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MITIGATING CISPLATIN-INDUCED KIDNEY DAMAGE: THE ANTIOXIDANT ROLE OF *AGARICUS BISPORUS*

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ABSTRACT

Cisplatin (CP) is one of the most effective chemotherapeutic agents and plays a major role in treating a variety of human solid tumors. However, the clinical use of CP is frequently limited because of its renal toxicity and production of reactive oxygen species (ROS) that intensify the cytotoxic effects. The use of antioxidants effectively counteracts the cytotoxic effects of CP. The antioxidant activities of a methanolic extract of Agaricus bisporus (white Butten Mushroom) have been suggested to protect against CP-induced nephrotoxicity in male albino rats. Male albino rats were randomly divided into four groups of six rats each. Group I is the normal control group, Group II is the cisplatin-treated group, Group III is the silymarin-treated group, and Group IV is the Agaricus bisporus-treated group. After 15 days of treatment, the kidney of each rat was excised, cleaned, weighed, rinsed in ice-cold saline, homogenized, and centrifuged. Collected renal tissue supernatant was used for the analysis of levels of malondialdehyde (MDA), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in all groups. A histological examination was also carried out in all groups. Agaricus bisporus-treated rats revealed a significant reduction in MDA levels and increases in GPx, CAT, and SOD activities in kidney tissue homogenates. Additionally, histopathological examinations revealed markedly ameliorated cisplatin-induced toxicity on kidney structure. Our results proved that Agaricus bisporus has antioxidant and protective effects against cisplatin-induced oxidative stress. Thus, it could be used as a dietary supplement to reduce the toxic side effects of anticancer drugs.

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1. INTRODUCTION

Nephrotoxicity is one of the most common kidney problems and occurs when the body is exposed to a drug or toxin when kidney damage occurs. Chronic renal failure induces a slow and progressive decline of kidney function. It is usually a result of complications from another serious medical condition. Cisplatin is a potent antitumor drug. Cisplatin-based combination chemotherapy regimens are currently used as frontline therapy in the treatment of testicular cancer, ovarian germ cell tumors, epithelial ovarian cancer, head and neck cancers, non-small cell lung cancers, malignant melanoma, carcinoids, penile cancer, and adrenocortical carcinoma. The therapeutic effects of cisplatin are significantly improved by dose escalation. However, high-dose therapy with cisplatin is limited by its cumulative nephrotoxicity and neurotoxicity (1). Cisplatin is a major antineoplastic drug for the treatment of solid tumors, but it has dose-dependent renal toxicity. It has multiple intracellular effects, causing direct cytotoxicity with reactive oxygen species such as apoptosis, inflammation, and fibrogenesis [2]. Nephrotoxicity is the poisonous effect of some substances, both toxic chemicals and medications, on the kidneys. Drugs are a common source of acute kidney injury. Compared with 30 years ago, the average patient today is

older and is exposed to more diagnostic and therapeutic procedures with the potential to harm kidney function [3]. Cancer is one of the most dreaded diseases and is currently taking a toll on human lives. With the distant hope of finding an effective cure, unless detected, radiotherapy is the most common modality of cancer treatment.

Cisplatin accumulated in the tubular epithelial cells of the proximal kidney tubule, causing nephrotoxicity characterized by morphological destruction of intracellular organelles, cellular necrosis, loss of microvilli, alterations in the number and size of the lysosomes, and mitochondrial vacuolization, followed by functional alterations including inhibition of protein synthesis, GSH depletion, lipid peroxidation, and mitochondrial damage. Several distinct mechanisms for cisplatin cytotoxicity in renal tubule cells have been proposed, including direct DNA damage (4). Chemotherapy and radiotherapy are the most common methods of cancer treatment. Cisplatin (Cis-diamino dichloro platinum II) is one of the most important chemotherapeutic drugs used to treat a wide range of solid tumors, including head, neck, ovarian, and lung cancers. However, the clinical usefulness of this drug is limited due to the induction of nephrotoxicity, a side effect that may be produced in various animal models [5]. 20% of the patients receiving high doses of cisplatin have severe renal dysfunction. Cisplatin DNA cross-links cause cytotoxic lesions in tumors and other dividing cells. DNA-damaging agents usually have less toxicity in non-proliferating cells, yet the quiescent proximal tubule cells are selectively damaged by cisplatin. The mechanism for this renal cell injury has been the focus of intense investigation for many years, and recent studies suggest that inflammation, oxidative stress injury, and apoptosis probably explain part of this injury [6].

