

RESEARCH ARTICLE

***Cinnamomum burmanii* Leaf Extract Potential on Hematological
Assessment of Rats Exposed to Polystyrene Nanoplastics**

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ABSTRACT:

The growth of the plastic industry alongside inadequate management of plastic waste has resulted in plastic pollution. Nanoplastic particles can be toxic and induce oxidative stress. This research explored the ability of *Cinnamomum burmanii* leaf extract to mitigate hematological alterations induced by exposure to low-dose nanoplastics polystyrene (NPs) in male albino rats. Normal control and negative control groups were administered with aquadest and NPs solution (10µL/kg) for 14 days respectively, followed by aquadest for the next 21 days. Groups 3, 4, and 5 received a combined treatment of NPs for 14 days and extract for 21 days (100, 200, and 400mg/kg). Each group consists of five rats. Animal treatments were administered through oral gavage. Then, the hematological parameters were analyzed. The results revealed that exposure to NPs caused a significant elevation in lymphocyte counts and a decrease in monocytes, red blood cells (RBC), hemoglobin (Hb), and hematocrit (Ct). Nevertheless, there was no significant impact observed on white blood cells (WBC), granulocytes, or platelet counts. Within the groups treated with *Cinnamomum burmanii* leaf extract, a reduction in lymphocyte and WBC counts was observed, alongside an increase in monocyte counts. However, there was no significant increase noted in red RBC, Hb, Ct, or platelet counts. *Cinnamomum burmanii* leaf extract may hold promise in improving the hemodynamic profile in bodies exposed to NPs.

KEYWORDS: *Cinnamomum burmanii*, Hematology, Immunology, Nanoplastics, Rat.

INTRODUCTION:

Plastic industry expansion alongside inadequate management of plastic waste has resulted in plastic pollution. In everyday life, plastic materials find extensive use owing to their cost-effectiveness, lightness, practicality, strength, and flexibility¹.

Although plastic is known to have relatively strong durability, Exposure to UV radiation, high temperature and environmental pressure can cause it to break down into smaller fragments². Nanoplastics are materials characterized by dimensions within the nano-scale, encompassing both their external measurements and any internal or surface structures falling within the range of 0.001 to 0.1µm^{3,4,5}. Microplastic particles have the potential to disintegrate into billions of nanoplastic particles, signifying that the pollution of nanoplastics can become prevalent globally^{6,7}. Nanoplastics pose a greater potential for harm compared to microplastics due to their ability to penetrate biological membranes, given their smaller size.

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Nanoplastics particles are generated during the process of fragmentation of microplastic fragments and can also originate from engineered materials used, for example, in industrial processes. Additionally, NPs can potentially come from sources other than the food itself, such as processing aids, water, air, equipment, and textiles. The effects of other processes, such as cooking or baking, may also contribute to the formation of NPs⁸.

When present in the body, nanoplastic particles can be toxic and stimulate oxidative stress⁹. NPs tiny size allows them to enter the human food chain through various means, including inhalation, consumption of beverages, and eating animals from their natural environment, potentially causing health disturbances^{10,11}. Additionally, NPs can be penetrated through contamination during food production processes, food washing, and the packaging of beverages in plastic materials. Moreover, NPs can also be indirectly consumed through personal care products such as toothpaste, lip balm, or other cosmetics⁹.

Nanoplastic particles can enter cells through various mechanisms. They can enter cells through endocytosis events¹², penetrate with the help of energy into the cytoplasm, leading to increased cellular cytolytic activity¹³, or particles with a size <50 nm can pass through epithelial cells in vitro through paracellular routes⁸.

Numerous studies have shown that exposure to nanoplastics can elevate reactive oxygen species levels, leading to the activation of subsequent signaling pathways that initiate complex molecular cascades, potentially culminating in oxidative damage heightened by inflammation and cellular demise^{14,15,16}. Thus, NPs pollutants pose significant health risks to exposed individuals. Solutions need to be sought to address this problem, including suppressing free radical reactions using antioxidants.

Numerous plants have been recognized for their abundance of antioxidant compounds, including polyphenols, vitamins, flavonoids, and carotenoids. These compounds serve to combat and prevent the onset of chronic diseases. Research using herbal drugs is now broadly recognized¹⁷. Antioxidants can neutralize oxidants from toxic substances, including NPs¹⁸. Compared to synthetic compound, previous studies using *Clitoria ternatea*¹⁹, *Mimosa pudica*²⁰, *Odina woodier*²¹, *Strobilanthes asperimus*²², *Cucurbita maxima*²³, and *Begonia versicolor*²⁴. One of the plants that contains many antioxidants is *Cinnamomum burmanii*²⁵. *C. burmanii* contains polyphenol and cinnamaldehyde components. Both of these components serve as anti-inflammatory agents and prevent apoptosis^{26,27}.

