Potential Protective Effects of *Ganoderma lucidum* Powder against Carbon Tetrachloride Induced Liver Disorders in rats: Biological, Biochemical and Immunological Studies

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ABSTRACT:

Liver is the main organ in the body for intense metabolism and excretion. A large number of chemicals and medicines/drugs used routinely in daily lives can cause disorders and possibly liver disease. The aim of exploring some aspects related to the potential hepatoprotective activity of Ganoderma lucidum versus carbon tetrachloride (CCl_4) intoxication in rat liver. When compared with the normal group rats, the CCl_4 treated rats showed significant ($p \leq 0.05$) decreased in different biological parameters. Also, biochemical parameters such liver enzymes activities were significant ($p \leq 0.05$) elevation when compared with the normal group rats. For immunological parameters, Alb was significant ($p \leq 0.05$) decreased by the rate of -29.44 and TNF-α increased by 93.28%. This also coincided with an imbalance in the oxidants/antioxidants status in the blood, which was represented by a decrease in the level of antioxidants and a high level of oxidants. All of those parameters were indicating the liver injury by CCl_4. Whereas animal treated/fed with Ganoderma lucidum powder (GLP) showed significant ($p \leq 0.05$) improvements in all previous status biomarkers indicating the protection against hepatic cell damage. A positive dose - response was recorded between the concentrations of GLP applied and the level of improvement noticed in all measured markers. In conclusion, GLP was effective in protecting against CCl_4-induced liver disorders. Present study recommended like of that algae powder by a concentrations up to 5% (w/w), amount to be included in daily diets, drinks and food supplementation after trial study on volunteer human.

Keywords: *Ganoderma lucidum, powder, biomarker of biological and immunity.*

Abbreviations: *Alb, albumin; GSH, reduced glutathione; GSSG, oxidized glutathione; GSH-Rd, glutathione reductase; GSH-Px, glutathione peroxidase; IL-1, Interleukin 1; IL-6, Interleukin 6; IL-8, Interleukin 8; MDA, malondialdehyde; Nitrite, NO_2; ROS, reactive oxygen species; OS, oxidative stress, TBA, thiobarbituric acid; TNF-α, tumor necrosis factor-alpha.*

INTRODUCTION

Liver is the vital organ, which plays a critical role in all vertebrates. It performs a number of life functions including processes many products released into the blood stream (e.g. glucose, plasma proteins and urea), synthesis some of the clotting factors needed to stop bleeding, produces and secretes bile to aid nutrient absorption, and stored several products (e.g. glycogen, fat, vitamins and minerals) **(Crawford, 1999; Elhassaneen, 1996 and Kebamo *et al.*, 2015)**. The liver also plays a very important part in the biotransformation/ removal of xenobiotics from the body, among which alcohol, food toxins, and medicinal agents are especially noteworthy **(Grażyna *et al.*, 2020; Yu *et al.*, 2020)**. Because of these vital functions, the liver is subjected to a variety of insults and is one of the most vulnerable organs in the body. Many studies reported that these liver functions are associated with the disturbance of hepatocyte biochemistry and inducing oxidative stress through generation of reactive oxygen species (ROS) **(Valko *et al.*, 2004; Rahman *et al.*, 2012)**. Many chemicals, which are used on a routine basis, produce cellular and metabolic liver damage **(Meyer and Kulkarni, 2001)**. The most commonly used chemical is carbon tetrachloride (CCl_4). It is anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals. World Health Organization **(WHO, 1999)** reports CCl_4 can induce hepatomas and hepatocellular carcinomas in rats and mice. In addition, it causes hepatotoxic effects by producing centrilobular necrosis and steatosis. **Vanitha *et al.*, (2007)** reported that six hours after single dose, (2ml/kg) of treatment of CCl_4 caused liver toxicity through disturbance in serum biomarker enzymes. **De-Groot and Noll, (1986)** involving lipid peroxidation of

membrane-bound fatty acids that results in destructing the cell membrane and intracellular organelles of the hepatocyte, explained the mechanism of hepatic injury by CCl4. All of those previous studies with the others indicated that one of the best models of injury produced in liver is by CCI_4.

Modern pharmacological therapy is expensive and associated with numerous side effects, which leads to patient noncompliance. Thus, there is a need to investigate alternative therapies, particularly those derived from plants, because they have a wide range of biological and medicinal activities, are cost effective, and have few side effects **(Elhassaneen *et al.*, 2016 a and b)**. *Ganoderma lucidum*, an oriental fungus, has a long history of use in different Asian countries, particularly China and Japan, for promoting health and longevity. It has been recognized as a medicinal mushroom for over 2000 years and widely used in folk medicine which was attributed with therapeutic properties, such as, antiaging effects, strengthening cardiac function, enhancing vital energy, increasing memory, and tonifying effects **(Wachtel-Galor *et al.*, 2011)**. In addition, *G. lucidum* acts to relieve cough and asthma, replenish Qi, ease the mind, and it is recommended for dizziness, palpitation, insomnia, and shortness of breath (State Pharmacopoeia of the People's Republic of China, 2000). In recent decades, its powerful effects have been documented as anticancer, antitumor, immune modulatory, anti-oxidant, antibacterial, antiviral and antidiabetic **(Tomasi *et al.*, 2004, Evans *et al.*, 2009, Ma *et al.*, 2008, Wu and Wang 2009, Zhong and Xiao 2009 and Gao, *et al.*, 2004)**. Most if not all studies related to the effect of *G. lucidum* on liver injury have been conducted by using mushroom extracts or one of its isolated bioactive molecules such as polysaccharides, terpenoids, steroids, nucleo-tides, phenols and glycol-proteins. However, the hepato-

protective effects of *G.Lucidum* powder and all of its constituents against liver damage in animal models are unknown. Therefore, this study was conducted with the aim of exploring some aspects related to the potential hepato-protective activity of *Ganoderma lucidum* against carbon tetrachloride intoxication in rat liver**.**

MATERIALS AND METHODS

Ethical approval

Biological experiments for this study were ethically approved by the Scientific Research Ethics Committee (Animal Care and Use), Faculty of Home Economics, Menoufia University, Shebin El-Kom, Egypt (Approval no. 02- SREC-08-2018).