Understanding the mechanisms for this side effect should allow clinicians to better prevent and/or treat this problem and provide a model for investigating drug-induced nephrotoxicity [7]. It has also been reported that cisplatin-induced nephrotoxicity is closely associated with increased lipid peroxidation in the kidney. In addition, cisplatin has been found to lower the activities of antioxidant enzymes and induce depletion of GSH. A large number of studies have reported the beneficial effects of a variety of antioxidants on cisplatin-induced nephrotoxicity [8].

2. MATERIALS AND METHODS

2.1. Plant material

White button mushroom (Agaricus bisporus) was purchased from a local Russian market.

2.2. Drugs and chemicals

Cisplatin vials were used to induce nephrotoxicity, and Silymarin (Ranbaxy Ltd) was used as a standard drug. Both were procured from a medical shop in Russia. All the other chemicals and reagents used in the study were obtained commercially and were of analytical grade.

2.3. Preparation of a methanol extract from mushrooms

Methanolic extract of Agaricus bisporus Fresh macro fungus was washed and dried in a hot oven at 370 for three days. Dried samples were packed into an airtight container to protect them from humidity. Fifty grams of dried mushrooms were extracted by stirring with 500 ml of methanol at 300 at 150 rpm for 24 hours. The water was then filtered through "Waterman No. 1 filter paper." The residue was again extracted with an additional 500 ml of methanol. The combined methanol extract was then rotary evaporated for 2 hours.

2.4. Experimental Animals

Male albino rats weighing 150–200 g were obtained from the Southern Federal University, Russia. They were housed in clean polypropylene cages under standard conditions of humidity (45±4%), temperature (25±20°C), and light (12 h light/12 h dark cycle) and fed a standard diet and water ad libitum. This study was approved by the Institutional Animal Ethics Committee (IAEC) (1416/PO/a/11/CPCSEA).

2.5. Experimental Design:

After one week of acclimatization, male albino rats were divided randomly into four groups of six animals each.

Group I: Normal control rats were treated with an oral dose of distilled water for 15 days.

Group II: On day 1, rats were treated with a single i.p. dose of cisplatin (16 mg/kg of body weight).

Group III: Rats were treated with an oral dose of silymarin (50mg/kg body weight/day) from the 2nd day to the 15th day for 14 days after a single, i.e., dose of cisplatin on day 1.

Group IV: Rats were treated with an oral dose of methanol extract of Agaricus bisporus (200 mg/kg of body weight/day) from the 2nd day to the 15th day for 14 days after a single i.p. dose of cisplatin on day 1. All groups used collected blood samples for biochemical and hematological significance studies.

2.6. Preparation of Kidney Homogenate

The rats were fasted overnight on the 15th day prior to the termination of the experiment. On the 16th day, the fasted rats were sacrificed under chloroform anesthesia. The kidney was quickly removed, washed in ice-cold isotonic saline, and blotted on ash-free filter paper. The tissues were then homogenized at 0.1 M. The homogenate was then centrifuged at 9000 rpm for 15 minutes in a cold centrifuge, and the supernatant was stored at 20°C to assay antioxidant enzyme activity [9].

2.7. Lipid Peroxidation Analysis

Lipid peroxidation was evaluated as malondialdehyde (MDA) production as described by Heath and Backer [10]. The animals were sacrificed by decapitation on the 16th day. The kidneys were dissected and immediately placed in ice-cold saline to prevent contamination with blood, and they were pressed on blotted paper, weighed, and homogenized in 1.5% KCl with the help of a Teflon homogenizer. To 1 ml of homogenate, 2.5 ml of trichloroacetic acid (TCA, 20%) was added and centrifuged at 3500 rpm for 10 min. The resulting pellet was dissolved in 2.5 ml of 0.05 M H2SO4, and then 3 ml of thiobarbituric acid was added and incubated at 37 for 30 minutes. The contents were then extracted into 4 ml of n-butanol, and the absorbance was measured spectrophotometrically at 530 nm.