Additionally, *C. burmanii* also contains trans-cinnamaldehyde, eugenol, essential oils, phenolics, and flavonoids that can suppress oxidative stress.

However, there is still limited information about the impact of *C. burmanii* on physiology of rats exposed to nanoplastics. Hence, this research was performed to investigate the capability of *C. burmanii* extract in the hematological parameters of rats after nanoplastic exposure.

MATERIALS AND METHODS:

The Animals:

All experimental protocols were authorized by the Faculty of Dental Medicine (Ethical Clearance Commission) at Universitas Airlangga, Indonesia (ethical clearance number 381/HRECC.FODM/IV/2023). Male Wistar rats (200-220 g) were procured from the Faculty of Pharmacy at Universitas Airlangga in Surabaya, Indonesia. These rats were placed under standardized controlled conditions (room temperature, balanced light-dark cycle). They were given free access to both rat food and water for the entirety of the experimental period.

Preparation of *C. burmanii* extract:

Leaves of the *Cinnamomum burmanii* plant were obtained from the Purwodadi Botanical Garden (Pasuruan, Indonesia). The leaves of the plant were left to air-dry at room temperature until they reached a consistent weight. Once dried, they were ground into a powder. Dried leaf material (500grams) was soaked in 1500mL of 96% ethanol for 48 hours. The resultant mixture was subsequently and subjected to evaporation (temperature of water bath maintained at 60-70°C). Afterward, the extract underwent further drying using freeze-drying, following the method described by Ugwah-Oguejiofor et al. (2019)²⁸. Before being administered to the experimental animals, the extract was reconstituted in distilled water daily.

Study design and experimental procedure:

Following a two-week acclimation period, five distinct treatment groups were established, including a normal control group, a negative control group, and three treatment groups receiving different doses of *Cinnamomum burmanii* extrac. Polystyrene nanoplastics (100nm, Sigma Aldrich) were used in this research. The NPs doses were selected based on our prior research findings and literature data^{29,30}. The administration of animal treatments was carried out through oral gavage, with a dosage of 0.5mL/kg BW. The animals were sacrificed after the treatment.

Preparation and hematological analysis:

Blood samples (1–1.5mL) were collected by heart puncture for hematological parameter analysis.

Hematological parameters were measured within a maximum of 3 hours after blood collection. White blood cells ($10^3/\text{mm}^3$), lymphocytes (%), monocytes (%), granulocytes (%), red blood cells ($10^6/\text{mm}^3$), hemoglobin (g/dL), hematocrit (%), thrombocytes ($10^3/\text{mm}^3$) were calculated using Coulter counters (CELL DYN 1700).

Data analysis:

Statistical analysis was carried out using a two-way analysis of variance (ANOVA) with a significance level set at 0.05%. This study used Statistical Package for the Social Sciences software 13 (IBM Corps, New York, USA).

RESULT:

Number of White Blood Cells:

As depicted in Figure 1, the white blood cell count had an insignificant difference between the normal control and negative control groups after NPs administration ($P > 0.05$). Conversely, a notable reduction in the white blood cell count was evident after the administration of 200 and 400mg/kg BW of *C. burmanii*.

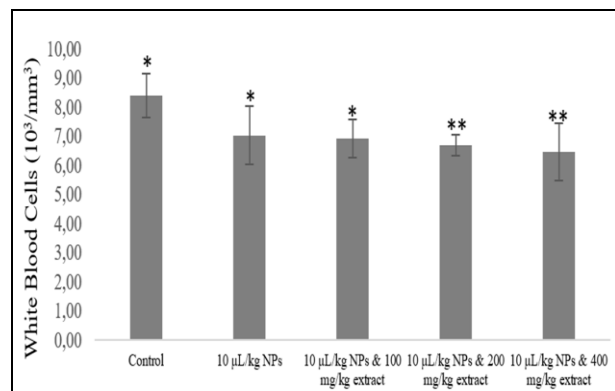


Figure 1. White blood cells ($10^3/\text{mm}^3$) post-exposure to NPs and administration of *C. burmanii* extract. Each bar represents the means $\pm$ standard deviation ($n = 5$). In comparison to both the normal control and negative control groups, the significance level** $p < 0.05$ was observed.

