IJPSR (2020), Volume 11, Issue 6 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 July 2019; received in revised form, 13 April 2020; accepted, 15 April 2020; published 01 June 2020

CULTURED MYCELIA OF PADDY STRAW MUSHROOM, *VOLVARIELLA VOLVACEA* (BULL: FR) SINGER PROTECTS WISTAR RATS FORM ACETAMINOPHEN-INDUCED HEPATOTOXICITY

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Keywords:

Antioxidant, Hepatoprotection, Paracetamol, SGOT, SGPT, ALP

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ABSTRACT: Even though numerous herbal preparations have been recommended in alternative systems of medicine against hepatic disorders, many of them cause severe toxicity upon prolonged use. *Volvariella volvacea* (Bull.: Fr.) Singer is a highly nutritious mushroom that can be incorporated into the regular diet without the fear of side effects. The protective effect of the aqueous ethanol extract of *V. volvacea* mycelia was evaluated against acetaminophen (APAP) induced hepatic damage in Wistar rats. A single dose of APAP (3 g/kg, p.o.) was used for inducing hepatic damage. The extract was administrated orally at doses of 250 and 500 mg/kg, once daily for 7 days. Treatment with APAP (3 g/kg) increased the activities of liver function enzymes serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase (ALP). APAP also reduced the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) and enhanced lipid peroxidation in liver tissue. Administration of *V. volvacea* extract (500 mg/kg, p.o.) decreased the activities of SGPT, SGOT, and ALP. It also enhanced the level of SOD, CAT as well as GPx and decreased the tissue MDA level. The results of the study revealed the protective effect of *V. volvacea* against APAP-induced hepatotoxicity. The activity is mediated through its antioxidant potential by scavenging the free radicals and also by maintaining the levels of hepatic antioxidant systems.

INTRODUCTION: Liver disease is a major concern throughout the world. Several drugs, chemicals, and other agents have been implicated in the etiology of liver diseases. Among these, the mechanism of paracetamol or acetaminophen (APAP) has been well established. APAP is a widely used analgesic and antipyretic drug that exert hepatotoxic effects in a dose-dependent manner [1, 2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(6).2948-54

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(6).2948-54

APAP is converted to a toxic reactive intermediate called N-acetyl-p-benzoquinone imine (NAPQI) by the action of cytochrome P450 system mainly located in the liver [3]. The precise role of oxidative stress in APAP-induced liver injury is not completely understood. It has been shown that binding of NAPQI to glutathione sulfhydryl groups results in the reduction of hepatic anti-oxidative capacity [4].

Also, it has been postulated that NAPQI can lead to direct oxidative damage to many cell components [5], which eventually leads to oxidative stress and liver toxicity. Antioxidants play a significant role in protecting living organisms from the toxic effect of various chemicals by preventing free radical formation [3].

The free radical-mediated hepatotoxicity can be effectively managed by the administration of agents that possess antioxidant, free radical scavenging, and anti-lipid peroxidation activities [6]. Search for completely effective and safe alternative drugs for the treatment of liver diseases is crucial because many of synthetic antioxidants currently in use for the purpose have been reported to have various side effects [7]. Macro-fungi, especially mushrooms, have been traditionally used in China and Japan to treat a variety of diseases for many years. Mushroom mycelium and its extracts have been studied widely for their vast pharmacological importance [8, 9].

Similar studies from our laboratory also showed the potent pharmacological effects, including the hepatoprotective activity of many mycelia, extracts [10, 11]. *Volvariella volvacea* (Bull.: Fr.) Singer (Agaricomycetideae) (paddy straw mushroom) is the most preferred edible mushroom in South Asian countries because of its excellent taste, high protein, amino acid, vitamins, and mineral content [12]. Earlier studies have illustrated the significant antioxidant activity and DNA protective effects of *V. volvacea* [13, 14].