2.8. Enzymatic Antioxidant Analysis

Superoxide dismutase (SOD) was assayed in the renal tissue supernatant by the method of Kakkar et al. [11]. Sinha et al. assessed the catalase (CAT) activity in the renal tissue supernatant [12]. Glutathione peroxidase (GPx) activity was assayed in the renal tissue supernatant by the method of Rotruck et al. [13].

2.9. Histopathological Analysis

After the animals were sacrificed, kidney samples were excised from the control and treated groups and washed with normal saline. They were fixed in 10% buffered formalin for 24 hours and embedded in paraffin wax. Cross sections of the kidney tissue (5-6m thick) were prepared and stained with hematoxylin-eosin dye (14).

2.10. Statistical Analysis

The outcomes were presented as the mean value of the Standard deviation. Within-group comparisons were performed using variance analysis using the ANOVA test. The student t-test determined whether there was a significant difference between the normal control and experimental groups. A probability level of less than 5% (P 0.05) was considered significant.

3. RESULTS

3.1. Effect of *Agaricus bisporus* on Renal Enzymatic Antioxidants in Cisplatin-induced Nephrotoxic Rats

The activities of enzymatic antioxidants in the kidney homogenates of all the groups of animals are shown in (**Table 1, Fig 1 & Fig 2**). Renal antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) levels were significantly lower in the cisplatin-treated group II compared to the normal control group I. Treatment with *Agaricus bisporus* group IV significantly (p 0.05) increased the levels of antioxidant enzymes like catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) when compared to cisplatin-treated group II. The silymarin-treated group III also significantly (p 0.05) increased the antioxidant enzyme level compared to the cisplatin-treated group II.

3.2. Effect of *Agaricus bisporus on* Renal Lipid Peroxidation in Cisplatin-induced Nephrotoxic Rats

The level of MDA in the kidney homogenates of group I, II, III, and IV animals is shown in (**Table 1, Fig 1&Fig 2**). Lipid peroxidation levels were significantly increased in the cisplatin-treated group II compared to the normal control group I. Treatment with *Agaricus bisporus* (Group IV) significantly (p 0.05) decreased the level of kidney tissue lipid peroxidation compared to the level of cisplatin-treated group II. The silymarin-treated group III also significantly (p 0.05) decreased the kidney tissue lipid peroxidation level compared to the cisplatin-treated group II.

3.3. Effect of *Agaricus bisporus* on Histopathological Examination in Cisplatin-Induced Nephrotoxic Rats

Group I:

Sections of a normal control rat kidney show that the glomeruli **(G)** are abundant in the cortex and morphologically normal. The tubules **(T)** are normal and lined by cells with abundant bright eosinophilic cytoplasm **(arrows).** The blood vessels and the interstitium are also normal (**Fig 3 A**).

Group II:

Sections of a cisplatin-treated rat kidney show that the glomeruli **(G)** are abundant in the cortex and morphologically abnormal. The tubules **(T)** show pathological changes characterized by sloughing off the lining epithelium (**arrows).** The blood vessels and the interstitium are also normal (**Fig 3 B**).

Group III:

Sections of silymarin-treated rat kidney show that the glomeruli (G) are abundant and morphologically normal in the cortex. While some of the tubules **(T)** show pathological changes characterized by sloughing off of the lining epithelium (**down arrows),** others show cells with abundant bright eosinophilic cytoplasm **(right arrows).** The blood vessels and the interstitium are also normal. Thus, there appears to be a partial reversal of the tubular pathological changes induced by cisplatin (**Fig 3 C**).

