreatus*. The whole quantity of phenols was detected to be 6.94 mg/g of GAE/g of *P. ostreatus* dry polar extract [59]. Hip et al. [60] reported the phenolic content in aqueous extracts of *Pleurotus* sp. and *P. ostreatus* were 9.01 and 7.23 mg GAE/g, respectively. Similarly, Gąsecka et al. [61] reported a wide range of total phenols (132.7 to 1154.7 mg GAE/100 g DW) of seven *Agaricus* spp. On the other hand, *P. ostreatus* showed the highest total flavonoid content (16.44 mg/ml). This value is higher than that detected by Rahimah et al. [62] recorded the total flavonoid content (6.67 mg/g) of *P. ostreatus* extract. On the contrary, Vieira et al. [63] reported the absence of flavonoids in *P. ostreatus.* The potency of flavonoids as a secondary metabolite depends on the number and position of free OH groups [64].

Substances that can inhibit or obstruct oxidation of substances are called antioxidants and recently attention has been focused on discovering bio-antioxidants of natural origin as eco-friendly alternatives [65-67]. Association of the antioxidant properties of phenolic compounds is due to redox reactions, which enable them to act as reducing agents or as donors of hydrogen atoms [68,69]. The antioxidant components of different mushroom species have antiallergic, anti-inflammatory, anti-aging, and anticarcinogenic properties [70-72]. The present study revealed that *P. ostreatus* had a relatively strong antioxidant activity comparable to that of ascorbic acid as a standard. In a similar work, Elhusseiny et al. [73] demonstrated the ABTS scavenging capacity of *Agaricus bisporus, Pleurotus columbinus*, and *Pleurotus sajor-caju* mushroom extracts exhibited higher antioxidant activities than that of Trolox.

Concerning with screening of antibacterial efficiency, the present results were compatible with data of Abou Baker et al. [74], Venturini et al. [75], Waithaka et al. [76], and Zalazar et al. [77] who recorded the strong sensitivity of Gram-positive bacteria to various mushroom extracts versus to Gram-negative. The difference in sensitiveness is due to the great variations in the infrastructure of Gram-negative bacterial cell wall and the additional layer of lipopolysaccharide barrier of cell wall that limit and regulate the entry of most molecules [78,79]. El-Sayed et al. [59] detected an evidenced growth inhibition zone of *S. aureus* (20 mm), followed by *C. albicans* (18 mm), and *E. coli* (16 mm). In general, the susceptibility of broad spectrum of bacteria to the fruit body extracts may be attributed to the existence of a wide diverse of molecular weight ingredients in mushrooms that enhance the porosity for ions penetration and suppress bacterial growth [80,81]. On the other hand, *Lactarius* fruiting bodies are considered as a good source of natural antibiotics with potential antibacterial activity owing to their high content of phenolic acids [82]. In this study, aqueous extracts of *P. ostreatus* and *P. pulmonarius* showed significant MIC values at 12.5 mg/ml against *S. aureus* ATCC 25923 and *S. pneumoniae* ATCC 49619. The antagonistic effect of the aqueous fruiting body extracts of both *Agaricus* sp. and *Pleurotus sajarcaju* were about 10% against microbial strains [83]. According to Kosanić et al. [84] the acetone extract of edible fruit *Craterellus cornucopioides* has an evidenced MIC against Gram-positive and Gram-negative bacteria.

Mushrooms are an evidenced therapeutic value because they contain a myriad of pharmacologically bioactive secondary metabolites [59,85] that help in enhancing the capacity of immune system to fight against carcinogens [86,87]. The therapeutic effects of medicinal mushrooms are due to the presence of lectin, β-glucan, ergosterol, arginine, and other diverse bioactive components [88,89]. From the current paper, *A. bisporus* extract showed a potential antitumor activity comparable to that of both *P. pulmonarius* and *P. ostreatus* extracts on tissue culture of Ehrlich cells with an evidenced reduction in the cell viability.

Regarding the human MFC-7 cell line, *A. bisporus* extract revealed a good inhibiting growth effect, recommending that it may be used as a potential sustainable natural agent for the therapy of human breast cancer. Chen et al. [90] and Grube et al. [91] showed that *A. bisporus* (white button mushroom) suppresses the activity of aromatase at the estrogen receptor *in vitro* and *in vivo* against MCF-7 cells, which is a major contributor to postmenopausal breast cancer in women. Abdalla et al. [92] indicated that *Agaricus blazei* extract limited breast cancer cell proliferation by inhibiting aromatase activity. Adams et al. [93] reported that drinking *A. bisporus* fruit body powder with green tea may inhibit cell proliferation of breast cancer. Also, Shin et al. [94] indicated that eating of mushrooms may lower the risk of breast cancer for pre-menopausal women. In addition, cytotoxic effect of *A. bisporus* extract is previously documented against different cancerous cell lines as melanoma-B16 [95]. The aqueous extracts of *P. ostreatus* and *Lentinus edodes* reduced the cell viability of leukemia cell lines to 70.64% and 66.2%, respectively [96]. The potential cytotoxicity of mushroom extracts has been attributed to the strong scavenging capacity and to the biodiversity of bioactive molecules such as phenolic compounds, α- and β-glucans, glycoproteins, proteins, fatty acids, terpenoids, and nucleoside antagonists [10, 97].

5 Conclusion

The current investigation indicated that the three mushroom extracts *Agaricus bisporus, Pleurotus ostreatus, and Pleurotus pulmonarius* are rich and cheap sources of protein, carbohydrate, phenolic, and flavonoid compounds. Thereby, they could help in reducing the oxidative damage as natural antioxidants and fight against many life-threatening diseases. The aqueous extracts have appreciable antioxidant, cytotoxic properties, and promising antimicrobial efficacy. *Agaricus bisporus* exhibits a high amount of phenolics content and potential antibacterial activity against *Staphylococcus aureus* ATCC 25923. Furthermore, it demonstrates a strong cytotoxic effect against EAC cells and MCF-7 cell lines. Therefore, further studies are required to isolate, identify, and purify the significant novel bioactive components and the detailed pathway analysis is being studied. *In-vivo* experiments and clinical studies must be done to emphasize the therapeutic capability of *Agaricus bisporus* mushroom as a source of medical and pharmaceutical applications.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare no conflict of interest regarding the publication of this paper.

Author Contributions

Conceptualization, G.A.Y. and D.M.B. G.A.Y., M.M.N., and D.M.B. carried out the experiments. G.A.Y. and D.M.B. analyzed and wrote the results. G.A.Y. edited and revised the final manuscript. G.A.Y. and D.M.B finalized and supervised the manuscript. All authors approved the final published version of submission.

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