A potent immunostimulant polysaccharide has been isolated from *V. volvacea* [15]. Recent studies conducted in our laboratory have revealed the potent antioxidant and antitumor activities of the aqueous ethanol extract of *V. volvacea* mycelia [16]. However, there are no reports on the hepatoprotective effect of this mushroom or its mycelia to the date. In this present study, we evaluated the hepatoprotective effects of the aqueous ethanol extract of *V. volvacea* mycelia against APAP-induced liver damage.

MATERIALS AND METHODS:

Animals: Female Wistar rats weighing 200 ± 20 g from Small Animal Breeding Centre, Kerala Agricultural University, Mannuthy, Thrissur, Kerala, India were used in the experiment. The animals were maintained under standardized environmental conditions (22-28 °C, 60-70% relative humidity, 12 h dark/light cycle) with free access to standard food (Sai Durga Feeds and Foods, Bangalore, India) and water ad libitum. The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govt. of India and by the approval of the Institutional Animal Ethics Committee (149/99/ CPCSEA dated 23-10-2009).

Production of the Mycelium and Preparation of Extract: Culture of *V. volvacea* (MTCC-957), obtained from the Microbial Type Culture Collection, Institute of Microbiology, Chandigarh, India, was grown in a medium comprising 10.0 g glucose, 3.0 g peptone 1.0 g dipotassium phosphate (K_2HPO_4), 0.25 g magnesium sulfate ($MgSO_4$ $7H_2O$), and yeast extract 1 g/L at 25 °C - 27 °C on an orbital shaker. After ten days of submerged growth, the cultures were filtered; the mycelium was separated and washed thoroughly with distilled water. Aqueous ethanol extract of cultured mycelium was prepared as described earlier [16].

Evaluation of Hepatoprotective Activity:

Experimental Design: Hepatoprotective activity against the APAP-induced chronic toxicity was determined by the method of Ajith *et al.*, [17,] with some modifications. The animals were divided into five groups of six animals each. Group I animals treated with a single dose of APAP (3 g/kg body weight) were served as control. Group II animals treated with distilled water were considered as normal. Group III and IV animals were treated orally with 250 and 500 mg/kg body weight of aqueous ethanol extract of *V. volvacea*, respectively, and group V animals were treated with 100 mg/kg body weight of silymarin, a standard drug. The silymarin and *V. volvacea* extract were suspended in distilled water and were administrated orally once daily for seven days. After 24 h of the final dose of drug administration, a single dose of APAP (3 g/kg body weight) was given orally to all the groups except the group II. Animals were sacrificed exactly after 12 h of APAP administration. Blood was collected directly from the heart, and serum was separated. Livers were excised, washed thoroughly in ice-cold saline to remove the blood.

Biochemical Analysis: Activities of serum glutamic oxaloacetate transaminase (SGOT), serum glutamate pyruvate dehydrogenase (SGPT) and alkaline phosphatase (ALP) were estimated by a kinetic method using the kit of Agappe Diagnostic Ltd., India with the aid of an SL 164 - UV/VIS double beam spectrophotometer (Elico India Ltd,

Hyderabad, India). The activities of transaminases were determined as the change in absorbance/min at 340 nm. Serum ALP activity was determined from the rate of release of para nitrophenol at 405 nm.

Determination of Antioxidant Status in the Liver: A 10% liver homogenate was prepared in phosphate buffer (0.05 M, pH 7) using a Polytron homogenizer. Homogenate was centrifuged, and the supernatant was used for the determination of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activities and also for the measurement of glutathione (GSH) and lipid peroxidation levels.

SOD activity was determined based on the ability of the tissue homogenate to scavenge the superoxide anion generated from the photo-illumination of riboflavin [18]. Tissue CAT activity was determined by the rate of decomposition of hydrogen peroxide [19]. The activity of GPx was determined by measuring the decrease in GSH content after incubating the sample in the presence of hydrogen peroxide and sodium azide [20]. Reduced GSH was determined according to the method of Moron *et al.,* [21] based on the formation of a yellow-colored complex with Ellman's reagent.