Group IV:

Sections of a rat kidney treated with *Agaricus bisporus* show that the glomeruli (G) are abundant in the cortex and morphologically normal. The tubules **(T)** show lining epithelium **(arrows)** whose cells show normal, abundant, eosinophilic cytoplasm**.** The blood vessels, the interstitium, and the limbs are both normal. Thus, *Agaricus bisporus* completely reversed the tubular pathological changes induced by cisplatin (**Fig 3 D**).

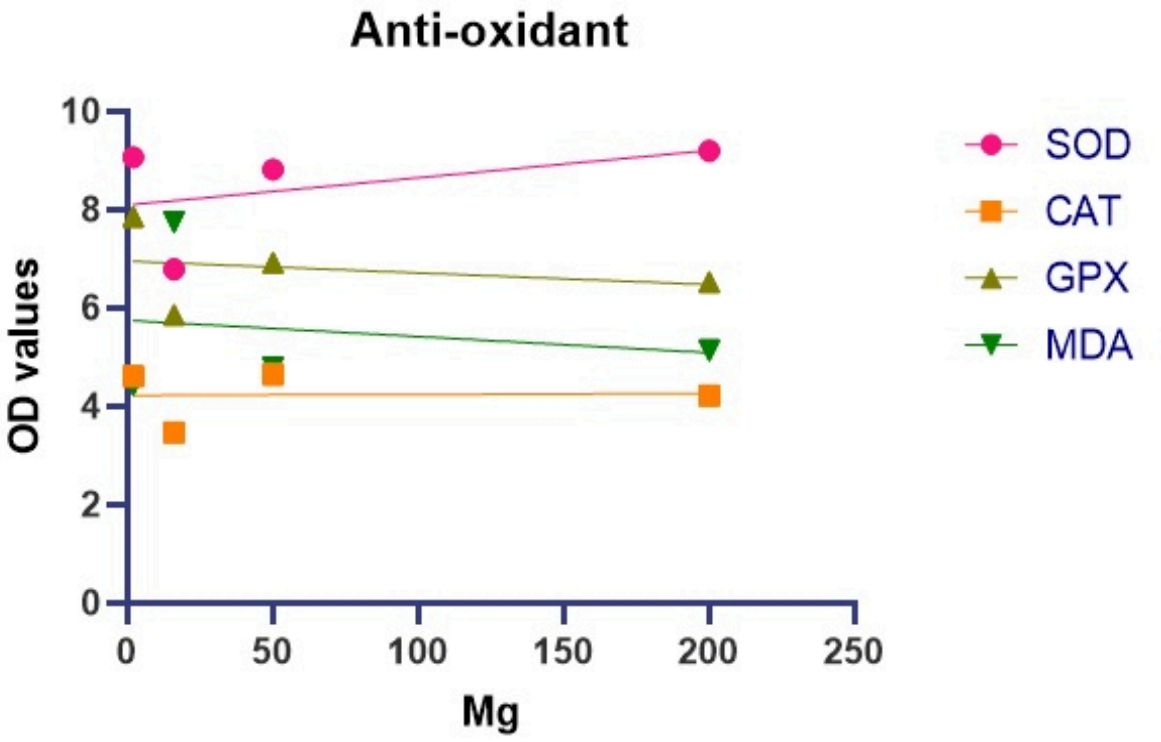

Figure 1. Observed values for the different concentration

Table 1. Effect of ***Agaricus bisporus*** on Renal Enzymatic Antioxidants and MDA in Cisplatin-induced Nephrotoxic Rats.

Groups	Treatments	SOD	CAT	GPX	MDA
I	Normal control (Normal saline 2ml/kg b.w) for 15 days	9.07±0.63	4.61±0.32	7.86±0.55	4.44±0.31.
II	Cisplatin (16mg/kg b.w i.p) was administered in a single dose.	6.79±0.47	3.47±0.24	5.86±0.41	7.75±0.54
III	Treated with silymarin (50mg/kg b.w) in cisplatin-induced rats for 15 days.	8.82±0.61	4.65±0.32	6.93±0.48	4.79±0.33
IV	In cisplatin-induced rats, *Agaricus bisporus* (200mg/kg b.w) was given for 15 days.	9.20±0.64	4.22±0.29	6.53±0.45	5.14±0.35

