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Efficacy of *Ganoderma lucidum* in Reducing Liver Dysfunction Induced by Copper Oxide Nanoparticles

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ABSTRACT

The increasing use of copper oxide nanoparticles (CUO-NPs) in many fields, especially medical and pharmaceutical, increases the need to study their toxic effects on human health, and to search for safe agents to protect or limit their harmful effects. The study was conducted on 24 male rats sporadic randomly into 4 equal divisions: CON group included healthy rats, CUO-NPs group was for CUO nanoparticles intoxicated rats, while in CUONPs+GL group the intoxicated rats received G. lucidum, and GL group, in which the rats received only G. lucidum. The experiment lasted for two weeks. After its completion the animals were sacrificed to obtain homogenous blood and tissue samples for the liver. Liver function biomarkers were measured, and hepatic levels of malondialdehyde and glutathione were also examined to detect oxidative stress in liver tissue. Our observations showed that there was a significant increase in serum biomarkers of liver function in rats treated with CUO-NPs compared to control rats. Moreover, copper oxide nanoparticles decreased the level of glutathione and increased the level of malondialdehyde in liver tissues. Co-administration of G. lucidum had a potentiating effect against hepatotoxicity, having a role in restoring biomarkers of liver function and copper-induced oxidative stress. Ganoderma lucidum may be recommended as an agent to restore liver function disturbances caused by exposure to copper oxide nanoparticles.

Key words: Liver, Oxidative stress, Copper, Nanoparticles

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INTRODUCTION

Nanoparticles (NPs) are gaining great interest as they contribute too many fields of science, such as materials science and chemistry. They are small in size (<100 nm) with at least one dimension as well as an increased surface-to-volume ratio. Recently, nanotechnology has entered the health field of the individual with positive results [1,2]. Nanoparticles of copper oxide (CuO-NPs) are consumed in many apps like magnetic, thermal and electrical devices as well as cosmetics [3,4]. Although the nanotechnology industry is expected to grow globally and develop new types of NPs, its risks cannot be neglected. The potential toxicity of NPs may depend on their type, interaction, duration of retention and distribution in the body. These particles can enter the human or animal body via the digestive tract, lungs or skin, with the ability to penetrate living cells, to settle in the main body organs and sabotage their functions [5,6]. Scientific research confirmed the toxic impact of nanoparticles on hepatocytes. Besides, oxidative stress has an essential role in the mechanics of poisoning with many chemicals [7,8]. As yet, many developing countries are using herbs mainly in medicine for their acceptance in the human body in addition to their fewer side effects [9]. *Ganoderma lucidum* (GL) is a macro fungus that grows on dead and deciduous trees. It has been used extensively for health promotion for more than two thousand years in many Asian countries, it is also known as the immortal mushroom [10,11]. GL contains bioactive components, including polysaccharides and triterpenes. Therefore, it has been used in a lot of pharmaceutical applications, particularly as an antioxidant, immuno-modulatory and hepato-protective agent [12].There is a need to evaluate safety factors that may be prophylactic or therapeutic against NPs toxicity. So that, this experiment was performed to investigate the perturbations in hepato-serous functional parameters as well as oxidative parameters caused by CuO nanoparticles in laboratory rats and to evaluate the role of GL in mitigating their adverse effects.

MATERIALS AND METHODS

Chemicals

Copper oxide nanoparticles dispersion (black liquid, purity=99.9%, APS=3-6 nm, concentration=3 wt %, ph =3, solvent=isopropyl alcohol IAP) was obtained from Nano-

shell LLC, Wilmington, USA. Whilst, *Ganoderma Lucidum* extract purchased from Restore Nature (USA), 100% plant-based capsule, a pharmacist-recommended natural vegetable supplement.

Experimental groups and treatments

A total of 24 rats were consumed in this experiment, at ages (15-21) weeks and weighed (190 - 230) g. They were housed under optimal conditions of ventilation, humidity, light and temperature, with abundant food and water. Further, animals were acclimatized a week to the laboratory conditions before beginning of current study. At the start of the experiment, the animals were separated into 4 divisions, 6 in each one) (Table 1).

Table 1: Laboratory rats and treatments.

Groups	Treatments (14 consecutive days)
CON	Healthy rats did not receive any treatment.
CUO-NPs	Rats received copper oxide nanoparticles at a dose of 250 mg/kg, by oral tube [13].
CUO-NPs+ GL	Rats poisoned with copper oxide nanoparticles, were given orally at a dose of 500 mg/kg [14] *Ganoderma lucidum*.
GL	Rats received only *Ganoderma lucidum* (500 mg/kg).

