Research Article

Effects of subchronic exposure of PSP *Ganoderma lucidum* on renal function and histopathology feature in *Rattus novergicus* Wistar strain

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Abstract

Background: *Ganoderma lucidum*, commonly referred to as Lingzhi in China, is a fungus that has been widely used through the centuries for the general promotion of health and longevity in Asian countries. **Aims and Objective:** To determine the effects of subchronic exposure of PSP *G. lucidum* on renal function and renal histopathology feature in *Rattus novergicus* Wistar strain. **Materials and Methods:** A total of 80 male and female Wistar rats, aged 2–3 months with a body weight of 200–300 g, were divided into four treatment groups: dose group 0 (control group), group PSP *G. lucidum* dose of 300, 600, and 1200 mg/kg for 90 days. Parameters measured were urea and creatinine levels and renal histopathology feature. **Result:** From the research, the highest urea levels were found in the group in which female Wistar rats were treated with PSP dose of 300 mg/kg/day with an average concentration of urea of 33.2 mg/dL, whereas creatinine levels were found to be equally high on treatment with PSP dose of 1200, 600, and 300 mg/kg/day with an average concentration of urea of 0.3 mg/dL. On histopathological examination, no morphological abnormalities were found. The results of one-way analysis of variance test showed no significant difference at all PSP *G. lucidum* doses. **Conclusion:** It is concluded that giving PSP *G. lucidum* in three variant doses does not cause dysfunction and histological damage to the renal function.

KEY WORDS: PSP *Ganoderma lucidum*; Subchronic Exposure; Urea; Creatinine; Renal Organ Histopathology

Introduction

In recent years, public interest in natural and alternative therapies has increased greatly in many countries, with the expanding use of medicinal plants and herbal medicines. Medicinal plants have been used for centuries as remedies for human diseases because they contain components of therapeutic value. The use of complementary traditional medicine that includes herbal medicines in the treatment of various diseases has expanded rapidly in both developed and developing countries, attributable to affordability, accessibility, and efficacy.[1]

Traditional medicine that is well known nowadays is derived from mushrooms. Many people have used medicinal mushrooms as a food supplement for health maintenance and as a therapeutic drug for medical purposes. Polysaccharides from mushrooms have shown a wide range of beneficial effects,

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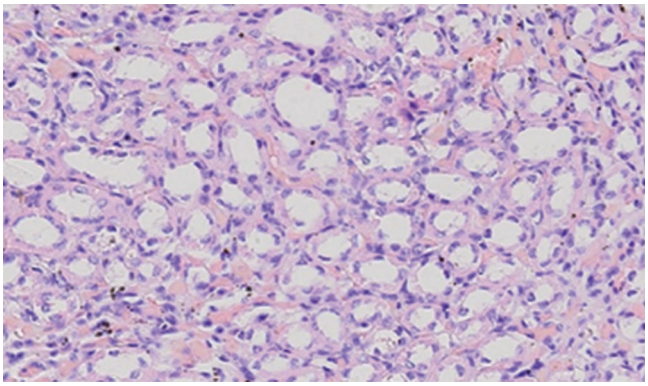

Figure 1: Histopathology picture of control male group at 600 × magnification using HE staining

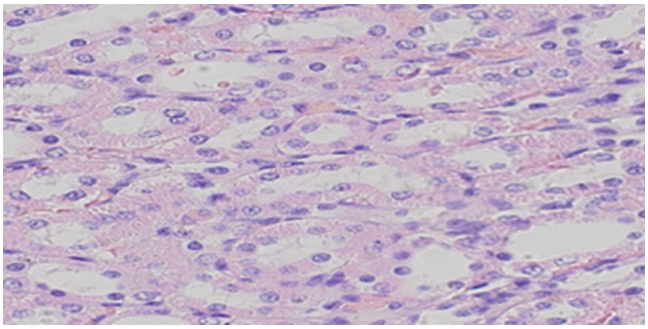

Figure 2: Histopathology picture of male group 1 dose 300 mg/kg PSP at 600 × magnification using HE staining