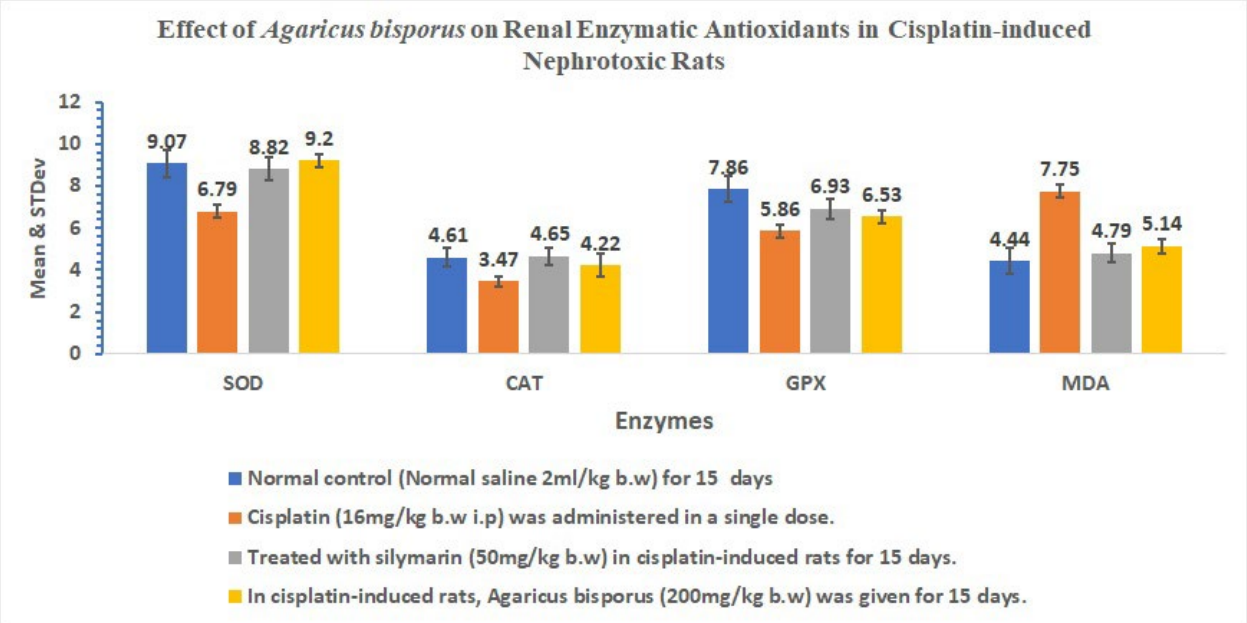

Figure 2. Effect of *Agaricus bisporus* on Renal Enzymatic Antioxidants in Cisplatin-induced Nephrotoxic Rats - Malondialdehyde (MDA) Levels in Cisplatin-induced Nephrotoxic Rats; Superoxide dismutase (SOD) level in cisplatin-induced nephrotoxic rats**;** Catalase (CAT) level in cisplatin-induced nephrotoxic rats**;** Glutathione peroxidase (GPx) in cisplatin-induced nephrotoxic rats.
*P 0.05 compared to the normal control group and **P 0.05 compared to the cisplatin-treated group were statistically significant

All values were expressed as mean SD (n=6). Statistically significant, *P 0.05 compared to the normal control group (I) and **P 0.05 compared to the cisplatin-treated group (II). SOD (Superoxide dismutase) = units/min/mg protein, CAT (Catalase) = moles/min/mg protein, GPx (Glutathione peroxidase) = moles/min/mg protein, MDA (Malondialdehyde) = moles/min/mg protein moles per minute/mg protein.