Percentage of Lymphocytes, Monocytes, and Granulocytes:

A significant difference in the percentage of lymphocytes ($P < 0.05$) was observed in both the negative control group and Group 1 (100mg/kg BW of *C. burmanii*). Exposure to NPs led to a decrease in the lymphocyte percentage in Groups 2 and 3 (200 and 400 mg/kg BW of *C. burmanii* respectively) as shown in Figure 2A. Figure 2B indicates that Group 2 experienced a significant decrease in monocyte percentage following NPs exposure. The administration of *C. burmanii* extract at all concentrations significantly restored the monocyte percentage. However, there was no significant difference observed in the percentage of granulocytes across all groups, as depicted in Figure 2C.

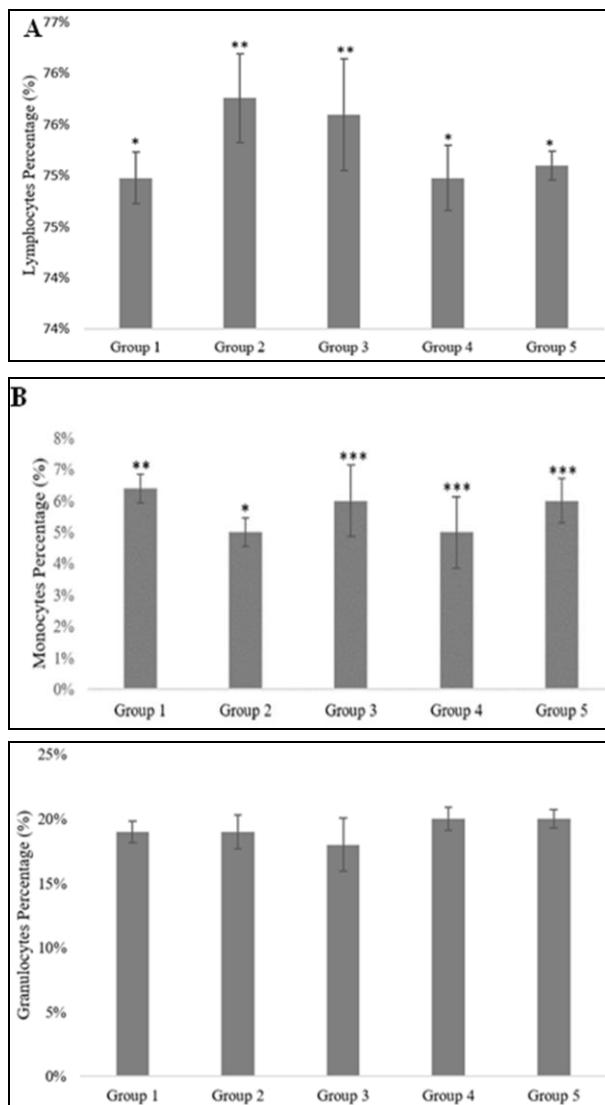


Figure 2. Lymphocytes percentage (A); Monocytes percentage (B); Granulocytes (C) after NPs exposure and administration of *C. burmanii* extract. Each bar represents the means $\pm$ standard deviation ($n = 5$). In comparison to both the normal control and negative control groups, the significance level ** $p < 0.05$ was observed.

Number of Red Blood Cells, Hemoglobin Concentration, and Percentage of Hematocrite:

Figure 3 indicates that exposure to nanoparticles (NPs) influenced the red blood cell number. The negative control group exposed to NPs displayed a significant difference in red blood cell count ($P < 0.05$). In comparison to the normal control group, all groups receiving *C. burmanii* administration exhibited a significant decrease in red blood cell count ($P < 0.05$). Notably, the administration of *C. burmanii* did not result in the restoration of red blood cell counts.

Regarding hemoglobin concentration, the negative control group (exposed to NPs) demonstrated a significant decrease in hemoglobin levels ($P < 0.05$).

Conversely, the group receiving *C. burmanii* administration showed no significant difference, as depicted in Figure 4.

NPs exposure also impacted the percentage of hematocrit, which notably decreased in all treatment groups ($P < 0.05$). However, the administration of 100, 200, and 400 mg/kg body weight of *C. burmanii* extract did not restore the percentage of hematocrit, as shown in Figure 5.

