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***RESEARCH ARTICLE***

# Protection of Exogenous Antioxidant of *Cinnamomum burmanii* as a Hepatoprotective on the Toxicological Responses of Nanoplastics in Rats (*Rattus norvegicus* L.)

**Hari Soepriandono[1], Sugiharto[1], Manikya Pramudya[1], Farah Annisa Nurbani[1], Firli Rahmah Primula Dewi[1], Lim Vuanghao[2], Aunurohim[3], Bayyinatul Muchtaromah[4], Alfiah Hayati[1]***

[1]Department of Biology, Faculty of Science and Technology, University of Airlangga, Indonesia
[2]Department of Toxicology, Advanced Medical and Dental Institute Universiti Sains Malaysia, Malaysia
[3]Department of Biology, Faculty Science and Data Analitics Institut Teknologi Sepuluh Nopember, Indonesia
[4]Department of Biology, Faculty of Science and Technology, Universitas Islam Negeri Maulana Malik Ibrahim Malang, Indonesia
*Corresponding Author E-mail: **alfiah-h@fst.unair.ac.id**

**ABSTRACT:**
Nanoplastics of polystyrene (NPs) are widely dispersed and pose a serious concern as non-biodegradable pollutants to human health. Given our unintentional exposure to toxic chemicals in everyday life, it is crucial to evaluate their toxicity and inhibition. This can be achieved by employing exogenous antioxidants sourced from natural substances. We investigated the toxicity of NPs and the protective impact of exogenous antioxidants on the liver in an animal model. Each experimental group received NPs alone (10µL/kg, for 14 days) as negative control. Three additional treatment groups were exposed to a combination of NPs (for 14 days) along with *Cinnamomum burmanii* leaf extract (CLE) at concentrations of 100, 200, and 400mg/kg for 28 days, and one control group was used as a reference. All treatments were administrated via oral gavage. The toxic effects and protection from NPs and CLE were investigated based on the levels of SGOT, SGPT, bilirubin, and ALP in the blood serum and specific changes in the liver cells of Wistar rats. The results indicated oxidative damage caused by NPs exposure accompanied by disruptions in enzymatic biochemical parameters, levels of SGPT, SGOT, and ALP, with no changes in bilirubin levels. Histological changes in the liver revealed inflammation, necrotic cells, and chromosomal condensation as signals of increased cell proliferation. The addition of CLE could mitigate the oxidative damage induced by NPs. In conclusion, overall, our comprehensive observations indicate adverse effects of NPs exposure on hepatocyte structure and function. Increased levels of SGPT, SGOT, and ALP indicate liver disturbances, although bilirubin level remains unchanged. The addition of CLE (400 mg/kg) is capable of restoring the disturbance caused by NPs.

**KEYWORDS:** *Cinnamomum burmanii*, medicine, nanoplastic, antioxidant, hepatoprotective.

## INTRODUCTION:

Based on international organizations, nanoparticles are within the range of one to 100 nm, and their toxic properties pose a global issue with potential threats to ecosystems. This is true for plastic nanoparticles, specifically polystyrene nanoparticles (NPs), originating from poorly managed plastic waste, causing ecotoxicological problems and environmental threats[1,2]. NPs result from degradation processes involving photolysis, oxidation, abrasion, hydrolysis, and long-term biodegradation. Individuals encounter nanoparticles of different sizes and varieties via inhaling

polluted air, consuming contaminated water and food, and various other routes of exposure[3,4]. Due to their very small size and diverse chemical nature, NPs easily infiltrate and accumulate in the body, affecting immune response and reproductive health[5].

The prevalence of NPs in the environment is estimated to result in the unintentional exposure of many individuals to thousands or even millions of NP particles annually. Nanoparticles entering the body may amass in different organs like the liver, lungs, intestines, and kidneys, leading to toxic damage[6,7]. Particularly concerning about the presence of NPs is their ability to penetrate cellular barriers, resulting in toxic effects on cells, tissues, organs, and organ systems[8]. Oxidative stress due to NPs is associated with the failure of tissue and organ functions, including in the immune, reproductive, and digestive systems. Histopathological changes (such as inflammation and necrosis) have been found in the digestive system and liver of animals exposed to 70 nm NPs[9,10].