Materials and chemicals

Dried fruits of the fungus *Ganoderma lucidum* (Reishi) were obtained from ElMisryia Company for Trading Herbs and Medical Plants (Haraz), Bab ElKhalk, Cairo, Egypt. Taxonomic confirmation of *G. lucidum* was carried out by Agricultural Plant Department, Faculty of Agriculture, Menoufia University, Shebin El-Kom, Egypt. Carbon tetrachloride (CCl_4), as 10% liquid solution, was obtained from ElGhohorya Company for Trading Drugs, Chemicals and Medical Suppliers, Cairo Egypt. Kit's assays for Alanine amino-transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and malondialdehyde (MDA) were purchased from Bio-Diagnostic, Dokki, Giza, Egypt. Albumin (Alb) was determined using kits purchased from El-Nasr Pharmaceutical Chemicals Company, Cairo, Egypt. TNF-α was assayed by kit was provided by Nawah Scientific, Almokattam, Cairo, Egypt. The kits provided by MyBioSource, Inc., San Diego, CA, USA, assayed GSH and GSSG. Casein was obtained from Morgan Chemical Co., Cairo, Egypt. All other chemicals and solvents used were of analytical grade were purchased from El-Ghohorya Company for

Trading Drugs, Chemicals and Medical Suppliers, Cairo Egypt.

Preparation of powder from G. lucidum

Dried fruits of *G. lucidum* were ground into a fine powder in high mixer speed (Moulinex Egypt, Al-Araby Co., Egypt). The material that passed through an 80-mesh sieve was retained for use.

Biological experiments

Animals:

Animals used in this study, adult male albino Sprague-Dawley rats (140±9.56 g per each) were obtained from Research Institute of Ophthalmology, Medical Analysis Department, Giza, Egypt.

Basal Diet (BD):

The BD prepared according to the following formula as mentioned by **Reeves *et al.*, (1993).**

Induction of liver intoxication in Rats:

Thirty-six male albino rats were administrated by intraperitoneal (IP) injection of carbon tetrachloride (CCl_4) in paraffin oil, 50% V/V (2 ml/kg bwt), twice a week for two weeks to induce chronic damage of the liver according to the method described by **Jayasekhar *et al.*, (1997).** Liver intoxication was confirmed by taking a random sample of experimental animals (4 rats) and measuring liver function tests.

Experimental design

All biological experiments performed a complied with the rulings of the Institute of Laboratory Animal Resources, Commission on life Sciences, National Research Council **(NRC, 1996)**. Rats (n=42 rats) were housed individually in wire cages in a room maintained at 26 ± 3 ^{0}C, relative humidity (54±4%), a 12-hr lighting cycle and kept under normal healthy conditions. All rats were fed on BD for one-week before starting the experiment for acclimatization. After one-week period, the rats were divided into main groups. First group (6 rats), as a

normal control group, fed on BD and injected with paraffin oil (2 ml /kg body weight) which was used as a vehicle for the treatment of animals in CCl_4 group. Second main group (36 rats) was injected with CCl_4 to induce liver impaired rats then classified into sex equal sub groups as follow: group (2), as a positive control group, fed on BD and groups (3-6) fed on BD containing 1, 2, 3, 4 and 5% (w/w) GLP, respectively. Each of the above groups was kept in a single cage for 28 days. Rats were weighted at the beginning of experimental then weekly and at the end of the experimental period.

Biological evaluation

During the experimental period (28 days), the diet consumed was recorded twice a weekly and body weight was recorded every week. The body weight gain (BWG, %), feed intake (FI) and feed efficiency ratio (FER) were determined according to **Chapman *et al.*, (1959)** using the following equations:

BWG% = (Final weight – Initial weight)/ Initial weight×100

FER = gain in body weight (g/28 day)/ feed intake (g/28 day)

Blood sampling

At the end of experiment period, 4 weeks, blood samples were collected after 12 hours fasting using the abdominal aorta and rats were scarified under anesthetized. Blood samples were received into clean dry centrifuge tubes and left to clot at room temperature. Then centrifuged for 10 minutes at 3000 rpm to separate the serum according to **Drury and Wallington, (1980)**. Serum was carefully aspirate, transferred into clean Eppendorf tubes and stored frozen at -20^{o}C until analysis.

Liver functions parameters

Serum alanine amino-transferase (ALT) and serum aspartate aminotransferase (AST) activities were measured in serum using the modified kinetic method of **Tietz *et al.*, (1976)** by using kit supplied by Biocon Company. Alkaline Phosphatase (ALP)

activity was determined using modified kinetic method of **Vassault *et al.*, (1999).**

Immunological assays

Albumin was determined in serum according to the method of **David *et al.*, (1954)** using kits purchased from El-Nasr Pharmaceutical Chemicals Company, Cairo, Egypt. TNF-α was determined such as mentioned by **Tavakkol et l., (2005)** by a sandwich enzyme-linked immune-sorbent assay (ELISA), utilizing two monoclonal antibodies directed against separate antigenic determinants on rat TNF- α. Adlitteram Diagnostic Laboratories Inc. (San Diego, CA, US) provided the kits for the assay.