The level of lipid peroxidation was measured as thiobarbituric acid reactive substance (TBARS) and is expressed as equivalents of malondialdehyde (MDA), using 1', 1', 3', 3'-tetramethoxypropane (TMP) as standard [22]. Protein content in the tissue was determined using Folin's phenol reagent using bovine serum albumin (BSA) as standard [23].

Histopathological Examination: Tissue slices from the livers of treated animals were fixed immediately in 10% neutral formalin for 24 h, dehydrated in graded (50-100%) alcohol, and embedded in paraffin, cut into 4-5 µm thick sections and stained with hematoxylin-eosin. The sections were evaluated for the pathological symptoms of hepatotoxicity, such as necrosis, fatty infiltration, fibrosis, lymphocyte infiltration, *etc.*

Statistical Analysis: All experimental data were expressed as mean ± SEM. The statistical analysis was done by one-way analysis of variance (ANOVA) followed by Dunnett test using InStat 3 software.

RESULTS:

Effect of the Extract on the Activities of SGPT, SGOT, and ALP: The activities of transaminases such as SGPT and SGOT and ALP are given in **Table 1**. A single dose of acetaminophen (3 g/kg) significantly elevated the SGPT, SGOT, and ALP activities when compared to the normal animals. There was approximately 1.99, 1.95, and 3.08 fold increase in SGPT, SGOT, and ALP, respectively, for APAP-treated animals compared to the normal animals. Treatment of *V. volvacea* mycelia extracts for seven days before APAP administration significantly prevented the elevation of trans-aminases and ALP activities. The activities of SGPT, SGOT, and ALP were found to be decreased (1.77, 1.60, and 1.79-fold respectively) in 250 mg/kg treated group with respect to the APAP control group. A similar decline in the activities of SGPT, SGOT, and ALP (2.42, 2.05, and 2.35-fold, respectively) was also observed in 500 mg/kg treated group. The treatment with positive standard (silymarin, 100 mg/kg) significantly prevented the elevation of transaminases and ALP activities. There was approximately 2.31, 1.22, and 1.35 fold reduction in the activities of SGPT and SGOT, and ALP, respectively, in the silymarin treated group. The fold increase values were calculated using the maximum values (mean ± SEM value) for the APAP control group and minimum values (mean ± SEM value) for the normal and treated groups.

TABLE 1: EFFECT OF *VOLVARIELLA VOLVACEA* MYCELIA EXTRACT ON HEPATIC TRANSAMINASES AND ALKALINE PHOSPHATASE IN RATS ADMINISTERED WITH APAP

Groups & Treatments	SGPT (IU/l)	SGOT (IU/l)	ALP (IU/l)
Control (APAP 3 g/kg)	91.50 ± 17.79	166.26 ± 5.04	526.40 ± 09.51
Normal	31.25 ± 05.78**	77.50 ± 5.10**	153.23 ± 14.49**
V. volvacea (250 mg/kg)	39.42 ± 02.11**	88.68 ± 12.33**	269.92 ± 18.54**
V. volvacea (500 mg/kg)	26.15 ± 04.31**	75.20 ± 3.43**	196.14 ± 25.94**
Silymarin (100 mg/kg)	28.34 ± 03.61**	120.62 ± 11.68**	361.23 ± 23.03**

Values are the mean ± SEM; n = 6. **p < 0.01 compared to control (Dunnett test)