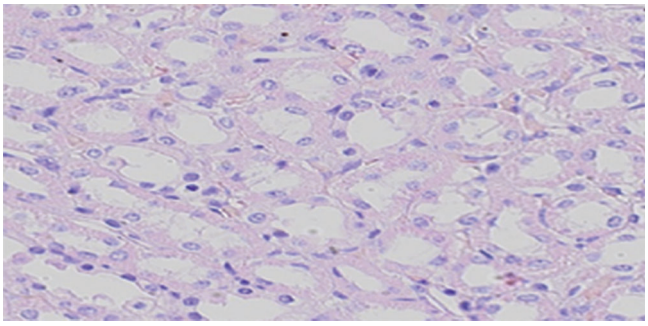

Figure 3: Histopathology picture of male group 2 dose 600 mg/kg PSP at 600 × magnification using HE staining

being the most important modulation of the immune system.[2] Several polysaccharides from mushrooms have been isolated and characterized. One example is *Ganoderma lucidum*, a white rot fungus, which has been widely used for the prevention and treatment of various human ailments in Asian countries.[3] Many reports about the pharmacological effects of extracts and metabolites from medicinal mushrooms, including *G. lucidum*, have attracted considerable global interest, particularly in the pharmaceutical industry.[4]

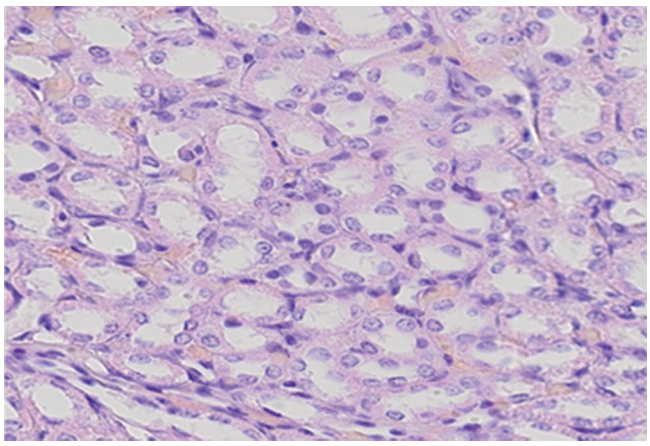

Figure 4: Histopathology picture of male group 3 dose 1200 mg/kg PSP at 600 × magnification using HE staining

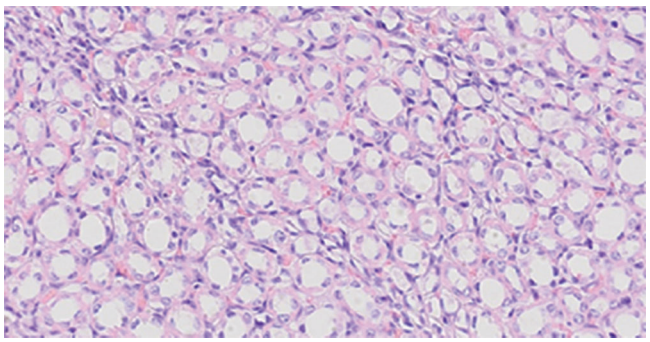

Figure 5: Histopathology picture of control female group at 600 × magnification using HE staining

