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Possible Hepato-Protective Effects of Sodium Copper Chlorophyllin against Chlorpyrifos Induced Toxicity in Adult Female Rats

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Abstract: Chlorpyrifos (CP), a widely used pesticide, leaves residues in crops, raising concerns due to oxidative stress and lipid peroxides. Sodium copper chlorophyllin (SCC), a water-soluble derivative of chlorophyll composed of sodium-copper salts, may offer protective effects. This study investigates SCC's potential to counteract CP-induced liver toxicity in rats and explores its role in reducing pesticide-driven oxidative damage. Thirty adult female albino rats were divided into five groups (6 rats each). Group 1 received distilled water (control), Group 2 was treated with CP (6.7 mg/kg), Group 3 received SCC (50 mg/kg), while Groups 4 and 5 received CP plus SCC at low (50 mg/kg) and high (100 mg/kg) doses respectively. All administered orally daily for six weeks. Blood samples for biochemical analysis, and liver tissues for histopathology were collected after sacrifice. No deaths or changes in appearance were observed. All groups except the CP-only group showed significant weight gain. CP administration caused notable increases in serum liver enzymes (ALT, AST, ALP), while SCC alone did not affect enzyme levels. Co-treatment with CP and SCC (both doses) significantly reduced these enzyme levels compared to CP alone, suggesting a protective effect. Additionally, CP elevated serum malondialdehyde (MDA) and lowered glutathione (GSH) levels, whereas SCC alone had no significant impact on these markers. SCC co-administration reversed these effects, decreasing MDA and increasing GSH levels. Histological findings aligned with the biochemical data. SCC demonstrates a protective role against CP-induced oxidative liver damage. Further research is warranted to validate these findings and clarify the mechanisms involved.

Key points: Process, Organization, Europe, modern, trend, country.

Introduction

Chlorpyrifos (CP) is a widely used, broad-spectrum organophosphorus insecticide that has been employed extensively to manage a range of pests in both agricultural and livestock settings [1]. The extensive use of organophosphate pesticides in public health and agricultural practices has resulted in significant environmental contamination, posing a substantial risk to human health due to the potential for both acute and chronic poisoning [2]. Residual levels of organophosphate pesticides have been frequently detected in soil, water sources, vegetables, grains, and various food products [3]. CP, particularly its ethyl derivative, has been associated with a range of adverse effects, including genotoxicity, teratogenicity, and immunotoxicity. Additionally, it has been linked to hepatotoxicity, as well as neurochemical alterations and neurobehavioral disturbances [4]. CP exerts its primary toxic effect through irreversible inhibition of the enzyme acetylcholinesterase, leading to the accumulation of acetylcholine at synaptic and neuromuscular junctions, which can result in neurotoxicity [5]. Chronic and prolonged exposure to CP has been associated with numerous adverse health effects, including impairments in the nervous, cardiovascular, and respiratory systems, as well as DNA damage, gene mutations, and elevated cancer risk [6]. Additionally, CP exposure has been linked to reproductive toxicity (including reduced sperm quality and quantity),

testosterone suppression, hematological alterations, hepatotoxicity, thyroid dysfunction, and neurotoxicity [4]. Beyond its cholinesterase-inhibiting activity, chlorpyrifos also induces cellular damage through oxidative stress which occurs due to an overproduction of reactive oxygen species (ROS) and/or a reduction in the antioxidant defense system [6]. The ROS, such as hydrogen peroxide (H2O2) and superoxide anion ($O_2^{\bullet -}$), are highly reactive molecules that can damage surrounding cellular components. Cell membranes are particularly vulnerable, especially due to their high content of polyunsaturated fatty acids, making them prime targets for lipid peroxidation [7]. This oxidative damage compromises membrane integrity and may lead to cell death. Lipid peroxides generated during this process can act as further pro-oxidants, amplifying oxidative stress and triggering the release of pro-inflammatory cytokines. This, in turn, initiates inflammatory responses that interfere with normal cellular function [8]. The antioxidant system plays a key protective role by neutralizing excess ROS and maintaining cellular homeostasis [9-12].