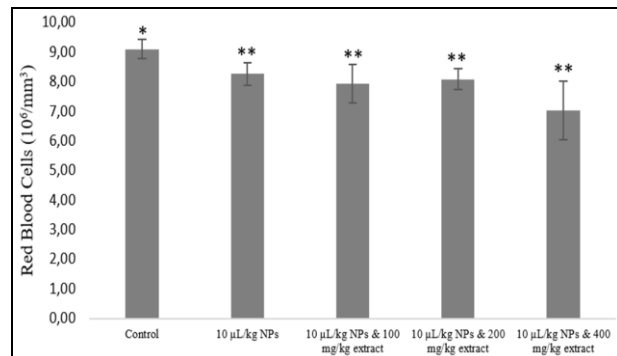


Figure 3. Number of red blood cells ($10^6/\text{mm}^3$) after NPs exposure and administration of *C. burmanii* extract. Each bar represents the means $\pm$ standard deviation ($n = 5$). In comparison to both the normal control and negative control groups, the significance level ** $p < 0.05$ was observed.

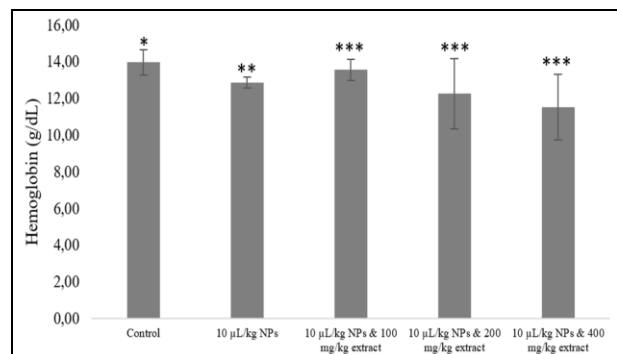


Figure 4. Hemoglobin concentration (g/dL) after NPs exposure and administration of *C. burmanii* extract. Each bar represents the means $\pm$ standard deviation ($n = 5$). In comparison to both the normal control and negative control groups, the significance level ** $p < 0.05$ was observed.

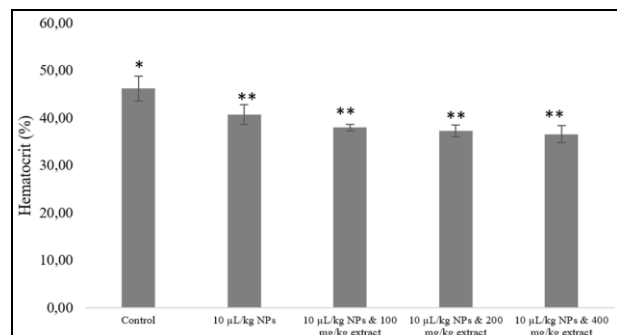


Figure 5. Hemoglobin concentration (g/dL) after NPs exposure and administration of *C. burmanii* extract. Each bar represents the means $\pm$ standard deviation ($n=5$). In comparison to both the normal control and negative control groups, the significance level ** $p < 0.05$ was observed.

Number of Thrombocytes:

Exposure to nanoparticles (NPs) resulted in a decrease in thrombocyte count. The negative control group showed a statistically significant distinction ($P < 0.05$). Administration of *C. burmanii* did not show a significant difference in increasing thrombocyte count, as depicted in Figure 6.

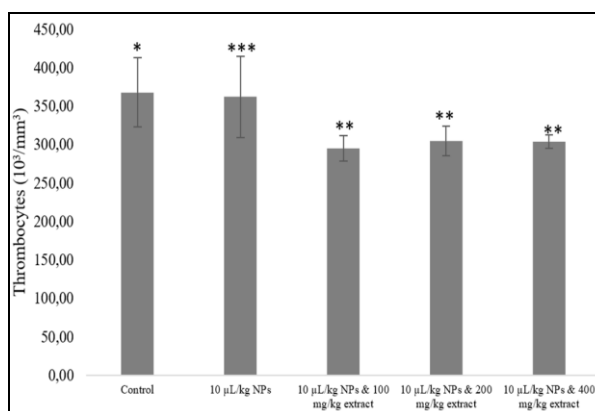


Figure 6. Number of thrombocytes ($10^3/\text{mm}^3$) after NPs exposure and administration of *C. burmanii* extract. Each bar represents the means $\pm$ standard deviation ($n = 5$). In comparison to both the normal control and negative control groups, the significance level ** $p < 0.05$ was observed.