The digestive system acquires energy through the use of relevant digestive enzymes, frequently employed to demonstrate biotoxicity and digestibility[11]. As of now, there is no proven pathway for the toxicity of nanoplastics on the liver of experimental animals. Nevertheless, numerous prior researches observed that the liver is among the main organs affected by substances, including nanoparticles, recognized for their toxic particles. The liver has a crucial function in digestion, metabolism, and immunity regulation[6,7,11].

Serving as a major metabolic organ, the liver regulates various metabolic pathways that connect different tissues and organs. It serves as the location for gluconeogenesis[12]. Glucose in the form of glycogen is a source of blood glucose[13]. The liver also undergoes the process of protein oxidation, providing energy. The result of protein metabolism forms amino acids, subsequently broken down into keto acids and ammonia[14]. Furthermore, the liver serves as a principal site for the metabolism of harmful chemicals. The liver's vital role involves detoxifying blood by processing various waste products in hemoglobin[15]. The liver synthesizes and secretes several types of enzymes for optimal regulation, including serum glutamic oxaloacetic transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT), as well as alkaline phosphatase (ALP)[16]. Exposure to NPs is suspected to trigger alterations in liver metabolism pathways, key metabolic enzymes, and enzymes stimulated by oxidative stress[17].

Natural resources have some potential medicinal value[18]. Research using herbal drugs is now broadly recognized[19]. Antioxidants, such as those found in the plant *Cinnamomum burmanii*, can neutralize oxidants from toxic substances, including NPs[20]. Compared to syntetic compound, previous studies using *Clitoria ternatea*[21], *Mimosa pudica*[22], *Odina woodier*[23], *Strobilanthes asperrimus*[24], *Cucurbita maxima*[25], and *Begonia versicolor*[26] reported that consumption of antioxidant from plant is less toxic and can avoid occurrence of chronic disease. These compounds work by accepting or donating electrons to eliminate the conditions of unpaired radicals[27]. One natural substance containing antioxidants is the plant *Cinnamomum burmanii* which is primarily found in Asia and Indonesia[28,29]. This plant contains flavonoid, cinnamaldehyde, etc. a source of antioxidants that can repair cell and tissue damage caused by toxic substances[30]. *C. burmannii* leaves demonstrate strong antioxidant properties (IC50=93.447ppm)[31]. Consequently, our hypothesis posits that exposure to nanoparticles will disturb liver health and function. In this research, a thorough assessment was conducted on the impact of nanoparticles and the potential extract on enzymatic biochemistry related to liver function, along with histopathological changes in the liver. These findings provide a new perspective on the biological consequences of nanoparticle exposure and the potential of *C. burmanii* in reinstating enzymatic biochemistry in hepatocytes.

## MATERIALS AND METHODS:

### Materials:

All procedures conducted in this study received approval from the Ethical Clearance Commission, Faculty of Dental Medicine, Universitas Airlangga, Indonesia (approval number 381/HRECC.FODM/IV/2023). This research utilized male *Rattus norvegicus* (Albino rats), Wistar strain, weighing 200-220grams (Faculty of Pharmacy, Universitas Airlangga, Indonesia). The rats were maintained in standard controlled conditions (temperature of 25±2°C, with a 12/12 light-dark cycle) and had unrestricted access to standard rat food and drinking water.

Preparation of *C. burmannii* leaves extract (CLE). Leaves of *C. burmanii* were collected from the Purwodadi Botanical Garden in Pasuruan, Indonesia. They were air-dried until reaching a constant weight, subsequently cut into small pieces, and finely powdered using a mixer grinder. 500
grams of *C. burmanii* powder was macerated in 1500mL of absolute ethanol (Merck) for 48 hours. Subsequently, it underwent further drying through freeze-drying and was stored at 4°C until future use[32]. The extract was re-suspended in distilled water daily during administration to experimental animals.