Sodium copper chlorophyllin (SCC) is a water-soluble compound derived from chlorophyll, consisting of sodium-copper salts. It has been utilized as a coloring agent and has demonstrated significant antimutagenic properties against various mutagens in both laboratory and live models [13]. Studies suggest its potential anticancer effects in animal trials. Additionally, SCC is commercially available for reducing body, fecal, and urinary odors in elderly individuals, as well as aiding in wound healing [14]. Its antimutagenic and anticancer capabilities are believed to stem from its ability to form complexes with mutagens and carcinogens, accelerating their elimination from the body. SCC is also a strong inhibitor of cytochrome P450 enzymes, which play a key role in activating various environmental carcinogens. By interfering with this enzymatic process, SCC helps reduce the bio-activation of harmful substances, potentially lowering the risk of carcinogenic effects [15].

The radical-scavenging ability of SCC is primarily linked to its porphyrin-based structure. Porphyrins have a central chelated metal within their molecular framework, which enables them to capture electrons. This unique structural property allows SCC and its related compounds to neutralize free radicals and inhibit metabolic activation processes, potentially reducing oxidative stress and carcinogenic effects [14].

The present study aimed to evaluate the protective effects of SCC against CP- induced hepatotoxicity in rats. Furthermore, to determine chlorophyllin's potential role in mitigating oxidative damage caused by this pesticide.

Materials and Methods

Chlorpyrifos (CP) 48% EC (Nanjing, Jiangsu,China.), sodium copper chlorophyllin (SCC) (Now Foods,395 Glen Ellyn, Rd, USA.), Chloroform (Noorbrok, England.), Formaldehyde (TEDIA company INC, USA.), Eosin and Hematoxylin (Bio path, Italy.) and Paraffin (Bio path, Italy.).

A total of thirty adult female albino rats, all sexually mature and weighing between 150 and 230 grams, were used in this study. Between November 2023 and March 2024, the animals were ethically sourced from the College of Veterinary Medical Sciences at Baghdad University and then transported to the animal facility at the College of Pharmacy, University of Basra. Prior to the start of the experiment, the rats were acclimatized for two weeks under controlled conditions. The environment was maintained with strict hygiene protocols, including the use of sterile, disposable plastic equipment, sanitized materials, and measures to minimize stress.

The animals were kept in a climate-controlled environment with air conditioning and a "12 hr. light/12 hr dark" photoperiod, The standard operating conditions often involve maintaining a temperature of twenty-five +/- five °C and moisture levels within an acceptable range. Three rats were housed in spacious plastic enclosures inside, with unrestricted access to fresh water and a consistent supply of rodent food pellets.

Thirty adult female albino rats were evenly distributed into five groups, each containing six rats. All animals were housed individually in separate cages. Body weight measurements were recorded at baseline, weekly intervals, and on the final day of the experiment (day 42), just before sacrifice.

Group 1 (Control) received distilled water (1 ml/kg body weight) orally via gavage daily. Group 2 (CP) administered CP at a dose of 6.7 mg/kg body weight (equivalent to 1/20th of the lethal dose) orally via gavage daily, following the protocol described by [16]. Group 3 (SCC) treated exclusively with SCC at a dosage of 50 mg/kg via oral gavage daily. Group 4 (CP + SCC Low Dose) received a combination of CP (6.7 mg/kg body weight) and SCC (50 mg/kg) via oral gavage daily. Group 5 (CP + SCC High Dose) administered both CP (6.7 mg/kg body weight) and a higher dose of SCC (100 mg/kg) via oral gavage daily throughout the trial.

At the conclusion of the six-week experimental period, the rats—having been fasted overnight—were euthanized. Blood samples were collected via intracardiac puncture and immediately processed. The blood was centrifuged at 855 × g for 10 minutes to separate the serum, which was then stored at –200 °C for subsequent biochemical analysis. The liver from each rat was excised for histopathological examination.

The serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), malondialdehyde (MDA), and glutathione (GSH) were measured using the enzyme-linked immunosorbent assay (ELISA) technique applied to animal serum samples.

The liver from each rat was dissected into small fragments and rinsed with distilled water to remove residual blood and debris. The samples were then fixed in 10% formaldehyde for tissue preservation. Selected fragments were dehydrated through a graded ethanol series and embedded in paraffin wax. Each embedded tissue block was sectioned into 3–4 μm thick slices using a microtome. The resulting sections were mounted onto thin glass slides and stained with hematoxylin and eosin (H&E) for histological analysis. Stained slides were examined under a light dissection microscope by a trained histopathologist, and representative images were captured using an integrated digital camera system.

Data analysis was performed using SPSS software version 26. The normality of data distribution was assessed using the Shapiro–Wilk test. Results were presented as means ± standard error of the mean (SEM).

For normally distributed data, statistical comparisons among groups were conducted using one-way analysis of variance (ANOVA). In cases where the data did not meet normal distribution criteria, the Kruskal–Wallis test was employed for non-parametric comparison. Graphical representations of the data were created using GraphPad Prism. Statistical significance was determined based on the following p-value thresholds: ****$p < 0.0001$, *$p < 0.001$, $p < 0.005$, $p < 0.05$.

Results and Discussion

Organophosphorus pesticides are among the most widely used chemicals in agriculture. Their extensive application has a profound impact on ecosystems and poses serious risks to human and animal health [17]. These compounds easily enter the human body through the food chain, as well as via direct exposure to contaminated air and dust, which often carry pesticide residues and plant particles [18, 19].

The World Health Organization (WHO) and the United Nations Environment Programme (UNEP) highlight that pesticides significantly endanger human health, whether people come into contact with them directly or indirectly. Over 26 million individuals are affected by pesticide poisoning each year, leading to nearly 220,000 deaths [20]. Beyond their typical toxic effects, pesticides like neonicotinoids and organophosphates generate free radicals and disrupt the balance between oxidants and antioxidants, even at very low exposure levels [21]. Fortunately, the human body is equipped with various defense systems—both enzymatic and nonenzymatic—that help combat the harmful effects of free radical species (FRS) and reactive oxygen species (ROS) [22].

The study found that none of the experimental groups experienced fatalities throughout the research period, and no noticeable changes in the rats' overall appearance were observed. Additionally, the rats did not exhibit any apparent signs of toxicity, such as excessive tearing or tremors. A

significant increase in body weight was recorded across all groups, except for the CP group, as illustrated in Figure 1.