DISCUSSION:

Polystyrene nanoplastics (NPs) have been extensively found in aquatic environments and food webs., indicating that their toxic effects have potentially spread extensively³¹. In the human inhabited environment, airborne nanoparticles (NPs) ranging in size from 6 to 562 nm present health risks to humans owing to their nanotoxicological characteristics, allowing them to traverse biological barriers. Additional research has indicated that NPs within living organisms are excreted only at minimal concentrations, with the remainder potentially accumulating in the body, penetrating the bloodstream, and adversely affecting blood cells^{31,32}. This is evident from research data showing that the oxidative stress of NPs can impact the health of blood cells. Nanoparticles (NPs) exert a suppressive influence on red blood cells (RBCs) through disruptions in lipid membrane composition, leading to damage and death of RBCs, subsequently affecting hemoglobin (Hb) and hematocrit (Ct) levels. The presence of oxidative stress induced by NPs leads to an imbalance between oxidant and antioxidant systems within cells. This condition triggers a series of reactions that damage lipid membranes, proteins, and DNA, contributing to the death of red blood cells, thus affecting RBCs³³. This situation indicates that NPs capable of crossing the blood vessel barrier can lead to pathophysiological events in blood cells.

The buildup of nanoparticles (NPs) within the body results in oxidative stress, which disturbs the dynamic equilibrium by elevating ROS levels. The increased toxicity of NPs, which elevates ROS levels, leads to lipid peroxidation, making them more biologically reactive and increasing intracellular permeability and membrane damage in red blood cells³⁴. Decreasing number of blood cells is likely attributed to physical damage to the cell membranes, which occurs as a result of nanoplastic particle aggregation at elevated concentrations and the adhesion of red blood cells to endothelial surfaces³⁵.

Some studies have also found that exposure to free radicals (ROS) in red blood cells causes membrane stretching and greatly reduces its mechanical stability, which can affect its function and alter its ability to transport oxygen effectively. The impacts of plastic particle pollution, encompassing nanoplastics and microplastics, can permeate various biological barriers and directly engage with lipid membranes. These membranes represent the final protective shield for cells against their external surroundings. Plastic particles can attach to lipid membranes, resulting in a considerable expansion of the lipid bilayer. This mechanical stretching of cell membranes has the potential to cause serious cell dysfunction³⁶. Exposure to smaller nanoparticles (NPs) can actively engage with cellular systems, hindering cell metabolism, which in turn leads to cytotoxicity in blood cells and has repercussions for health³⁷.

For examining red blood cells (RBCs), this study also observed the cytotoxic impact of nanoparticles (NPs) on the leukocyte population, encompassing lymphocytes, monocytes, and granulocytes in the blood of rats. The research results showed an increase in the number of lymphocytes. This increase is believed to be caused by NPs exposure inducing increased secretion of proinflammatory and anti-inflammatory cytokines and enhancing lymphocyte proliferation³⁸. but this did not affect the number of monocytes and granulocytes. In this study, the number of monocytes and granulocytes was not influenced by NPs exposure.

On the other hand, there have been many efforts to reduce the toxicity of NPs by adding exogenous antioxidants. The extract of *Cinnamomum burmannii* leaves contains compounds such as saponins, tannins, triterpenoids, and flavonoids, which are antioxidant compounds³⁹. These compounds is expected to reduce or inhibit cell damage and death caused by NPs exposure. During immune surveillance, the host provides defense versus foreign antigens⁴⁰. Lymphocytes and leukocytes play a role in neutralizing toxins, after the administration of the extract, except for an increase in the number of

monocytes. However, in this research, *Cinnamomum burmannii*'s antioxidant activity appears to be relatively weaker in neutralizing oxidative stress caused by NPs, resulting in less clear effects on the number of red blood cells, Hb, and Ct. This could be due to the possibility that the antioxidant content in the leaves is smaller compared to the extract from the bark of *Cinnamomum burmannii*, as stated by (Sirait et al., 2023)⁴¹, which indicates that cinnamon bark (*Cinnamomum burmannii*) has very strong antioxidant activity. In other studies, *Cinnamomum burmannii* exhibited antibacterial, anti-inflammatory, and antioxidant activity⁴².

CONCLUSION:

Ethanol extract of *C. burmannii* leaves exhibits pharmacological effects as a hematoprotector. The mechanism of antioxidant action occurs by suppressing the formation of oxidative stress. However, this study has not provided optimal information regarding the potential of *C. burmannii* leaf extract as a hematoprotector.

CONFLICT OF INTEREST:

The authors affirm that they do not have any conflicts of interest.

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