Effect of the Extract on the Innate Antioxidant Enzymes: The activities of hepatic innate antioxidant enzymes such as SOD, CAT, and GPx

were lowered significantly in the APAP control group with respect to the normal group **Table 2**. There was approximately 1.39, 1.51, and 1.64 fold decrease for SOD, CAT, and GPx, respectively, in the APAP control group than that of the normal group. The treatment with the mycelia extracts significantly protected the hepatic antioxidant status. There was approximately 1.11, 1.25, and 1.45 fold increase in the activities of SOD, CAT, and GPx, respectively, for 250 mg/kg extract-treated group. Similarly, there were 1.63, 1.48, and 1.94 fold increase in the activities of SOD, CAT, and GPx, respectively, for 500 mg/kg extract-treated group with respect to the control group. Silymarin administration significantly protected the hepatic antioxidant status against the APAP-induced hepatic damage. There were 1.27, 1.22, and 1.23 fold increase in the activities of SOD, CAT, and GPx, respectively, in the silymarin treated group compared to that of the control group.

TABLE 2: EFFECT OF *VOLVARIELLA VOLVACEA* MYCELIA EXTRACT ON THE ACTIVITIES OF HEPATIC ANTIOXIDANT ENZYMES IN RATS ADMINISTERED WITH APAP

Groups & Treatments	SOD (U/mg protein)	CAT (U/mg protein)	GPx (U/mg protein)
Control (APAP 3 g/kg)	08.20 ± 0.52	36.32 ± 7.81	11.70 ± 0.53
Normal	13.63 ± 1.52**	75.49 ± 8.64**	22.70 ± 2.69**
V. volvacea (250 mg/kg)	10.64 ± 0.94^{NS}	63.02 ± 8.42 ^{NS}	20.10 ± 2.41*
V. volvacea (500 mg/kg)	15.54 ± 1.34**	70.94 ± 5.50**	26.70 ± 2.94**
Silymarin (100 mg/kg)	11.25 ± 0.20 ^{NS}	59.21 ± 5.20 ^{NS}	16.20 ± 1.18 ^{NS}

Values are the mean ± SEM; n = 6. **p < 0.01, NSp> 0.05 compared to control (Dunnett test)

Effect of the Extract on Level of GSH: APAP significantly decreased the level of GSH **Fig. 1**. There was a 1.63 fold decrease in the level of GSH for the APAP-treated group with respect to the normal group. But the treatment with the extract significantly enhanced the level of GSH. There was approximately 1.51 and 1.77 fold increase in the level of GSH for 250 and500 mg/kg extract-treated groups, respectively.

Similarly, silymarin (100 mg/kg) significantly enhanced the level of GSH than that of control. There was an approximately 1.14 fold increase in the level of GSH in the silymarin (100 mg/kg) treated group with respect to the control group.

Effect of the Extract on Lipid Peroxidation: Treatment with APAP treatment significantly elevated (91.38 fold) the hepatic lipid peroxidation levels compared to the normal group **Fig. 2**. However, the administration of *V. volvacea* extract significantly decreased the lipid peroxidation level.

There were approximately 1.39, and 1.78 fold decrease in 250 and500 mg/kg extract treated group with respect to APAP control. Similarly, silymarin (100 mg/kg) significantly decreased the lipid per-oxidation in connection with APAP control. There was an approximately 1.24 fold decrease in the lipid peroxidation level in the silymarin treated group with regards to APAP control.

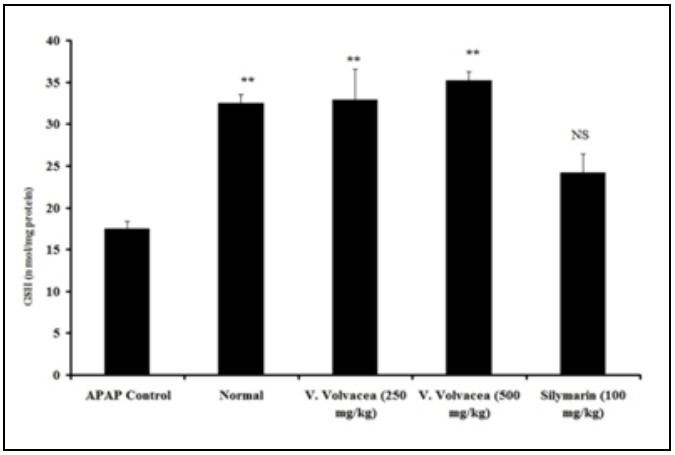

FIG. 1: EFFECT OF *V. VOLVACEA* MYCELIA EXTRACT ON THE LEVEL OF HEPATIC GSH IN RATS ADMINISTRATED WITH APAP APAP – acetaminophen, Values are mean ± SEM; n = 6., **P<0.01, NSP>0.05 with respect to control (Dunnett test)