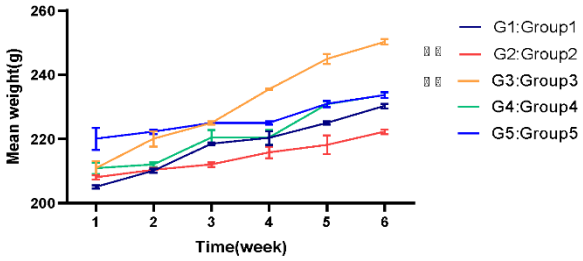
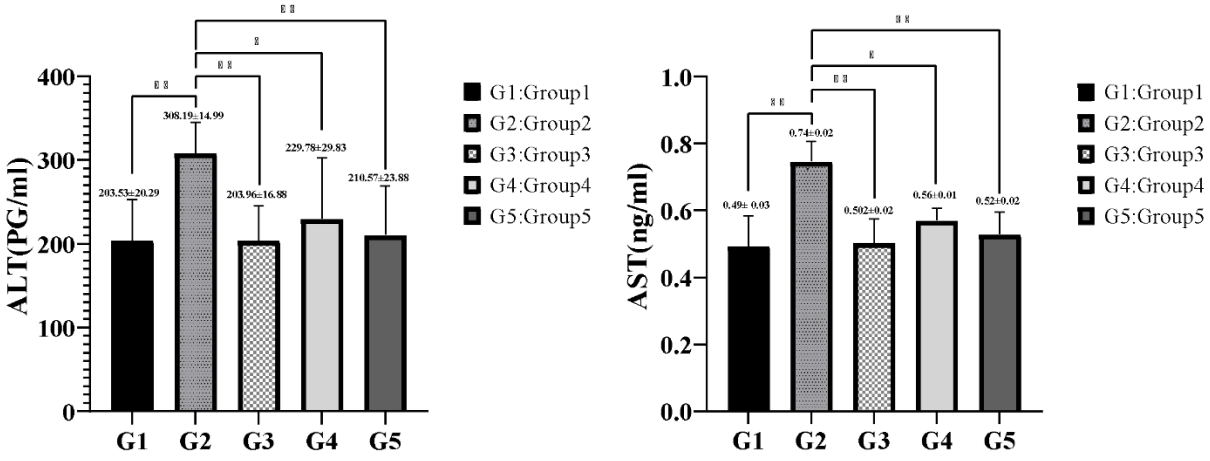


Figure (1): Differences in the rat's body- weights in the research groups. All data existing as mean±SEM. G1 (control), G2 (6.7mg/kg Chlorpyrifos (CP)), G3 (50 mg/kg Sodium copper chlorophyllin (SCC)), G4 (CP+ 50 mg/kg SCC low dose), G5 (CP+ 100 mg/kg SCC high dose)**.** P<0.05 is significant difference.

Experimental results showed a notable increase in body weight across all treatment groups, except for the group exposed to CP, which exhibited a significant reduction in weight gain—likely due to oxidative stress [23, 24].

Administration of CP at 6.7 mg/kg body weight for 42 consecutive days (group 2) led to a significant elevation in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) in female rats. In contrast, treatment with SCC alone at a dose of 50 mg/kg (group 3) did not cause any significant changes in these liver enzyme levels when compared to the control group (group 1). Moreover, co-treatment with CP and SCC at either a low dose (50 mg/kg; group 4) or a high dose (100 mg/kg; group 5) resulted in a marked reduction in serum ALT, AST, and ALP levels relative to group 2, indicating a potential protective effect of SCC against CP-induced hepatotoxicity, as illustrated in Figure 2.

The liver serves as a vital organ responsible for detoxifying harmful substances and metabolizing pesticides [25]. Exposure to pesticides may impair liver health, leading to functional issues that can be detected through alterations in biochemical markers such as ALT, AST, ALP, serum bilirubin, total protein, and albumin—all of which are key indicators used in liver function assessments [26].



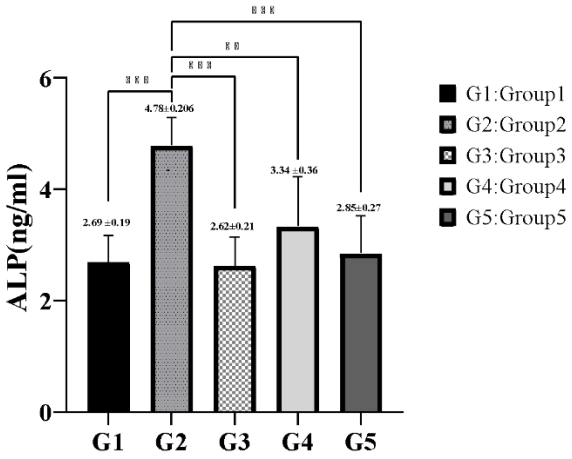


Figure (2): Effect on ALT, AST and ALP levels in different experimental groups of female rats. G1 (control), G2 (6.7mg/kg Chlorpyrifos (CP)), G3 (50 mg/kg Sodium copper chlorophyllin (SCC)), G4 (CP+ 50 mg/kg SCC low dose), G5 (CP+ 100 mg/kg SCC high dose)**.** Values are expressed as mean and SEM (****p<0.0001, ***p<0.001, ** p<0.005, * p<0.05).