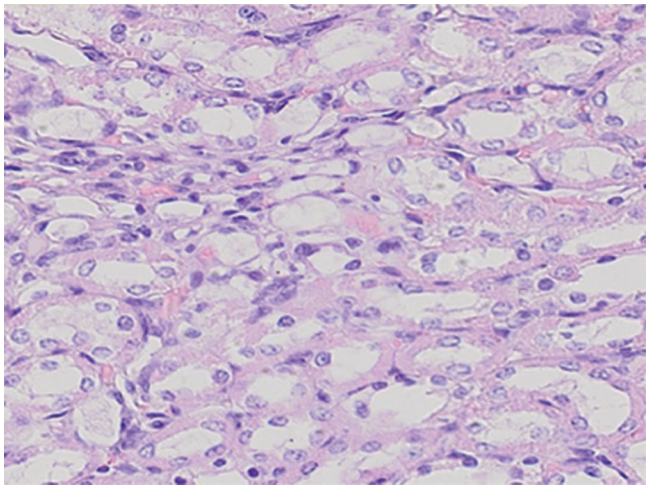

Figure 6: Histopathology picture of female group 1 dose 300 mg/kg PSP at 600 × magnification using HE staining

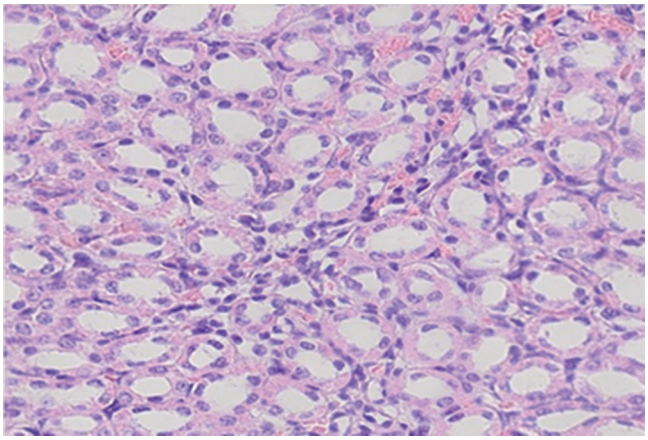

Figure 7: Histopathology picture of female group 2 dose 600 mg/kg PSP at 600 × magnification using HE staining

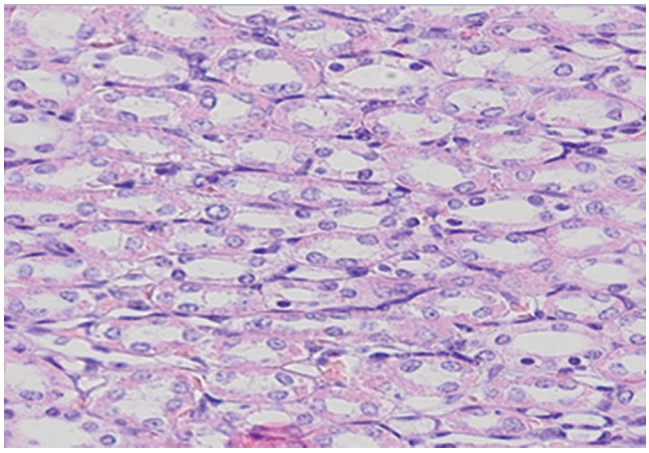

Figure 8: Histopathology picture of female group 3 dose 1200 mg/kg PSP at 600 × magnification using HE staining

G. lucidum has bioactive carbohydrates, including β-glucans, that are usually viewed as biological response modifiers (BRMs).[2] Immunological modulation is involved in the prevention of several diseases, including cancer or pathogen infections, because the polysaccharide may enhance the immune response.[5] The molecular mechanism of biological activity of polysaccharides may involve several pathways. *G. lucidum* polysaccharides, especially β-D-glucans (1→3), branching at the C-6 position, have antitumoral effect by stimulating the host defense mechanism, whereas ganoderic acids, composed of highly oxygenated triterpenes, can exert direct cytotoxicity against tumor cells or regulate tumor cell cycle.[6] The antioxidant activity of *G. lucidum* can also contribute to its antiatherogenic effect through the neutralization of free radicals and impairment of nitric oxide production.[7] As a consequence, this mushroom has been largely used in the form of dietary supplements, powders, extracts, and capsules as an alternative or complementary therapy for many diseases such as cancer, cardiovascular diseases, autoimmune diseases, and others.[8] Nevertheless, there is little information addressing the possible toxic effects caused by *G. lucidum* intake.