**Study design and experimental procedure:**
After two weeks of acclimatization, rats were randomly divided into five groups: one control group, one negative control group, and three treatment groups with varying concentrations of CLE. The exposure to NPs (100nm, Sigma Aldrich) was carried out at a dose of 10µL/kg for 14 days in this study. The selection of NPs concentration was according to our previous research and literature data[5,33]. Subsequently, the selected concentrations of CLE for treatment were 100, 200, and 400mg/kg BW,[34] administered for 28 days after the completion of NPs exposure. The treatment for all animals was conducted via oral gavage with a volume of 0.5mL/kg BW. Animals were sacrificed after the completion of treatment under light anesthesia.

**Measurement of SGOT, SGPT, ALP and Bilirubin Levels:**
To evaluate liver function impairment, the levels of SGOT, SGPT, ALP, and bilirubin in rat serum were examined. For serum samples, whole blood was collected in serum separation tubes, allowed to stand for 30 minutes, and then serum was separated by centrifugation (5–10 minutes, 3000rpm). Total serum SGOT, SGPT, ALP, and bilirubin were measured on the Horiba Pentra C200 autoanalyzer (Clinical Chemistry Analyzer, France).

**Histopathological Analysis:**
Histological processing involved fixing rat liver tissues in 10% Neutral Buffered Formalin (NBF) to preserve the tissues. Subsequently, microscopic examination was conducted on 5 µm tissue sections embedded in paraffin. Tissue sections were stained using the Haematoxylin and Eosin (HE). Each section was scrutinized under a light microscope.

**Data analysis:**
Significant differences between various groups of all animals were determined using one-way analysis of variance (ANOVA), with each test conducted at a probability level of 0.05%. The statistical analysis was performed using the Windows Statistical Package for the Social Sciences software v.24 (IBM Corp., New York, USA).

## RESULT:

**Analysis of SGOT, SGOT, ALT, and Bilirubin Levels:**
The determination of SGOT and SGPT levels in the serum serves as a good indicator of liver function manifestation. In this study, the biochemical parameters SGOT and SGPT ($p < 0.05$) showed that NPs exposure significantly increased SGOT levels (41±0.58 IU/L) compared to the control group (38.4±0.49 IU/L). However, the addition of CLE was able to reduce SGOT levels. The higher the concentration of CLE (100, 200, and 400mg/kg), the more significant the decrease in SGOT levels compared to the negative control (Figure 1).

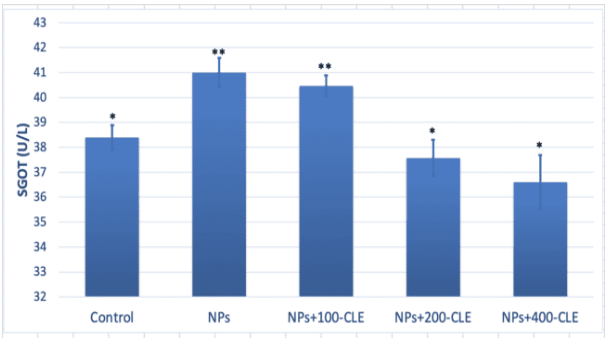


**Figure 1. SGOT levels in rats after NPs exposure and recovery process with various concentrations of CLE**

Similar trends were observed in the measurement of SGPT levels. NPs exposure significantly increased SGPT levels (17.98±0.46 IU/L) compared to the normal control (15.66±0.4 IU/L), indicating that NPs exposure can disrupt normal liver function. The administration of CLE was able to reduce or restore SGPT levels to those in the normal control, sequentially from low to high CLE concentrations (Figure 2).