Post of the experiment, all animals were sacrificed, all animals were sacrificed. Blood was taken by puncturing the animals' hearts. To assess liver biochemical function, serum was separated by centrifugation at 3500 rpm for 10 minutes. Liver tissues were collected using the midline incision technique, rinsed with isotonic saline, and frozen at −80°C for biochemical tissue tests.

Biomarkers of liver function

Concentrations of enzymes related to liver function in the blood serum, were assessed following the vital diagnostic instructions. Using an automated biochemical analyzer (Hitachi Ltd., Japan).

Biomarkers of oxidative stress

The level of glutathione (GSH) in liver tissue (µg/mL) was assessed by an enzymatic method according to the previously modified procedure [15]. Whereas, the level of malondialdehyde (MDA) in hepatocytes (µl/ml) was determined using a spectro-photometer as defined in the previous study [16].

Statistics

Data were preceded using SPSS program (version 25). The difference between study groups was measured by one-way ANOVA, and then Duncan's post hoc test was followed. The mean ± SD was significant at $p < 0.05$.

RESULTS

In rats poisoned with CUO-NPs, liver biomarker activity was significantly increased ($p < 0.05$) compared to control animals. Besides, the hepatic MDA level was significantly elevated compared to the control group, on the contrary a marked decrease in hepatic GSH activity occurred. Co-administration of GL to CUO-NPs intoxicated rats caused a significant reduce in serum markers of liver function compared to CUO-NPs intoxicated rats (Figure 1).

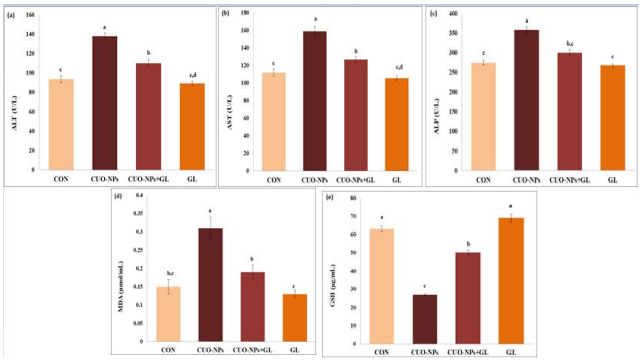

Figure 1: Effect of *Ganoderma lucidum* on serum liver function mark The effect of *G.Lucidum* on ers (a, b, and c) and oxidative stress markers (d, e) in liver tissue among experimental rats. The data were represented as mean ± SD. Different letters express significant intra-column differences (P < 0.05).

DISCUSSION

Result confirmed that the liver is a target organ for the toxicity of CUO-NPs. Our previous reports are in agreement with this finding, as we found that the liver damage could be caused by high concentrations of ZnO nanoparticles [17] as well as from gold nanoparticles [18]. In addition, our results were compatible with the findings of other studies that reported that the toxic effect of CuO nanoparticles was caused by reactive oxygen species (ROS) generated [19,20]. Excessive generation of ROS is the critical operator involved in diverse upsets by triggering oxidative stress, causing clear harm by hitting macromolecules like albuminoids and nuclear deoxyribonucleic acid (DNA) [21,22].The use of some natural antioxidants such as GL contributes to the reduction of ROS generation and thus provides protection against the various degenerative diseases that they cause [23,24]. It has many liver protective effects because it contains the biologically active substances such as triterpenoids, polysaccharides, sterols, steroids, peptides, and others. Generally, toxic substances to the liver may cause damage to hepatocytes, causing oxidative stress and inflammation in the liver, and may develop

into cirrhosis, ending in hepatocellular carcinoma [25]. Recently, numerous studies have demonstrated the powerful efficacy of GL in scavenging free radicals, which considerably inhibits the evolution of oxidative stress as well as inflammation. So, it is possible to employ GL as a curing against liver damage caused by hepatotoxic agents [26]. CCl4 is one of the most potent hepato-toxicants, so it is exploited for scientific research purposes to estimate liver preventive agents [27]. The oldest study demonstrating the therapeutic effect of GL on liver injury was conducted by Lin et al in 1974, they confirmed that GL extract significantly reduced inflammation in the liver and provided effective protection against CCL4-induced liver injury in mice [28]. In 2013, Pan et al demonstrated that dosing with GL extract markedly lowered the level of lipid peroxidation in rats, due to its free radical scavenging action [29-32]. Therefore, we preferred antioxidants such as GL to combat cellular damage caused by free radicals especially in hepatocytes.

CONCLUSION

Administration of *Ganoderma lucidum* had a significant role in restoring liver function disorders caused by exposure to copper oxide nanoparticles in rats.

CONFLICT OF INTEREST

None.

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