There are many cases about mushroom poisoning in our society. Mushroom poisoning leads to a number of symptoms that may vary from slight gastrointestinal discomfort to liver and renal failure.[9] Among some chronic toxic effects caused by mushroom, the most frequent problem is renal toxicity. The extract of the mushroom *Lentinus sajor-caju* (formerly known as *Pleurotus sajor-caju*) can affect the renal function, decreasing glomerular filtration rate by more than 50%.[10] Early studies reported that a lectin derived from the mushroom *Marasmius oreades* caused a glomerular thrombotic lesion in mice.[11] In addition, several classes of antibacterial, antifungal, antiviral, and antitumoral agents are nephrotoxic, which can cause acute renal failure.[12] It is well known that many medicinal mushrooms have substances with these properties, thus their toxicity to renal effect must also be taken into consideration.

Renal system helps the body to dispose waste materials that enter the body through a filtration mechanism, to absorb substances that are still needed, as well as to augment. Indicator of renal function can be seen from urea and creatinine test. If there is a disturbance in the function of the renal filtration then urea and creatinine levels will increase and this increase can be used as an indicator of renal function impairment. If the renal function is damaged or impaired, it will be very harmful to the body as waste materials should be excreted, otherwise they will turn into toxicants that will ultimately lead to harmful diseases such as renal failure that can damage the body.[13]

The World Health Organization notes that inappropriate use of traditional medicines or practices can have negative or dangerous effects and that further research is needed to ascertain the efficacy and safety of several practices and medicinal plants used by traditional medicine systems.[14] Most medicinal plants have not been thoroughly evaluated for their toxicity profiles. Herein, the impacts of the long-term intake of *G. lucidum* supplemented to *R. novergicus* were evaluated. Physicochemical parameters of the urine and creatinine levels of the metabolites that reflected the renal function and renal histopathology feature were analyzed.[15]

Materials and Methods

Study Group

Animal experiments were carried out with *R. novergicus*, Wistar strain tail number 80, including 40 males and 40 females, aged 6 weeks and weighing 100–150 g, in CV Gamma Scientific Biolab, Malang, Indonesia. Rats were divided into four groups (@ 10 tail): negative control and the PSP with dose groups 300, 600, and 1200 mg/kg/day. PSP per sonde for 90 days. PSP doses were obtained from PT Sahabat Lingkungan Hidup, Surabaya, Indonesia. The parameters measured in this study were renal function (urea and creatinine) and renal organ histopathology, and parameter measurements were taken at the Central Laboratory, Saiful Anwar Hospital, Malang, Indonesia. Slides were prepared in organ gross Anatomic Pathology

Laboratory, Airlangga University, Surabaya, Indonesia, after getting ethical clearance from the Health Research Ethics Committee (number 400/112/K.3/302/2014).

Biochemical Test

Creatinine: This enzymatic method is based on the conversion of creatinine with the aid of creatininase, creatinase, and sarcosine oxidase to glycine, formaldehyde, and hydrogen peroxide. Catalyzed by peroxidase, the liberated hydrogen peroxide reacts with 4-aminophenazone and HTIBa to form a quinone imine chromogen. The color intensity of quinone imine chromogen formed is directly proportional to the creatinine concentration in the reaction mixture.

$$\text{Creatinine} + H_2O \xrightarrow{\text{creatininase}} \text{creatine}$$

$$\text{Creatine} + H_2O \xrightarrow{\text{creatinase}} \text{sarcosine} + \text{urea}$$

$$\text{Sarcosine} + O_2 + H_2O \xrightarrow{\text{SOD}} \text{glycine} + \text{HCHO} + H_2O_2$$

$$H_2O_2 + \text{4-aminophenazone} \xrightarrow{\text{POD}} \text{quinone imine chromogen} + H_2O + \text{HI} + \text{HTIB}$$

Creatine of the sample is destroyed by creatinase, SOD, and catalase during incubation in R1.

a) 2,4,6-triido-3-hydroxybenzoic acid

Urea: Kinetic test was performed with urease and glutamate dehydrogenase. Urea is hydrolyzed by urease to form ammonium and carbonate.