Biomarker antioxidants

Glutathione fractions (GSH and GSSG) were measured colorimetric- ally in serum samples such as described by **Ellman, (1959).**

Biomarker oxidants

Serum nitrite (NO_2) was determined flourometric such as described by **Misko *et al.*, (1993).** Serum malon-aldialdehyde (MDA) content was measured by the thiobar-bituric acid (TBA) method according to the methods of **Buege and Aust, (1978).**

Statistical Analysis

All data were statistically analyzed using a computerized cost at program by one-way ANOVA. Results were given as means ± Standard Deviation (SD). Differences between treatments at $P \leq 0.05$ were considered significant **(Snedecor and Cochran, 1967).**

RESULTS AND DISCUSSION

Effect of GLP consumption on BWG, FI and FER of hepatic disorder rats induced by CCl_4

BWG, FI and FER of rats injected by CCl_4 and consumed *G. lucidum* powder (GLP) were shown in Tables (1) and Figure (1). From such data it could be noticed that the CCl_4-treated rats exhibited significantly ($p \leq 0.05$) decreased in BWG (-51.69), FI (-35.50) and FER (-26.76) compared to the normal

group. However, supplementation of the rat diets with GLP (1.0 to 5.0 g/100g) for 28 days significantly ($p \leq 0.05$) increased the levels BWG, FI and FER with the positive control group. The rate of increasing in all those parameters exhibited a dose dependent increase with GLP consumption. Such data are in agreement with that observed by **Salman, (2016) and Elhssaneen *et al.*, 2019; and Essa, 2021)** in different genus of algae. In addition, **Hamzawy *et al.*, (2013) and Abd El-Rahman (2021)** reported that hepatic rats reveal significant reduction of the body weight and feed intake. Furthermore, **Morresion and Hark, (1999)** showed that liver disease can lead to malnutrition and the major causes of malnutrition in patients with liver disease are poor dietary/feed intake (FI), maldigestion, malabsorption and abnormalities in the metabolism and storage of macro and micro nutrients. With the same context, **Dickerson and Lee, (1988)** reported that many patients with acute or chronic liver disease are ill and commonly lose weight. Additionally, **Elbanna, (2014), Mansour, 2017, Tahoon, 2019 and Elhassaneen *et al.*, (2021)** found that injected rats by CCl_4 caused decrease in both FER and BWG and improved by consumption plant parts contains bioactive compounds such as found in GLP.

Effect of G. lucidum consumption on liver functions of hepatotoxic rats induced by CCl_4

Liver functions of rats injected CCl_4 and consumed *G. lucidum* powder (GLP) were shown in Table (2) and Figure (2). From such data it could be noticed that the CCl4-treated rats exhibited significantly ($p \leq 0.05$) increased levels of AST (74.29%), ALT (123.55%) and ALP (176.56%) compared to the negative control group. However, supplementation of the rat diets with GLP (1.0 to 5.0 g/100g) for 28 days significantly ($p \leq 0.05$) decreased the levels of AST, ALT and ALP. The rate of decreasing

was raised with the increasing of the GLP consumption rate.

CCl_4-induced liver damage is commonly used to experimentally study the hepato-protective effects of drugs **(Manibusan *et al*., 2007; Susilo *et al.*, 2019).** Such liver damage came through metabolizes CCl_4 to trichloromethyl (CCl3-) radicals by the liver cytochrome P450 which reactively bind to O_2 to form trichloromethyl peroxyl (CCl3OO-) radicals. These radicals subsequently cause lipid peroxidation of membrane-bound fatty acids. Furthermore, the structure and function of the cell membrane and intracellular organelles of the hepatocyte become disrupted. In the present study, CCl4 administration induced severe damage to liver cells, demonstrated by increased serum AST, ALT and ALP levels. Serial enzyme measurements, AST, ALT and ALP are often considered sensitive markers for determining the course of liver damage due to their presence of the cytoplasm facilitates blood flow after liver cell damage **(Pagana and pagana, 1997 and Sayed Ahmed, 2016).** Our data also indicated that GLP significantly ($p \leq 0.05$) reduced AST, ALT and ALP levels which demonstrating that it can prevent cell damage. Such preventive effects could be attributed to GLP content of some important bioactive compounds. In similar studies, *G. lucidum* extracts mainly polysaccharides or triterpenoids exhibit protective activities against liver injury induced by toxic chemicals including CCl_4 **(Wachtel-Galor *et al.*, 2011; and Susilo *et al.*, 2019).**

Effect of G. lucidum consumption on immunological markers of hepatotoxic rats induced by CCl_4

Immunological parameters of rats injected CCl_4 and consumed *G. lucidum* powder (GLP) were shown in Tables (3) and Figure (3). The CCl4-treated rats exhibited significantly ($p \leq 0.05$) decreased serum Alb levels (-29.44%) and significantly ($p \leq 0.05$) increased TNF-α levels (93.28%) compared to the normal control group. The consumption of *G.*

lucidum extract attenuated these CCl4-induced alterations in Alb and TNF-α level. The rate of attenuation was raised with the increasing of the GLP consumption level. In similar studies, CCl_4-induced significant decrease in the serum albumin content as the consequence of liver injury **(Wang, *et al.*, 2007, Abd El-Rahman, 2013 and Abd El-Fatah, 2013).** In addition, **Koneri, *et al.*, (2008),** reported that hypoalbuminaemia is most frequent in the presence of advanced chronic liver diseases. Hence, decline in serum albumin can be deemed as a useful index of the severity of cellular dysfunction in chronic liver diseases. In this study, GLP significantly ($p \leq 0.05$) increased serum Alb levels which demonstrating that it can prevent or repair the hepatocyte damage. Such role of GLP in manipulation the hypo-albuminemia could be of a high degree of importance because human albumin serum is the main protein of blood plasma and makes up around 50%. Transport protein bind to various ligands and carry them around such as water, fatty acids, hormones, bilirubin, thyroxine (T4), pharmaceuticals and cations (including Na^+, K^+ and Ca^{2+}). Thus, the main function of albumin is to regulate the oncotic pressure of blood **(Farrugia, 2010).**