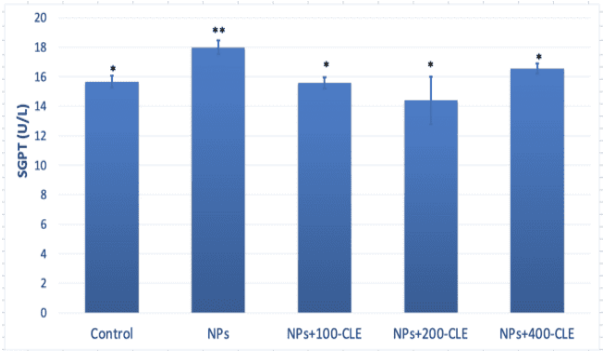


**Figure 2. SGPT levels in rats after NPs exposure and recovery process with various concentrations of CLE**

ALP enzyme functions in converting proteins into energy for liver cells. When liver cells are disrupted, ALP is released into the bloodstream, resulting in increased levels. This also occurred in this study, where ALP levels increased after NPs exposure. The level of 87.54 IU/L was higher than the level of 80.32 IU/L in the normal control. While the administration of CLE at 100mg/kg did not result in a reduction of ALP levels, there was a significant decrease when the CLE concentration was increased to 200 and 400mg/kg (Figure 3).

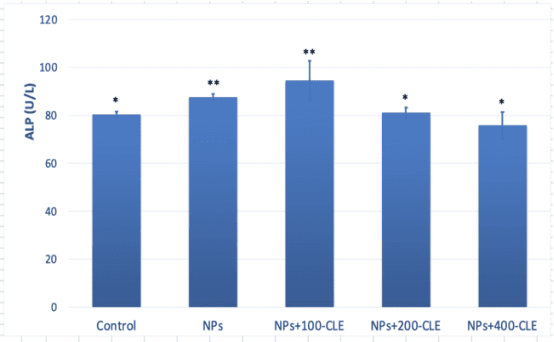


**Figure 3. ALP Levels in rats after NPs exposure and recovery process with various concentrations of CLE**

Increased bilirubin levels indicate liver disturbances. However, in this study, there were no significant (P>0.05) changes in bilirubin levels in both the control (0.772mg/dL) and all combination of NPs with CLE treatment groups, respectively (0.770; 0.758; 0.742; and 0.704mg/dL). This suggests that NPs exposure did not alter blood bilirubin levels (Figure 4).

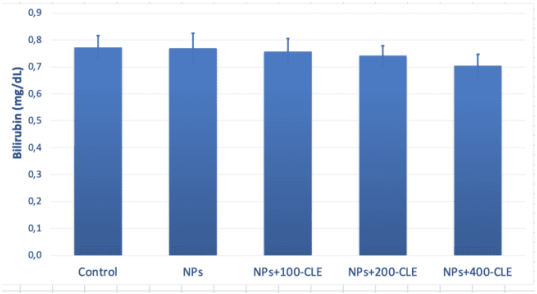


**Figure 4. Bilirubin levels in rats after NPs exposure and recovery process with various concentrations of CLE**

## Histopathological Analysis:

Administration of NPs alone led to changes in the cell and tissue structure of male Wistar rat livers compared to the control group, indicating toxic effects. Hepatocytes were arranged neatly, with large round nuclei, clear nucleoli, and peripheral chromatin distribution. Some cells had two nuclei each (Figure 5.A). NPs exposure caused changes in liver structure, with a large number of Kupffer cells observed in the sinusoid walls. Sinusoids experienced inflammation, indicating infiltration of erythrocytes and mononuclear cells around the sinusoids, hepatocyte degeneration, focal necrosis, and chromosomal condensation in early hepatocyte mitosis (Figure 5.B). Treatment with CLE at 100 and 200 mg/kg still showed symptoms similar to the negative control, including sinusoid dilation, hepatocyte degeneration, necrosis, erythrocyte infiltration, etc. (Figure 5.C, 5.D). The addition of CLE at a concentration of 400 mg/kg showed recovery of hepatocyte structure similar to the control, with normal sinusoids containing many Kupffer cells and dominant normal hepatocytes (Figure 5.E).