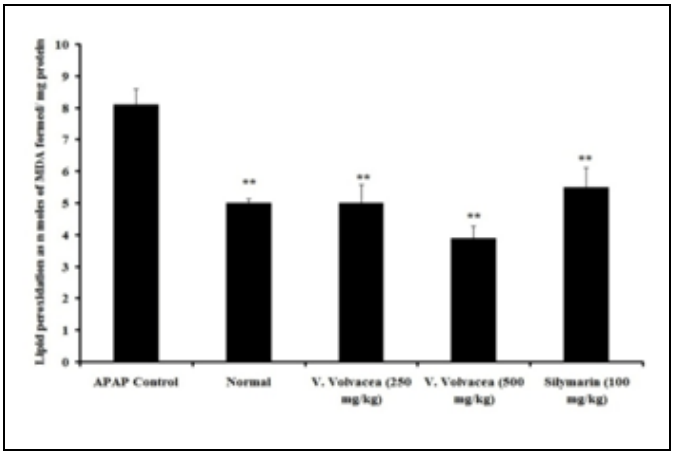

FIG. 2: EFFECT OF *V. VOLVACEA* MYCELIA EXTRACT ON THE LEVEL OF HEPATIC LIPID PEROXIDATION IN RATS ADMINISTRATED WITH APAP APAP – acetaminophen, Values are mean ± SEM; n = 6., **P<0.01 with respect to control (Dunnett test)

Histopathological Observation: Histopathological examination of livers challenged with APAP showed centrilobular necrosis, ballooning degeneration, inflammatory and fatty infiltration of lymphocytes. Whereas the liver sections of rats treated with the extract showed well-preserved architecture **Fig. 3**.