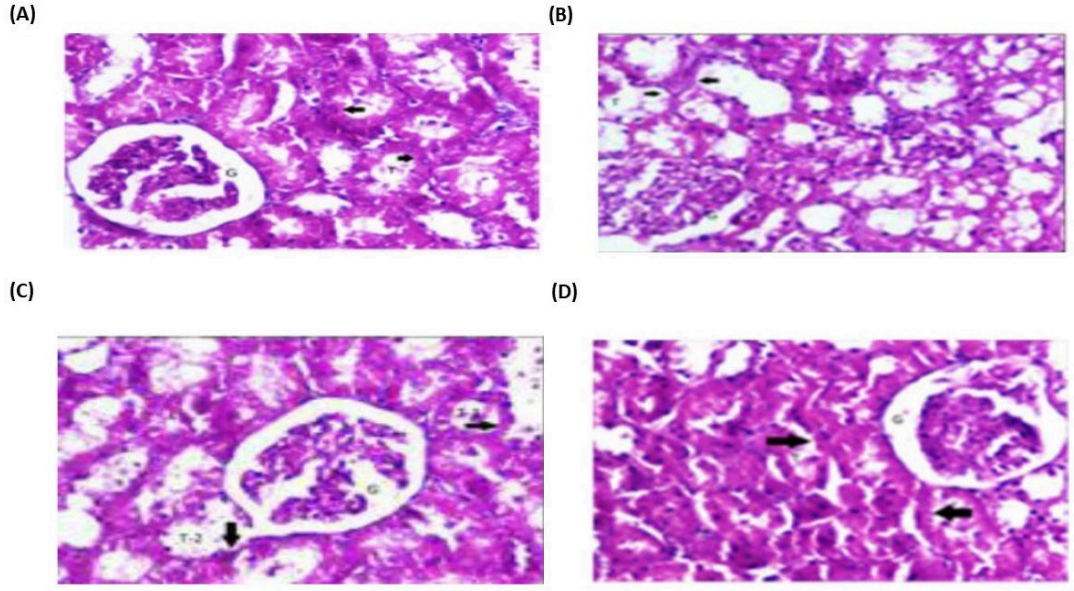

Figure 3. Effect of *Agaricus bisporus* on Histopathological Examination in Cisplatin-induced Nephrotoxic Rats. (A) Section of normal rat kidney (Group I) shows normal organization of tubular epithelial cells (**T**) and glomeruli **(G)**; (B) Section of cisplatin-treated rat kidney (Group II) demonstrating severe necrosis of tubular epithelial cells (T) and glomeruli (G); **(C)**A section of a rat kidney treated with Silymarin (Group III) demonstrates regenerative changes in tubular epithelial cells (T) and glomeruli (G); (D)A section of rat kidney treated with *Agaricus bisporus* (Group IV) shows complete regenerative changes in tubular epithelial cells (**T**) and glomeruli (**G**)**.**

4. DISCUSSION

Furthermore, our results also revealed that cisplatin caused a significant decline in the activity of the antioxidant enzymes (CAT and SOD), significant depletion of GSH, and enhancement of MDA production in the renal tissue. These findings are consistent with those of Ali *et al.* [15], Fouad *et al.* [16], and Yadav *et al.* [17]. Cisplatin nephrotoxicity occurs as a result of oxidative stress and increased generation of superoxide anion, hydrogen peroxide, and hydroxyl radicals due to the increased activity of NADPH oxidase, xanthine oxidase, and adenosine deaminase [18]. These free radicals damage the lipid components of the cell membrane *via* peroxidation and denaturation, which leads to enzymatic inactivation [19]. Moreover, Berne date extract significantly mitigated the lipid peroxidation in the rat kidney induced by cisplatin, as manifested by decreased MDA content accompanied by increased GSH content and enhanced enzymatic activities of CAT and SOD. Our data are in agreement with El Arem *et al.* [20], who found that date fruit aqueous extract has a nephroprotective role against trichloroacetic acid-induced oxidative stress in rats, as manifested by a reduction in MDA content and enhancement of antioxidant enzyme activity. Similar results were obtained by Saafi-Been Salah et al. [21], who revealed the antioxidant effect of date palm fruit extract on oxidative stress and nephrotoxicity induced by dimethoate in rats.