Urease.

$$\text{Urea} + 2H_2O \longrightarrow 2NH^{4+} + CO_3^{2-}$$

In the second reaction, 2-oxoglutarate reacts with ammonium in the presence of glutamate dehydrogenase (GLDH) and the coenzyme NADH to produce L-glutamate, in this reaction 2 moles of NADH are oxidized to NAD^+ for each mole of urea hydrolyzed.

$$NH^{4+} + \text{2-oxoglutarate} + \text{NADH} \xrightarrow{\text{GLDH}} \text{L-glutamate} + NAD^+ + H_2O$$

The rate of decrease in the NADH concentration is directly proportional to the urea concentration in the specimen and is measured photometrically.

Renal Histopathology

Renal histopathology was observed by hematoxylin and eosin staining and microscope BX 53 (Olympus) at 600 × magnification. Histopathology liver identification was examined by degradation of tubular, tubular cast, dilated tubules, vacuoles, and mononuclear infiltration.

Statistical Analysis

This study used a one-way analysis of variance (ANOVA) to determine the effect of PSP on urea and creatinine levels in Wistar-type rats. Then post hoc test was carried out to identify the differences between the groups. Statistical Product and Service Solutions (SPSS) software, version 20 (IBM, New York) was used for data analysis.

Results

From Table 1, it can be seen that urea levels in the female group are relatively larger than those in the male group. In the female group, the average urea levels are highest in the PSP treatment dose of 300 mg/kg/day with an average concentration of urea of 33.2 mg/dL, whereas the average urea levels are lowest in normal treatment female group who did not receive PSP treatment dose with an average concentration of urea of 27.1 mg/dL. In the male group, the average urea levels are highest in the PSP treatment dose of 600 mg/kg/day with an average concentration of urea of 28.8 mg/dL, whereas the average urea levels are found to be lowest in the PSP treatment dose of 300 mg/kg/day with an average concentration of urea of 23.5 mg/dL. On the basis of the results of measurements of serum creatinine, the average level of creatinine in the PSP treatment doses of 1200, 600, and 300 mg/kg/day is found to be equally high: 0.3 mg/dL. On the basis of one-way ANOVA test, it can be concluded that 95% confidence interval, giving the PSP, does not provide a meaningful difference in the rising levels of urea and creatinine due to the significance $p > 0.05$. There are no morphological changes on renal histopathology feature including degradation of tubular, tubular cast, dilated tubules, vacuoles, and mononuclear infiltration in all treatment doses.

Discussion

G lucidum, commonly referred to as Lingzhi in China, is a fungus that has been widely used through the centuries for the general promotion of health and longevity in Asian countries. It has been known to have numerous pharmacological effects including immunomodulatory, anti-inflammatory, anticancer, antidiabetic, antioxidative and radical scavenging, and antiaging effects.[16] Triterpenes are primarily isolated from the spores of *G. lucidum* and have shown remarkable pharmacological and therapeutic activities on multiple human diseases including cancer.[17] Smina et al.[18] showed that triterpenes extracted from *G. lucidum* have antioxidative properties *in vitro* and can reduce oxidative damage by directly scavenging free radicals generated in the cell.