On the other side, in this study, GLP significantly ($p \leq 0.05$) decreased serum TNF-α levels which demonstrating that it can prevent tissue damage. Such role of GLP in suppression the TNF-α could be of a high degree of importance because it is a pro-inflammatory cytokine, which plays an important role in initiating the tissue inflammatory reaction **(Kim *et al.*, 2003).** TNF-α damages endothelial cell, promotes leukocyte adhesion of vascular endothelial cells, increases vascular permeability, and stimulates Interleukin 1 (IL-1) production by vascular endothelial cells, endothelin, and other inflammatory mediators, leading to tissue inflammation **(Ferrero-Miliani, 2007).** Also, TNF-α stimulates neutrophil degranulation "outbursts," which produces oxygen free radicals, proteases and lipids, leading to

tissue damage **(Gao, 1999).** Furthermore, TNF-α is releasing IL-1, Interleukin 6 (IL-6) and Interleukin 8 (IL-8) , and in inflammatory reactions, causing a "cascade effect" and aggravating tissue damage **(Bentrem and Joehl, 2003).** In similar studies, treatment patients' groups given extracts from the medicinal mushrooms including *G. lucidum* were found to demonstrate decreased expression of tumor markers, increased natural killer (NK) cells activities, and higher survival rate, compared to control Groups **(Kodama *et al*., 2003; Gao *et al*., 2004 and Venturella *et al*., 2021).**

Effect of G. lucidum consumption on glutathione fractions of hepatotoxic rats induced by CCl_4

Data presented in Table (4) and Figure (4) showed effect of feeding GLP on serum glutathione fractions content of rats treated with CCl_4. It was observed that the mean value of GSH and GSSG for control normal group were 8.61 and 0.671µmol/L. The CCl4-treated rats exhibited significantly ($p \leq 0.05$) decreased serum GSH (-31.36%) and GSSG (-14.75%) compared to the normal control group. Supplementation of the rat diets with GLP (1.0 to 5.0 g/100g) attenuated these CCl4- induced alterations in GSH and GSSG levels. In addition, a GLP dose dependent increase in all glutathione fractions studied was seen.

GSH is a tripeptide-thiol (γ-glutamyl cysteinyl-glycine) that has received great interest in many aspects related to its biosynthesis, regulation and various functions within cells **(Voet and Voet 1990).** Its role in detoxifications process represent the main function through as a key conjugate of xenobiotics electrophilic metabolites and as an important antioxidant **(Elhassaneen, 1996).** The antioxidant functions of GSH include serving as a nonenzymatic scavenger of oxyradicals and its role in the activities of the antioxidant enzymes system (glutathione peroxidase, GSH-Px and glutathione reductase, (GSH-Rd) **(Wu, *et* al., 2004**

and Almaadawy *et al.*, 2016) Therefore, determination of this small molecule is very important for present-day nutrition, medicine and pharmacy. Data of the present study with the others **(Hasegawa *et al.*, 1995 and Meharam and Sayed- Ahmed, 2019)** suggested that CCl_4 might block secretion of glutathione fractions from liver to blood because of intracellular structural failure, elevation of the lipid peroxidation and/or the energy depletion suggested by the marked decrease in glycogen content. Various components of GLP, in particular polysaccharides, terpenoids, phenolics, and flavonoids show antioxidant activity **(Wu and Wang 2009; Wong *et al.*, 2013).** In addition, **Wachtel-Galor *et al.*, (2011)** reviewed that antioxidants from *G. lucidum* were found to be absorbed quickly after ingestion inducing elevate in the plasma total antioxidant activity of human subjects. On the other side, a fall in serum glutathione fractions observed generally in the present study accompanied by a concomitant decreased in the ratio of GSH/GSSG. **Di Giulio, (1991)** reported that the effect of oxygen-generating compounds refers to its effect on the so-called redox state (GSH / GSSG) of cells or tissues. In the healthy cell, the ratios of GSH/GSSG is typically very high i.e.>10. The CCl_4-treated rats exhibited significantly ($p \leq 0.05$) decreased in serum redox state (GSH/ GSSG) by -19.48%. The consumption of GLP by 5% increased that GSH/GSSG ratio to exactly value recorded by the group of normal rats. It is proposed that GLP suppress CCl_4-induced oxyradicals fluxes, which may result in a decrease in the GSH/GSSG ratio.

Effect of G. lucidum consumption on oxidative stress of hepatotoxic rats induced by CCl_4

Oxidative stress (OS) of rats injected CCl_4 and consumed ***G.*** *lucidum* powder (GLP) were shown in Tables (5) and Figure (5). From such data it could be noticed that the

CCl4-treated rats exhibited significantly ($p \leq 0.05$) increased levels of MDA (118.44%), and NO_2 (103.77%) compared to the normal control group. However, supplementation of the rat diets with GLP (1.0 to 5.0 g/100g) for 28 days significantly ($p \leq 0.05$) decreased the levels of MDA and NO_2. GLP- dose dependent decrease in all the oxidative stress studied was seen.

CCl_4-induced liver damage came through metabolizes CCl_4 to its radicals (trichloromethyl, CCl_3-) by the liver cytochrome P450 which reactively bind to O_2 to form trichloromethyl peroxyl (CCl_3OO^-) radicals. Such radicals subsequently cause lipid peroxidation of membrane-bound fatty acids. Double bonds in fatty acids form peroxide products by reacting with free radicals, and lipid radicals can be formed subsequently upon removal of electrons **(Cheeseman and Salter, 1993).** Because of lipid peroxidation, harmful degradative products, namely malondialdehyde (MDA) can be formed in cell membranes. MDA shows mutagenic effect via reacting with guanine nucleotide in DNA **(Cline et al., 2004).** Also, cross linking with the membrane components leads to changes in membrane properties including disturbance in membrane fluidity, inactivation of enzymes and receptors in membranes, cell injury and may cause the formation of atherosclerotic plaques **(Kris-Etherton *et al.*, 1999 and Nilanjana., 2013*).*** On the other side, nitric oxide synthase catalyzes the conversion of L-arginine to citrulline and highly reactive free radical species, nitric oxide (NO) **(Manahan, 1989).** NO, can react with O_2 and water to form nitrite (NO_2) and nitrate (NO_3); with the amino and thiol groups of protein to produce nitrosylated species; with hemoglobin to form iron-nitrosyl adducts and nitrate in blood; and with superoxide anion to make nitrate **(Manahan, 1989; Misko *et al.*, 1993).**