Observations of the portal vein in the control group revealed the structure of endothelial cells lining the portal vein, supporting its function in carrying blood from most of the digestive tract. The blood then passed through healthy hepatocytes with centrally located nuclei through the hepatic sinusoids and drained into the central vein (Figure 6.A). Exposure to nanoparticles resulted in alterations in the hepatic portal vein structure, leading to necrosis in certain hepatocytes and infiltration of leukocytes around the hepatic portal vein, hepatic artery, and bile duct (Figure 6.B). As the concentration of CLE administered increased, the inflammation or leukocyte infiltration decreased. This was evident in cross-sections of rat livers given 100, 200, and 400 mg/kg CLE, where leukocyte infiltration was less compared to the group exposed to NPs (negative control) (Figure 6.C, 6.D, 6.E)..

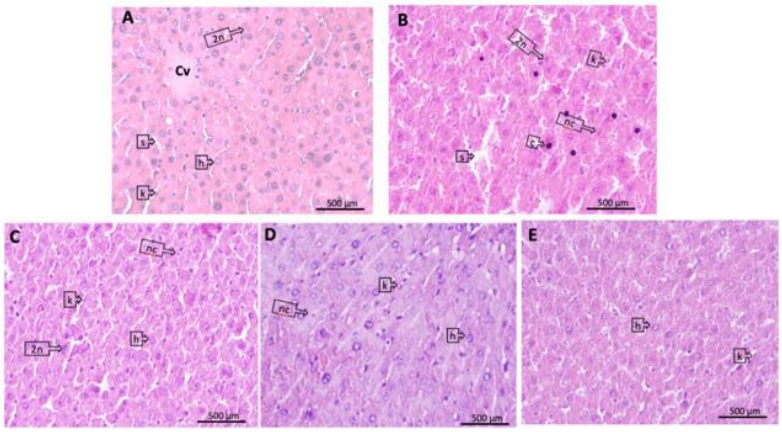


**Figure 5. Rat Liver Sections. (A) Control group showing normal liver architecture, (B) Rats exposed to NPs (14 days), showing inflammation, (C, D, E) Rats exposed to NPs (14 days) followed by various concentrations of CLE (100, 200, and 400 mg/kg, for 21 days). Central vein (CV), hepatocytes (h), sinusoid (s), Kupffer cells (k), chromosomal condensation (c), nucleus (n), a cell with two nuclei (2n), necrosis (nc) (H&E ×400).**

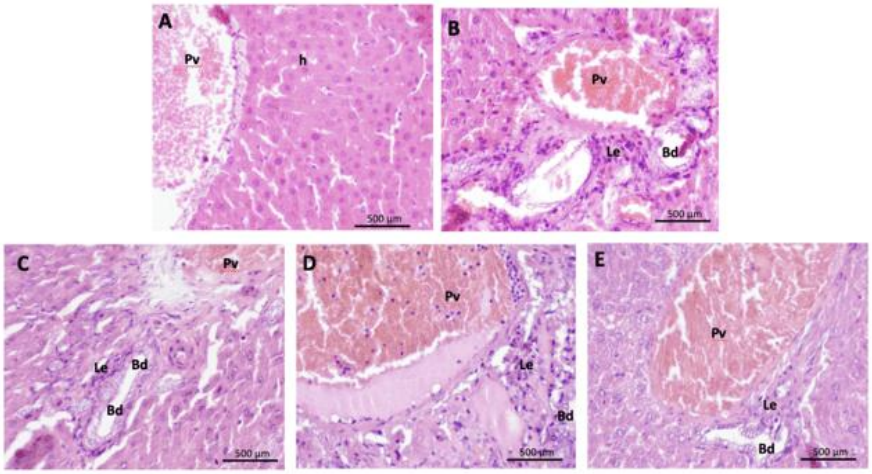


**Figure 6. Section of the hepatic portal vein in rats. (A) The control group shows a normal hepatic portal architecture. (B) Rats exposed to NPs (14 days) exhibit inflammation. (C, D, E) Rats exposed to NPs (14 days) followed by varying concentrations of CLE (100, 200, and 400 mg/kg, for 21 days). Portal vein (Pv), hepatocytes (h), bile duct (Bd), leucocyte (Le) (H&E ×400)**