G. lucidum are also heteropolysaccharides that have α-(1→4)-d-glucopyranosyl and β-(1→6)-D-galactopyranosyl with branches at *O*-6 of glucose and *O*-2 of galactose. Polysaccharides from mushrooms showing a β-linkage have shown a boost in the human immune system and the modulation of the immunological response under certain circumstances, thus they are commonly termed BRMs. Immunological modulation is involved in the prevention of several diseases, including cancer or pathogen infections, because the polysaccharide may enhance the immune response. The molecular mechanism of

Table 1: Descriptive data of renal function and histopathology feature

Parameters	Treatment groups															
	Male dose 0		Female dose 0		Male + PSP 1200		Female + PSP 1200		Male + PSP 600		Female + PSP 600		Male + PSP 300		Female + PSP 300	
	Mean ± SD	Min–max	Mean ± SD	Min–max	Mean ± SD	Min–max	Mean ± SD	Min–max	Mean ± SD	Min–max	Mean ± SD	Min–max	Mean ± SD	Min–max	Mean ± SD	Min–max
Urea	25.0 ± 2.24	22.5–29.4	27.1 ± 2.94	23.1–32.2	26.1 ± 4.01	16.2–31.3	29.5 ± 3.16	26–35.7	28.8 ± 3.84	23.3–34.1	31.3 ± 3.21	28.1–37.3	23.5 ± 3.27	19.6–29.5	33.2 ± 8.05	26.3–48.5
Creatinine	0.3 ± 0.06	0.22–0.37	0.3 ± 0.8	0.22–0.48	0.3 ± 0.07	0.14–0.39	0.3 ± 0.04	0.26–0.37	0.3 ± 0.03	0.25–0.35	0.3 ± 0.05	0.22–0.36	0.3 ± 0.04	0.24–0.38	0.3 ± 0.03	0.26–0.33

biological activity of polysaccharides may involve several pathways. Physicochemical properties, such as molecular weight, primary structure, solution conformation, and polymer charge, among others, may play a role in determining whether and with what affinity polysaccharides bind to the receptors and show the biological activity.[5] Glucose forms the major share of the sugar molecules with xylose, mannose, galactose, and fucose in different conformations. It is hypothesized that the polysaccharides extracted from different parts of *G. lucidum* induce different immune responses with varying immune potencies.[19]

Several studies have shown the benefits of *G. lucidum* to renal function. Study by Pan et al.[20] indicated that FYGL, a protein from *G. lucidum*, can serve as a nutritional supplement or a health-care food for the diabetic therapy or protection. The research treated diabetic nephropathy mice with *G. lucidum.* Because the pathogenesis of diabetic nephropathy is closely associated with oxidative stress, many phytochemicals were reported to have multiple functions.[21] The study hypothesized that FYGL can restore the renal function via its antioxidant activity. To test this hypothesis, Pan et al.[20] evaluated whether different doses of FYGL exert protective effects on renal function and morphology in diabetic nephropathy mice. This true experimental study also aimed to determine the effects of subchronic exposure of PSP *G. lucidum* on renal function and renal histopathology feature of *R. novergicus* Wistar strain. Parameters measured were urea, creatinine levels, and renal histopathology feature.

Creatinine is excreted by the renals by filteration glomerulus, and if there is a disturbance in the function of the renal filtration, the creatinine levels in the blood increase, which can be used as an indicator of renal dysfunction.[13] So if there is a decrease in the filtration rate of glomerulus will decrease and blood creatinine levels will increase. Therefore, blood creatinine levels can be used to estimate the rate of filtration glomerulus.[22] The following are the results of analysis of creatinine levels in Wistar rats treated with high levels of PSP doses of 1200 , 600, and 300 mg/kg/day. The results of measurements of creatinine levels presented earlier show that the average level of creatinine in the PSP treatment doses of 1200, 600, and 300 mg/kg/day is equally high (0.3 mg/dL). According to Hall,[23] normal serum creatinine levels in Wistar rats are 0.2–0.9 mg/dL. Meanwhile, according Malole and Pramono,[24] normal creatinine levels in rats are 0.2–0.8 mg/dL. Factors that may affect creatinine levels are gender, state of starvation, and the size of the muscle tissue. The use of mice that have a diverse age also affects plasma creatinine levels. This is related to increasing age, the number of damaged glomerulus normally also increased.[23]

In the measurement of serum creatinine levels, Wistar rats showed that, in the male group, the mean creatinine levels of normal group and groups with PSP doses of 300, 600, and 1200 mg/dL were the same (i.e., 0.3 mg/dL), whereas in the female group, the mean creatinine levels of normal group and groups with PSP doses of 300, 600, and 1200 mg/dL were found to be at 0.3 mg/dL. This suggests that the creatinine levels, in both the males and the females, of the normal group and groups with PSP treatment dose of 300, 600, and 1200 mg/dL are still within the normal ranges.