Daily administration of CP (6.7 mg/kg body weight) for 42 days in group 2 led to a significant increase in serum malondialdehyde (MDA) levels, alongside a notable decrease in glutathione (GSH) concentration in female rats. In contrast, treatment with sodium copper chlorophyllin (SCC) alone at 50 mg/kg (group 3) did not produce significant changes in MDA or GSH levels compared to the control group (group 1).

However, co-administration of CP with SCC—either at a low dose (50 mg/kg; group 4) or a high dose (100 mg/kg; group 5)—resulted in a marked reduction in serum MDA levels and a corresponding elevation in GSH levels relative to the CP-only group (group 2), as demonstrated in Figure 3.

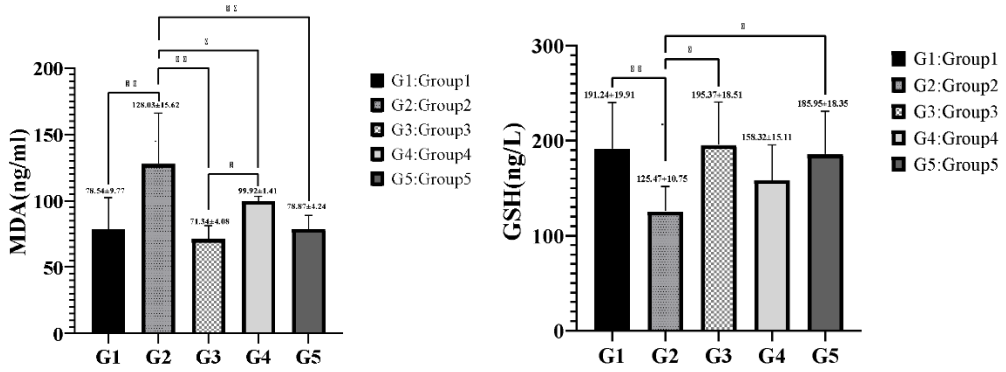


Figure (3): Effect on serum oxidative stress markers (malondialdehyde (MDA) and glutathione (GSH)) levels in different experimental groups of female rats. G1 (control), G2 (6.7mg/kg Chlorpyrifos (CP)), G3 (50 mg/kg Sodium copper chlorophyllin (SCC)), G4 (CP+ 50 mg/kg SCC low dose), G5 (CP+ 100 mg/kg SCC high dose)**.** Values are expressed as mean and SEM (****p<0.0001, ***p<0.001, ** p<0.005, * p<0.05).

Chlorpyrifos (CP) primarily triggers oxidative stress and promotes the formation of lipid peroxides, which weaken the body's antioxidant defenses and lead to programmed cell death (apoptosis) [27]. Once inside the cells, CP builds up and causes an increase in reactive oxygen species (ROS), a key driver of apoptosis [28].

Liver samples from all experimental groups were excised and examined under a light microscope. Control Group (G1): Histological analysis revealed normal hepatocyte architecture, intact central veins, and well-defined hepatic sinusoids. CP-Treated Group (G 2): Liver sections exhibited pathological alterations, including enlargement of hepatocytes with degenerative changes, pyknotic nuclei with lightly stained chromatin, loss of the classical radiating hepatic architecture, pronounced

vacuolization, and thickening with congestion of the central vein. SCC-Only Group (G3): Liver architecture appeared normal and comparable to the control group. Sections showed well-defined hepatic lobules, with cords of hepatocytes radiating from the central vein to the periphery. Hepatic plates were distinctly separated by narrow sinusoids, and hepatocytes and central veins remained unaltered. CP + Low-Dose SCC Group (G4): Hepatocytes demonstrated preserved morphology similar to the control group; however, the central vein appeared thickened and congested. CP + High-Dose SCC Group (G5): Liver sections indicated substantial histological improvement. Hepatocytes retained normal architecture, and the central vein appeared narrowed and devoid of congestion, closely resembling the structure observed in groups 1 and 3.