In the present study, we attempted to investigate the effect of a methanolic extract of *Agaricus bisporus* on cisplatin-induced nephrotoxicity in rats. Due to the accumulation of cisplatin in proximal and distal nephrons, reactive oxygen species (ROS) were elevated. Free radicals like superoxide anion, hydrogen peroxide, and hydroxyl radical increased, decreasing the antioxidant enzyme production in cisplatin-induced rats. [22] Superoxide is the primary ROS produced in the course of oxygen metabolism, which is a highly reactive, cytotoxic ROS. Superoxide is converted to a far less reactive product, hydrogen peroxide, by a family of metalloenzymes known as SOD, which constitutes a front line of defense against ROS-mediated injury. [23] Oxidative stress is the major cause of the development of chronic renal failure. The cisplatin-induced animals show a decrease in tissue SOD levels, which may be due to the depletion of copper and zinc in the kidney, which are essential for the activity of enzymes. In the present study, the treatment with *Agaricus bisporus* and silymarin significantly increased SOD levels in kidney tissue compared to the cisplatin-induced group. Catalase (CAT) is a common enzyme that catalyzes the decomposition of hydrogen peroxide into water and oxygen. [24] CAT is highly effective in inhibiting various ROS-mediated injuries and could protect the kidney from cisplatin-induced nephrotoxicity. [25] The cisplatin-induced animals show a decrease in tissue CAT level compared to

the cisplatin-induced group. However, the treatment with *Agaricus bisporus* and silymarin significantly increased the kidney tissue CAT level, which shows its antioxidant activity during nephrotoxicity. Glutathione peroxidase (GPx) is humans' most important antioxidant enzyme and is highly expressed in the kidney. It is involved in scavenging and inactivating hydrogen and lipid peroxides, protecting the body against oxidative stress, and removing peroxides and peroxynitrite that can cause renal damage. [26].The treatment with *Agaricus bisporus* and silymarin significantly increased GPx levels in kidney tissue, which reveals their antioxidant efficacy against oxidative stress induced by cisplatin.

Lipid peroxidation (LPO) is generated naturally in small amounts in the body, mainly by the effect of several ROS, i.e., hydroxyl radicals and hydrogen peroxide. An increase in the concentration of end products of LPO is evidence of the involvement of free radicals in human disease. [27] Oxidative stress can damage proteins and DNA that are more significant targets of injury than lipids and LPO, which often occur late in the injury process [28]. It is reported that cisplatin-mediated renal tissue injury increases kidney tissue LPO levels due to the release of free radicals, which is directly interrelated with an increase in LPO levels during nephrotoxic conditions. The treatment with *Agaricus bisporus* significantly reduced the kidney LPO level. It counteracted the formation of free radicals induced by cisplatin-mediated nephrotoxicity, which displayed its protective role in preventing renal damage. The standard drug, silymarin, also exhibited a similar effect during nephrotoxicity. In this study, cisplatin-induced animals showed an increased LPO level in the kidney, comparable to the measurement of previous reports. [29]

From this study, our results also clearly showed that marked dilation of proximal convoluted tubules with sloughing off of almost the entire epithelium due to desquamation of tubular epithelium was evident. Cellular debris in the tubular lumen and increased tissue in the interstitium indicate cisplatin-induced renal necrosis. [30] The treatment with *Agaricus bisporus* protects the renal tubular necrosis and glomerulus from the effect of cisplatin-treated group animals.

5. CONCLUSION

The present study revealed that the methanolic extract of *Agaricus bisporus* possessed potential antioxidant activity in an experimental model system. The results indicate that Berne date extract protects the kidney tissue against cisplatin-induced nephrotoxicity in rats through antioxidant, anti-inflammatory, and antiapoptotic effects. Therefore, Berne date extract is a potential candidate for preventing renal injury, a major and dose-limiting problem during a cisplatin course. The crude extract may have antioxidant properties due to phenols, flavonoids like quercetin, and other phytochemical molecules. Further investigations into the mechanism of action of *Agaricus bisporus* are required and may have a considerable impact on future clinical treatments of patients with renal failure.

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ETHICAL APPROVAL

Nil

COMPETING INTEREST

The authors declare no conflict of interest.

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