Several studies indicated that the excess production of nitric oxides in the body has been investigated in the pathogenesis and tissue destruction of a

growing number of nutritional, communicable, immunological and inflammatory diseases including septic shock, arthritis, graft rejection obesity, anemia, cardiovascular disease, and diabetes **(Jacob *et al.*, 1992; Elhassaneen *et al.*, 2020; Mehram *et al.*, 2021).** High levels of MDA and NO_2 were noted in the present study represents an important finding to support this study hypothesis, i.e. The toxicity of CCl_4 is linked to oxidative stress and free-radical damage. Therefore, highly significant decreasing rate on the formation of MDA and NO_2 in serum as the result of GLP treatment proposed that hepatoprotection might also be mediated by the radical-scavenging properties, and lipid peroxidation and nitric oxide synthase inhibition of *G. lucidum*. In similar studies, **Lin *et al.* (1991)** found that hot water extracts of *G. lucidum* had significant radical-scavenging activity against both superoxide and hydroxyl radicals in similar studies. In addition, **Jia *et al.* (2009)** found that treatment of rats with *G. lucidum* bioactive compounds, polysaccharides, leads to decrease the levels of lipid peroxidation and increase the levels of enzymatic and nonenzymatic antioxidants. In our opinion, if there were no change in the antioxidant defense system of rats treated with GLP, it would be difficult to observe low levels of MDA and NO_2.

CONCLUSION

Ganoderma lucidum powder (GLP) was effective in protecting against CCl_4-induced liver disorders. These results supported previous hypothesis of the present study that contains several classes of phytochemicals with other compounds that are able to prevent or inhibit CCl_4 hepatotoxicity. Through one or more of the following mechanisms: 1) Inhibition of excessive enzymatic activity expressed in liver functions, 2) raising the rate of immune markers in the blood, 3) improving the state of the antioxidant defense system in serum, and 4) reducing the

degree of oxidative stress in serum i.e. formation of oxidants. Therefore, we recommended like of that algae (*Ganoderma lucidum)* powder by concentrations up to 5% (w/w), amount to be included in our daily diets, drinks and food supplementation after trial study on volunteer human.

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Table 1. Effect of GLP consumption on BWG, FI and FER of hepatotoxic rats induced by CCl_4.

Value	Control (-) Std diet	Control (+) CCl_4	*Ganoderma lucidum* powder (GLP, w/w)				
			1	2	3	4	5
BWG (%)							
Range	0.81-0.94	0.41-0.47	0.50-0.53	0.59-0.67	0.60-0.79	0.65-0.87	0.78-0.81
Mean	0.89 [a]	0.43 [e]	0.51 [d]	0.62 [c]	0.73 [ab]	0.78 [ab]	0.79 [a]
SD	0.06	0.05	0.02	0.04	0.10	0.05	0.03
% of change	0.00	-51.69	-42.70	-30.34	-17.98	-12.36	-11.24
FI (g/day/rat)							
Range	12.01-13.13	7.54-8.08	9.02-9.94	10.15-11.41	10.65-11.88	11.59-12.38	11.74-12.90
Mean	12.59 [a]	8.12 [c]	9.20 [b]	10.89 [ab]	11.50 [a]	12.10 [a]	12.20 [a]
SD	0.78	0.45	0.64	0.71	0.72	0.53	0.62
% of change	0.00	-35.50	-26.93	-13.50	-8.66	-3.89	-3.10
FER							
Range	0.068-0.072	0.049-0.054	0.051-0.063	0.051-0.058	0.060-0.069	0.059-0.070	0.062-0.067
Mean	0.071 [a]	0.052 [c]	0.055 [c]	0.056 [c]	0.063 [b]	0.064 [b]	0.065 [b]
SD	0.002	0.009	0.005	0.004	0.004	0.006	0.002
% of change	0.00	-26.76	-22.54	-21.13	-11.27	-9.86	-8.45

[*] *Means in the same row with different letters are significantly different at p≤0.05*

Table 2. Effect of *G. lucidum* consumption on liver functions of hepatotoxic rats induced by CCl_4.

Value	Control (-) Std diet	Control (+) CCl_4	*Ganoderma lucidum* powder (GLP, w/w)				
			1	2	3	4	5
Serum Aspartate aminotransferase (AST) activity (U/L)							
Range	46.11 -56.76	85.55 -97.45	77.45 -88.42	70.65 -79.62	60.66 -71.33	54.72 -68.44	53.78 -63.09
Mean	52.87 ^{e}	92.15 ^{a}	81.42 ^{b}	76.76 ^{c}	65.92 ^{d}	60.51 ^{d}	58.65 ^{d}
SD	5.66	8.99	6.44	5.76	7.12	8.63	7.03
% of change	0.00	74.29	54.00	45.18	24.68	14.45	10.93
Serum alanine aminotransferase (ALT) activity (U/L)							
Range	26.77 -35.76	66.76 -73.90	55.09 -66.20	49.02 -56.12	41.03 -52.55	34.44 -40.81	34.78 -43.22
Mean	31.12 ^{e}	69.57 ^{a}	59.15 ^{b}	52.65 ^{c}	46.82 ^{cd}	37.79 ^{d}	36.21 ^{d}
SD	4.34	6.92	5.54	4.91	6.12	4.90	5.21
% of change	0.00	123.55	90.06	69.19	50.44	21.43	16.36
Serum alkaline phosphatase (ALP,U/L)							
Range	98.99 -117.03	271.9 -321.17	255.67-281.72	220.98-266.20	287.11-2016.54	137.78-166.54	130.86 -151.45
Mean	106.43 ^{g}	294.34 ^{a}	270.12 ^{b}	243.98 ^{c}	202.29 ^{d}	152.54 ^{e}	139.09 ^{f}
SD	10.32	27.14	13.66	25.85	14.12	20.89	11.23
% of change	0.00	176.56	153.80	129.24	90.07	43.32	30.69

* Means in the same row with different letters are significantly different at $p \leq 0.0$

Table 3: Effect of *G. lucidum* consumption on immunological markers of hepatotoxic rats induced by CCl_4.