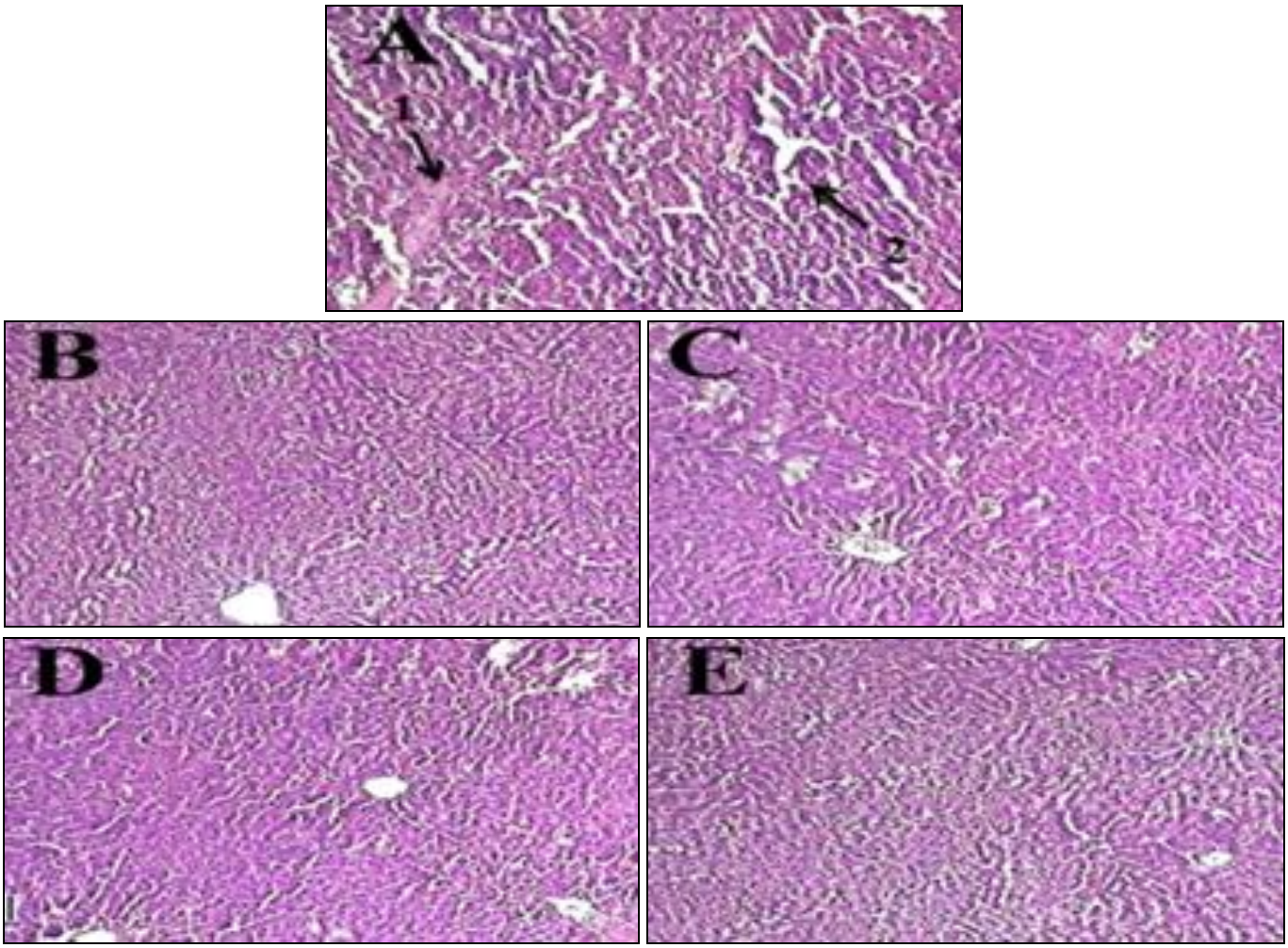

FIG. 3: HISTOPATHOLOGICAL ANALYSIS OF LIVER TISSUES FROM RATS TREATED WITH MYCELIA EXTRACT OF *V. VOLVACEA* AND APAP (A) Liver from APAP-treated control group showing (1) ballooning degeneration and (2) fatty infiltration (B) Liver from normal group (C) Liver from *V. volvacea* (250 mg/kg b.wt) and APAP-treated group (D) Liver from *V. volvacea* (500 mg/kg b.wt) and APAP-treated group(E)) Liver from Silymarin (100 mg/kg b.wt) and APAP-treated group.

DISCUSSION: Liver injuries induced by APAP is a commonly used model for the screening of hepatoprotective drugs, and the extent of hepatic damage is assessed by the increased levels of cytoplasmic enzymes (SGPT and SGOT) in circulation [24]. APAP is reported to increase the SGPT, SGOT, and ALP activities and exacerbate oxidative injury [17]. The rise in activities of SGPT, SGOT, and ALP has been attributed to the damage of the structural integrity of the liver because these enzymes are cytoplasmic in location and are released into circulation after cellular damage [24]. The results of this study revealed that the *V. volvacea* mycelia extract (250 and 500 mg/kg) have potent preventive activity against APAP-induced hepatotoxicity. The amelioration of liver toxicity by the extract is evident from its significant effect on the SGOT, SGPT, and ALP activities in **Table 1**. *V. volvacea* extract showed a dose-dependent effect in reducing the hepatotoxicity. The higher dose of the extract (500 mg/kg) exhibited more activity than the lower dose (250 mg/kg).