## DISCUSSION:

Our findings offer evidence of the detrimental impact of NPs on liver function, demonstrated by elevated levels of SGOT, SGPT, and ALP in the serum. SGOT and SGPT, found in hepatocyte cytoplasm, are used as diagnostic biomarkers for liver disorders. These enzymes cause specific chemical changes in the body. Damage to the liver results in the release of these enzymes into the bloodstream[35].

Although the formation of NPs from plastic waste has been demonstrated, there is limited understanding regarding the negative impacts of these plastic particles on organisms at the subcellular or molecular levels. NPs can efficiently translocate across cell membranes[36]. These materials can dissolve in the hydrophobic lipid bilayer core, forming single-chain polymer networks that break down. Alterations in the structure and dynamics of the bilayer disrupt crucial functions of the cell membrane, ultimately resulting in cell death[37]. When NPs enter hepatocytes, they can accumulate, causing increased cell pressure by inducing higher levels of reactive oxygen species (ROS). The presence of high ROS in cells alters normal enzymatic function. Increased ROS by NPs can enhance cytotoxicity and induce apoptosis mediated by endoplasmic reticulum (ER) stress in cells[38].

The biochemical cytotoxicity mechanism for SGPT and SGOT levels occurs when hepatocytes are damaged, and SGPT and SGOT enzymes are released into the bloodstream. Therefore, increased levels of SGPT and SGOT indicate hepatocyte dysfunction. Additionally, toxic NPs can cause inflammation and oxidative stress in liver cells, activating NF-κB signalling pathways or Reactive oxygen species (ROS) can stimulate the transcription of genes associated with inflammatory and oxidative stress responses. This may include genes encoding SGPT and SGOT enzymes. Inflammation and oxidative stress responses induced by NPs can produce free radicals and reactive oxygen molecules that damage hepatocyte structures. Similarly, ALP, an enzyme found in high amounts in the liver, is used to assess hepatocellular and hepatobiliary abnormalities. In this study, an increase in ALP levels occurred after NPs exposure. This increase is caused by hepatocyte injury, which can lead to liver diseases (hepatitis or cirrhosis)[39]. Bilirubin levels, as a good indicator of the absence of pathological manifestations of liver function, showed that NPs did not significantly affect this enzyme.

In the observation of liver histology, it is evident that there is a change in liver structure due to NPs exposure (Figure 5.B). Structural changes show hepatocytes undergoing necrosis, swelling, and many hepatocytes undergoing chromosomal condensation. The presence of chromosomal condensation indicates the beginning of mitosis[40]. This is different from the control group (Figure 5.A). However, in vivo administration of CLE caused hepatoprotective activity against NPs toxicity. Hepatocyte enzyme levels returned to normal, as in the control group. In other studies, *Cinnamomum burmanii* exhibited antibacterial, anti-inflammatory, and antioxidant activity[41]. CLE, containing flavonoids, saponins, tannins, polyphenols, flavonoids, quinones, triterpenoids, and cinnamaldehyde, acts as an antioxidant[42]. These compounds contribute to the body's protection from oxidative damage caused by free radicals. The antioxidant contained in *Cinnamomum* may delays or inhibits oxidative damage to a target molecule[43]. Previous study using *Cinnamomum malabatrum* also showed its potention against acute inflammation[44].

## CONCLUSION:

NPs exposure produces adverse effects on hepatocyte structure and function. Levels of SGPT, SGOT, and ALP increase, indicating liver disturbances, although bilirubin levels remain unchanged. The addition of CLE (400mg/kg) can restore the disturbances caused by NPs.

## CONFLICT OF INTEREST:

The authors declare that they do not have any conflict of interests.

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