Administration of CP resulted in pronounced hepatic injury. Microscopic examination revealed enlarged hepatocytes, extensive vacuolation, and degenerative changes indicative of cytotoxic stress. The presence of pyknotic nuclei and chromatin condensation highlighted the onset of cellular apoptosis or necrosis. Structural disorganization, including the loss of the classical hepatic lobular architecture, along with thickened and congested central veins, confirmed CP's damaging effect on liver morphology—consistent with previous reports on organophosphate-induced oxidative stress and hepatotoxicity.

In contrast, the group treated solely with SCC (50 mg/kg) did not cause any significant changes in serum levels of ALT, AST and ALP compared to the control group in female rats. In addition, liver histology of SCC group indistinguishable from the control group, indicating that SCC itself has no adverse hepatic effects. The preservation of normal architecture, including clearly defined hepatic lobules and central veins, suggests a favorable safety profile.

Co-administration of CP (6.5 mg/kg) with SCC (50 mg/kg) showed partial hepatoprotection. While hepatocyte integrity was relatively maintained, congestion and central vein thickening persisted—implying that the lower SCC dose provided incomplete protection against CP-induced damage.

Most notably, treatment with CP (6.7 mg/kg) alongside a higher dose of SCC (100 mg/kg) led to a remarkable histological improvement. Normal hepatocyte morphology was restored, and the central vein appeared narrow and devoid of congestion. This observation highlights SCC's potential dose-dependent efficacy in mitigating CP-induced hepatotoxicity, possibly by modulating inflammatory responses and scavenging free radicals, though further mechanistic studies would be needed to confirm this hypothesis.

These findings collectively suggest that SCC may exert hepatoprotective effects against CP toxicity in a dose-dependent manner, supporting its potential as a therapeutic agent in mitigating pesticide-induced liver injury.

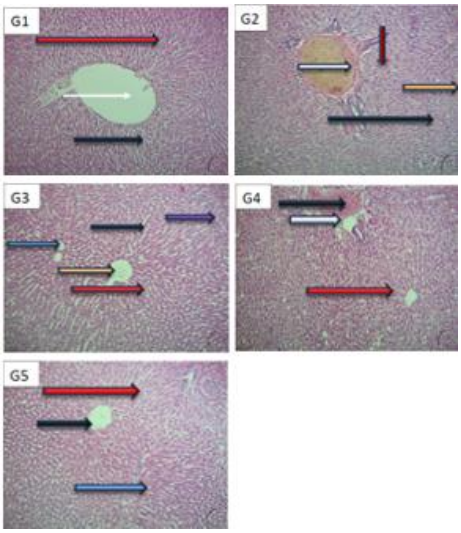


Figure (4): Light micrographic section of female rat liver (stained by the H and the E) 200X. G1 (control), G2 (6.7mg/kg Chlorpyrifos (CP)), G3 (50 mg/kg Sodium copper chlorophyllin (SCC)), G4 (CP+ 50 mg/kg SCC low dose), G5 (CP+ 100 mg/kg SCC high dose).

Conclusion

Histological findings aligned with the biochemical data. SCC demonstrates a protective role against CP-induced oxidative liver damage. Further research is warranted to validate these findings and clarify the mechanisms involved.

Disclosure Statements

Ethics approval and consent to participate

All animal procedures were conducted in compliance with the international ethical guidelines for health-related research involving humans and animals, as outlined by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). Additionally, protocols adhered to the principles set forth by the World Organisation for Animal Health (OIE). The experimental design received formal approval from the Ethics Committee of the University of Basra, College of Pharmacy (Approval No. EC71, dated 01/01/2024).

Consent for publication

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