Value	Control (-) St. diet	Control (+) CCl_4	*Ganoderma lucidum* powder (GLP, w/w				
			1	2	3	4	5
Albumin concentration, (Alb, g/dl)							
Range	3.90 -4.36	1.79 -3.06	2.79 -3.05	2.90 -3.30	3.29 -3.66	3.48 -3.82	3.56 -3.97
Mean	4.11 [a]	2.90 [e]	2.97 [d]	3.13 [c]	3.49 [bc]	3.69 [b]	3.82 [b]
SD	0.23	0.12	0.10	0.21	0.22	0.19	0.26
% of change	0.00	-29.44	-27.74	-23.84	-15.09	-10.22	-7.06
Tumor necrosis factor-α level, (TNF-α, ng/L)							
Range	1.26 -1.50	2.41 -2.77	2.12 -2.37	1.85 -1.97	1.64 -1.89	1.59 -1.71	1.46 -1.76
Mean	1.34 [d]	2.59 [a]	2.22 [b]	1.92 [b]	1.75 [bc]	1.63 [bc]	1.61 [bc]
SD	0.11	0.20	0.13	0.08	0.13	0.06	0.18
% of change	0.00	93.28	65.67	43.28	30.60	21.64	20.15

[*] *Means in the same row with different letters are significantly different at p≤0.05*

Table 4. Effect of *G. lucidum* consumption on glutathione fractions of hepatotoxic rats induced by CCl_4.

Value	Control (-) St diet	Control (+) CCl_4	*Ganoderma lucidum* powder (GLP, w/w)				
			1	2	3	4	5
Reduced glutathione concentration, (GSH, µmol/L)							
Range	7.59 -8.55	5.02 -5.87	5.90 -7.33	5.79 -7.91	7.11 -7.74	7.20 -8.29	6.03 -8.06
Mean	8.61 [a]	5.91 [d]	6.52 [c]	6.88 [c]	7.41 [b]	7.84 [b]	7.99 [b]
SD	1.10	0.98	0.87	1.14	0.39	0.59	1.14
% of change	0.00	-31.36	-24.27	-20.09	-13.94	-8.94	-7.20
Oxidized glutathione concentration (GSSG, µmol/L)							
Range	0.61 1-0.708	0.483 -0.662	0.541 -0.619	0.551 -0.622	0.545 -0.660	0.510 -0.718	0.580 -0.649
Mean	0.671 [a]	0.572 [cd]	0.583 [c]	0.587 [c]	0.608 [b]	0.610 [b]	0.620 [b]
SD	0.045	0.102	0.054	0.042	0.059	0.112	0.038
% of change	0.00	-14.75	-13.11	-12.52	-9.39	-9.09	-7.60
GSH/GSSG ratio (%)							
Value	12.832 [a]	10.332 [c]	11.184 [b]	11.721 [b]	12.188 [a]	12.852 [a]	12.887 [a]
% of change	0.00	-19.48	-12.84	-8.66	-5.019	0.156	0.429

[*] *Means in the same row with different letters are significantly different at p≤0.*

Table 5. Effect of *G. lucidum* consumption on oxidative stress of hepatotoxic rats induced by CCl_4.

Value	Control (-) Std diet	Control (+) CCl_4	*Ganoderma lucidum* powder (GLP, w/w)				
			1	2	3	4	5
Malondialdehyde concentration (MDA, nmol/mL)							
Range	0.161 -0.194	.0.329 - 0.412	0.313-0.352	0.280 -0,314	0.275 -0.296	0.218 -0.246	0.208-0.263
Mean	0.179 [e]	0.391 [a]	0.331 [a]	0.299 [ab]	0.284 [b]	0.229 [c]	0.223 [c]
SD	0.033	0.031	0.029	0.044	0.039	0.059	0.045
% of change	0.00	118.44	84.92	67.04	58.66	27.93	24.58
Nitrite (NO_2, nmol/L)							
Range	2.25 -2.54	4.51 -5.24	3.92 -5.13	3.23 -4.98	2.99 -4.08	3.10 -3.88	2.32 -3.32
Mean	2.39 [e]	4.87 [a]	4.65 [a]	4.05 [b]	3.66 [c]	3.54 [c]	2.85 [d]
SD	0.17	0.43	0.87	1.01	0.49	0.48	0.56
% of change	0.00	103.77	94.56	69.46	53.14	48.12	19.25

[*] *Means in the same row with different letters are significantly different at p≤0.05*