These findings are also confirmed by histopathological observations of liver tissue. The positive standard used in the current study, silymarin, is a well-established hepatoprotective drug [25].

The ability of silymarin in preventing drug-induced hepatotoxicity is associated with its ability to act as a radical scavenger, thereby protecting membrane permeability [25, 26]. Tissues have evolved an antioxidant defense system, including enzymatic and non-enzymatic antioxidants to prevent the oxidative damage. This antioxidant system is significantly inactivated by lipid peroxides or free radicals generated during APAP-induced hepatic toxicity [17]. The results of the present study indicated that SOD, CAT, and GPx activities were significantly decreased in the liver in response to APAP treatment than normal rats, implying increased oxidative damage to the liver. On the contrary, SOD, CAT, and GPx activities were significantly elevated by the administration of *V. volvacea* extract to APAP intoxicated rats, suggesting its ability to restore/maintain the activity of hepatic enzymes. APAP is a powerful inducer of cytochrome P-450 and produces a highly reactive quinone-imine, which combines with sulphydryl groups of proteins and cause rapid depletion to intracellular GSH [27,] and this depletion of GSH is a critical determinant of cell survival and death in oxidative stress conditions [28]. Therefore, maintaining the GSH level is very critical to overcoming the toxic effect of APAP. In the present study, the hepatic content of GSH was significantly decreased in APAP intoxicated rats compared with the normal group of rats. However, treatment with *V. volvacea* extract significantly elevated the GSH level suggesting that *V. volvacea* could protect the APAP-induced depletion of hepatic GSH.

The exact mechanism by which the extract exhibits hepatoprotective activity is not clear. But there are many reports showing that lipid peroxidation by free radical derivatives of APAP is one of the principal mechanisms of APAP-induced liver damage leading to disturbance of cell membrane integrity [29, 30]. In the present study, APAP-induced toxicity causes an increase in the levels of lipid peroxidation in liver tissue. However, *V. volvacea* extract administration caused a significant reduction in lipid peroxidation levels as compared to the APAP-induced group. Earlier studies conducted in our laboratory have also revealed the potent antioxidant potential of V. volvacea [16]. This free radical scavenging and antioxidant power of the *V. volvacea* mycelia extract in terms of prevention of lipid peroxidation and boosting of antioxidant defense mechanisms could be the possible reason behind its exhibited hepato-protective effect. *V. volvacea* is well known for its high content of proteins, amino acids, vitamins, and minerals. Our previous study disclosed the presence of carbohydrates, polyphenols, proteins, and saponins in *V. volvacea* mycelium extract [16]. The effect observed in the present study might be due to the cumulative effects of these constituents. However, further detailed studies are needed to elucidate the function of its individual components.

CONCLUSION: In summary, the hepatotoxicity induced by APAP increased the levels of SGPT, SGOT, and ALP and decreased the hepatic antioxidant status in rats. However, the aqueous ethanol extract of *V. volvacea* mycelia significantly protected the animals from APAP-induced acute hepatotoxicity by restoring the antioxidant status and also by reducing the levels of SGPT, SGOT, and ALP. The protective effect is mediated by the significant antioxidant activity of the extract, and further studies are needed to confirm the clinical applications of the extract in humans.

ACKNOWLEDGEMENT: The authors gratefully acknowledge Dr. K. A. Rony and Dr. T. A. Ajith for their valuable suggestions and kind help during the study.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest in publishing the manuscript. All the authors are associated and contributed to the work, and there are no competing financial interests.

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How to cite this article:
Mathew J, Smina TP, Sudheesh NP and Janardhanan KK: Cultured mycelia of paddy straw mushroom, *Volvariella volvacea* (bull: fr) singer protects Wistar rats form acetaminophen-induced hepatotoxicity. Int J Pharm Sci & Res 2020; 11(6): 2948-54. doi: 10.13040/IJPSR.0975-8232.11(6).2948-54.