On the basis of the theory described earlier by Hall,[23] it can be analyzed from the measurement data of creatinine levels in male and female groups that the average creatinine levels were relatively

similar due to the influence of age of Wistar rats. In addition, other factors that play a role are the famine conditions that can be measured by feeding with the same relative level of 35 mg/kg. In this case, gender has no significant effect on creatinine levels of both male and female Wistar rats. Thus, it can be concluded that exposure to PSP *G. lucidum* has no effect on creatinine levels of Wistar rats at doses of 300, 600, and 1200 mg/dL.

Measurements of serum urea levels of Wistar rats showed that, in the male group, the average level of urea in the normal group is 25.0 mg. In treatment groups, the highest urea level found in the group treated with a PSP dose of 600 mg/dL is 28.8 mg whereas low urea levels found in the group treated with a dose of 300 mg PSP/dL is 23.5 mg. Measurements of serum urea levels of Wistar rats showed that, in the female group, the average level of urea in the normal group is 27.1 mg. In treatment groups, the highest urea levels found in the group treated with a PSP dose of 1200 mg/dL is 29.5 mg whereas low urea level found in the group treated with a PSP dose of 300 mg/dL is 33.2 mg.

Normal urea level in mice, observed by Malole and Pramono,[24] was 15–21 mg/dL,[24] judging from the four treatment groups, all of which showed a high value compared to normal. According to Nikolic et al.,[25] high levels of urea, creatinine, and electrolyte balance in the blood are signs of damage of muscle, liver, brain, and other tissues. High levels of urea in all treatment groups might be due to feeding with high protein content. Protein consumed will affect the distribution of amino acids in the blood that affects plasma urea levels.[23]

In the renal organ histopathology, both the control group and the treatment groups showed no morphological changes. These results are similar to those obtained in clinical pathology examination of renal function, in which the results of tests of renal function in experimental animals were normal. It is marked with an average index of 0 on examination degradation scale tubular, tubular cast, dilated tubules, vacuoles, and mononuclear infiltration.

Conclusion

Exposure of extract of PSP *G. lucidum* does not have a significant effect on both renal function and renal organ gross histopathology at treatment doses of 300, 600, and 1200 mg/kg, so it be said that PSP *G. lucidum* is safe for renal function.