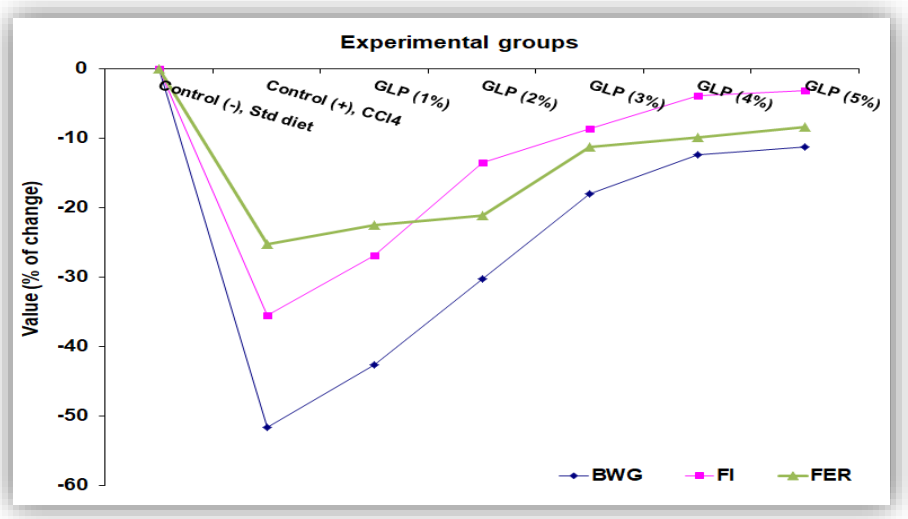

Figure 1. *Effect of GLP consumption on BWG, FI and FER of hepatic disorder rats induced by CCl_4*

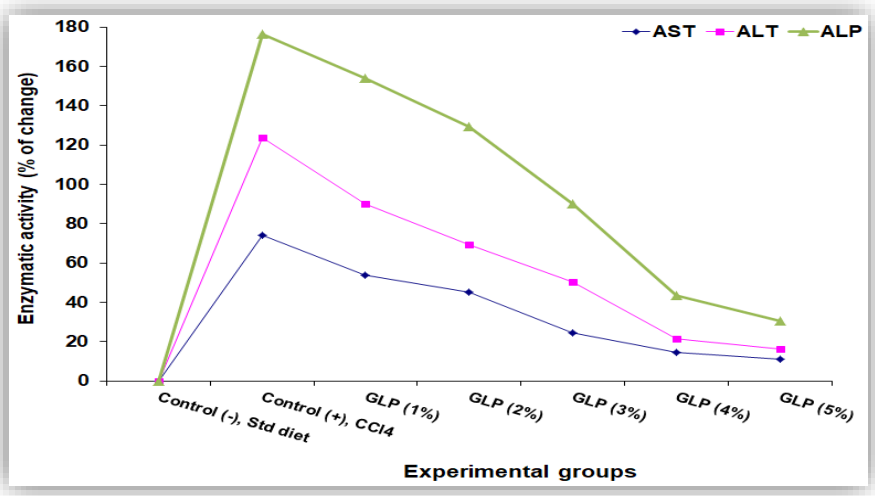

Figure 2. *Effect of G. lucidum consumption on liver functions of hepatotoxic rats induced by CCl_4*

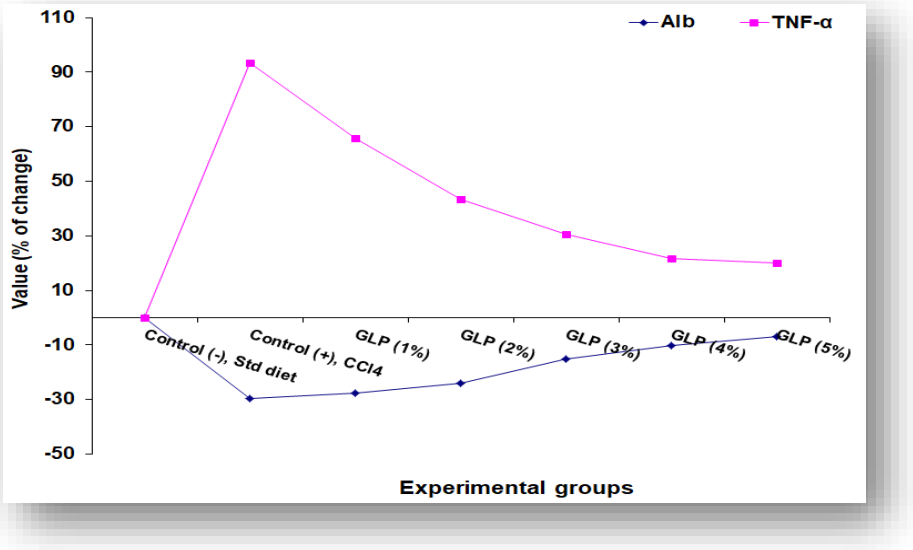

Figure 3. *Effect of G. lucidum consumption on immunological markers of hepatotoxic rats induced by CCl_4*

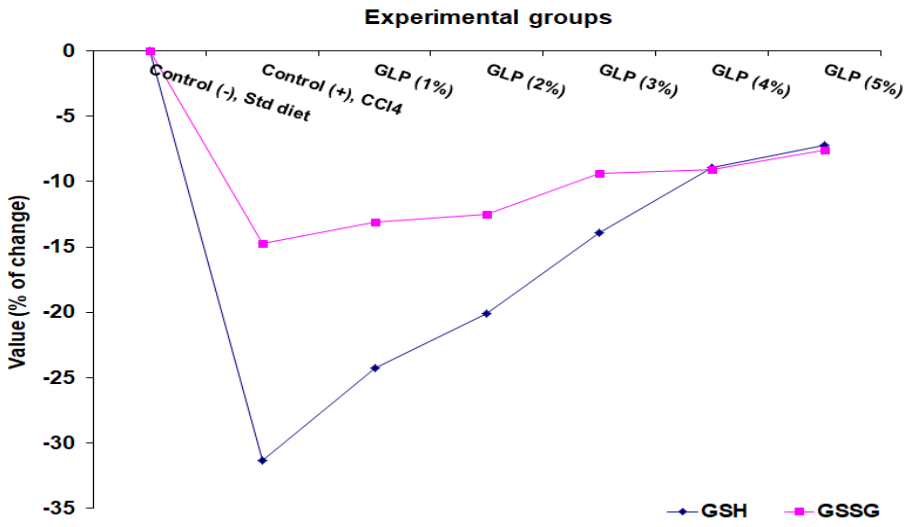

Figure 4. *Effect of G. lucidum consumption on glutathione fractions of hepatotoxic rats induced by CCl_4*