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References

1. Salawu OA, Chindo BA, Tijani AY, Obidike I, Salawu TA, Akingbasote AJ. Acute and sub-acute toxicological evaluation of the methanolic stem bark extract of *Crossopteryx febrifuga* in rats. Afr J Pharm Pharmacol. 2009;3(12):621–6.
2. Bohn JA, BeMiller JN. (1→3)-β-D-Glucans as biological response modifiers: A review of structure-functional activity relationships. Carbohydr Polym. 1995;28:3–14.
3. Paterson RRM. Ganoderma—A therapeutic fungal biofactory. Phytochemistry. 2006;67(18):1985–2001.
4. Zaidman Z, Yassin M, Mahajna J, Wasser SP. Medicinal mushroom modulators of molecular targets as cancer therapeutics. Appl Microbiol Biotechnol. 2005;67:453–68.
5. Villares A, Vivaracho LM, Guillamón E. Structural features and healthy properties of polysaccharides occurring in mushrooms. Agriculture. 2012;2:452–71.
6. Xu Z, Chen X, Zhong Z, Chen L, Wang Y. *Ganoderma lucidum* polysaccharides: Immunomodulation and potential anti-tumor activities. Am J Chin Med. 2011;39:15–27.
7. Woo WH, Man RYK, Siow YL, Choy PC, Wan EWY, Lau CS, Karmin O. *Ganoderma lucidum* inhibits inducible nitric oxide synthase expression in macrophages. Mol Cell Biochem. 2005;275: 165–71.
8. Lull C, Wichers HJ, Savelkoul HFJ. Antiinflammatory and immunomodulating properties of fungal metabolites. Mediators Inflamm. 2005;2:63–80.
9. Eren SH, Demirel Y, Ugurlu S, Korkmaz I, Aktas C, Güven FMK. Mushroom poisoning: Retrospective analysis of 294 cases. Clinics. 2010;65:491–6.
10. Tam SC, Yip KP, Fung KP, Chang ST. Hypotensive and renal effects of an extract of the edible mushroom. Life Sci. 2002;38: 1155–61.
11. Warner RL, Winter HC, Speyer CL. *Marasmius oreades* lectin induces renal thrombotic microangiopathic lesions. Exp Mol Pathol. 2004;77:77–84.
12. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet. 2005;365:417–27.
13. Wahjuni RS, Bijanti R. Uji Efek Samping Formula Pakan Komplit Terhadap Fungsi Hati dan Ginjal Pedet Sapi Friesian Holstein. J Bioteknologi. 2006;22:3.
14. World Health Organization. *Traditional Medicine,* 2008, Fact sheet no. 134.
15. Rubel R, Santa HSD, Tararthuch AL. Renal function in mice after long-term intake of *Ganoderma lucidum* (Leyss:Fr) Karst mycelium produced by solid-state cultivation. J Med Res Dev. 2012;1(1):1–7.
16. Sanodiya BS, Thakur GS, Baghel RK, Prasad GB, Bisen PS. *Ganoderma lucidum*: A potent pharmacological macrofungus. Curr Pharm Biotechnol. 2009;10(8):717–42.
17. Yuen JW, Gohel MD. Anticancer effects of *Ganoderma lucidum*: A review of scientific evidence. Nutr Cancer. 2005;53(1): 11–17.
18. Smina TP, Mathew J, Janardhanan K, Devasagayam TP. Antioxidant activity and toxicity profile of total triterpenes isolated from *Ganoderma lucidum* (Fr.) P. Karst occurring in South India. Environ Toxicol Pharmacol. 2011;32(3):438–46.
19. Chan W, Law H, Lin Z, Lau Y, Chan G. Response of human dendritic cells to different immunomodulatory polysaccharides derived from mushroom and barley. Int Immunol. 2007;19(7):891–99.
20. Pan D, Zhang D, Wu J, Chen C, Xu Z, Yang H, et al. A novel proteoglycan from *Ganoderma lucidum* fruiting bodies protects renal function and ameliorates diabetic nephropathy via its antioxidant activity in C57BL/6 db/db mice. Food Chem Toxicol. 2014;63:111–18.
21. Zhang L, Yang J, Chen X, Zan K, Wen X, Chen H. Antidiabetic and antioxidant effects of extracts from Potentilla Discolor Bunge on

diabetic rats induced by high fat diet and Streptozotocin. J Ethnopharmacol. 2010;132(2):518–24.

22. Kramer JA, Pettiet SD, Amin RP, Bertram TA, Car B, Cunningham M, et al. Overview of the application of transcription profiling using selected nephrotoxicants for toxicology assessment. Environ Health Perspect. 2004;112:460–64.
23. Hall RL. *Clinical Pathology of Laboratory Animals in Animal Model in Toxicology*, 2nd edn. CRC Press, 2007.
24. Malole MBM, Pramono CSU. Penggunaan Hewan-Hewan Percobaan di Laboratorium. Bogor, Pusat Antar Universitas Biotekonologi IPB, Bogor, 1989.
25. Nikolic J, Cvetkovuc T, Sokolovic D. Role of quercetin on hepatic urea production in acute renal failure. Ren Fail. 2003;25:149–55.

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