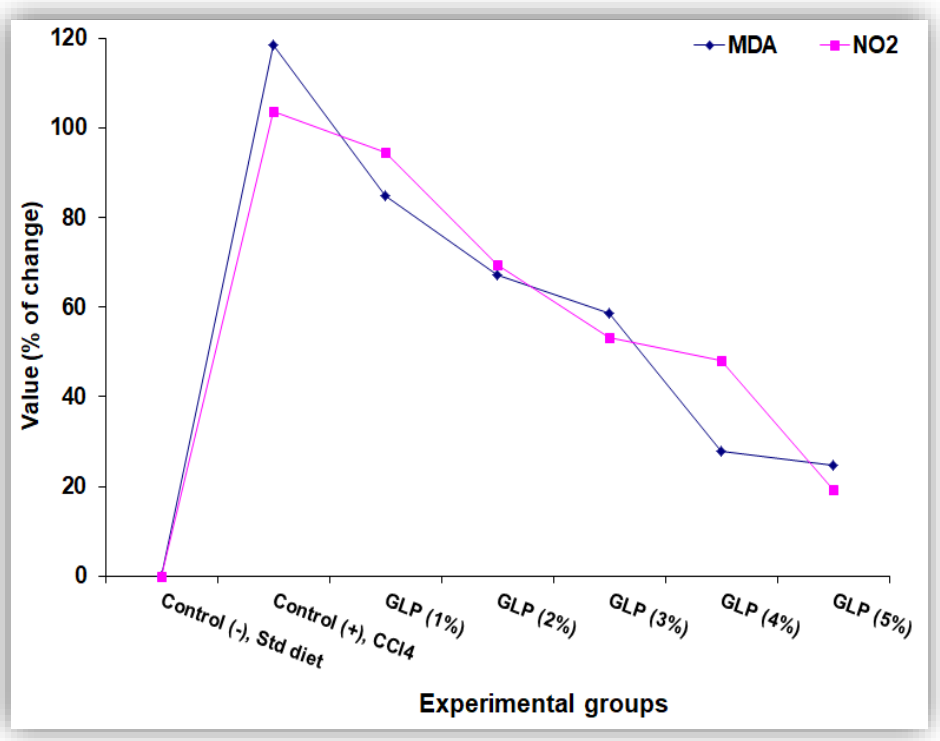

Figure 5. *Effect of G. lucidum consumption on oxidative stress of hepatotoxic rats induced by CCl_4*

التأثيرات الوقائية المحتملة لمسحوق الجانوديرما ضد اضطرابات الكبد التي يسببها رابع كلوريد الكربون في الجرذان: دراسات بيولوجية وبيوكيميائية ومناعية

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[٣] قسم التغذية وعلوم الأطعمة- كلية الاقتصاد المنزلى - جامعة المنوفية - شبين الكوم – مصر

الملخص العربي

يعد الكبد هو العضو الرئيسي في الجسم لعمليات التمثيل الغذائي والاخراجى المكثفة ، يمكن أن يتسبب عدد كبير من المواد الكيميائية والأدوية المستخدمة بشكل روتيني في الحياه اليومية في حدوث اضطرابات وربما أمراض خطيرة للكبد. هدفت الدراسة استكشاف بعض الجوانب المتعلقة بالنشاط الوقائي لفطر الجانوديرما ضد تسمم الكبد برابع كلوريد الكربون في الجرذان. ولقد أظهرت المعاملة برابع كلوريد الكربون انخفاضًا معنويًا ($p\leq0.05$) في مختلف المعايير البيولوجية التى تشمل معدل الزيادة فى الوزن والمستهلك من الغذاء ونسبة كفاءة الغذاء . كما أظهرت العوامل الكيموحيوية مثل أنشطة إنزيمات الكبد ارتفاعًا معنويًا ($p\leq0.05$) بالمقارنة مع المجموعة الطبيعية. أما بالنسبة للدلائل المناعية ، انخفض مستوى الألبيومين معنويا ($p\leq0.05$) بمعدل -٢٩,٤٤ وزاد معامل النخر الورمى بنسبة ٩٣,٢٨٪. كما تزامن ذلك مع حدوث خلل في حالة المؤكسدات / مضادات الأكسدة في الدم ، والذي تمثل في انخفاض مستوى مضادات الأكسدة الجلوتاثيون (الصور المختزلة والمؤكسدة) وارتفاع مستوى المواد المؤكسدة (المالونالدهيد وفوق اكسيد النتريك). وتشير كل هذه الدلائل إلى الأضرار الخطيرة التى يسببها رابع كلوريد الكربون فى الكبد. بينما أظهرت الحيوانات المعالجة التي تم تغذيتها بمسحوق فطر الجانوديرما الى حدوث تحسنًا معنويًا ($p\leq0.05$) في جميع المؤشرات السابقة والتي تشير إلى تاثيرات الحماية من تلف الخلايا الكبدية. تخلص الدراسة الى ان مسحوق فطر الجانوديرما كان له تأثيرا فعالاً في الحماية من اضطرابات الكبد التي يسببها رابع كلوريد الكربون . لذا نوصي باستخدام مسحوق هذا الفطر بتركيزات تصل إلى ٥٪ (وزن / وزن) من الوجبة الغذائية اليومية ضمن الوجبات والمشروبات والمكملات الغذائية بعد عمل دراسة تمهيدية على اناس متطوعين.

الكلمات المفتاحية: *مسحوق الجوانودرما ، الدلائل البيولوجية والمناعية.*