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Anticancer Activity of Ethanol Extract of *Begonia medicinalis* on Colorectal Cancer Rat Model Induced With 7,12-Dimethylbenz[A]Anthracene

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ABSTRACT

Colorectal cancer remains one of the leading causes of cancer-related deaths after lung cancer, highlighting the urgent need for more effective therapies with minimal side effects. *Begonia medicinalis* has been reported to have potential anticancer properties. This study aimed to evaluate the anticancer activity of *Begonia medicinalis* extract by assessing neutrophil concentration in a 7,12-dimethylbenz[a]anthracene (DMBA)-induced colorectal cancer rat model. The research employed a laboratory-based experimental approach with a post-test-only group design, comprising five groups with five replications each: treatment group I receiving a 25 mg/kg body weight, treatment group II receiving a 50 mg/kg body weight, treatment group III receiving a 100 mg/kg body weight, an normal group that was not DMBA-induced and did not receive therapy, and a negative control group that was DMBA-induced but did not receive therapy. The results of this study demonstrate that *Begonia medicinalis* extract effectively suppresses neutrophil concentration in a DMBA-induced colorectal cancer rat model. Treatment with 50 mg/kg body weight and 100 mg/kg body weight doses successfully reduced neutrophil cell levels in the experimental subjects, with the best results seen at the 100 mg/kg body weight dosage. This study provides new insights into the effects of plant-based therapies, *Begonia medicinalis* extract, in modulating the immune system by suppressing neutrophil concentration in a colorectal cancer rat model.

Key Messages:

- This study highlights *Begonia medicinalis* as a promising natural compound with anticancer potential, specifically in reducing neutrophil concentration in colorectal cancer, a novel approach not widely explored in current oncology treatments.
- The findings provide a strong foundation for further pharmacological and mechanistic studies, supporting the development of complementary therapeutic agent for colorectal cancer.

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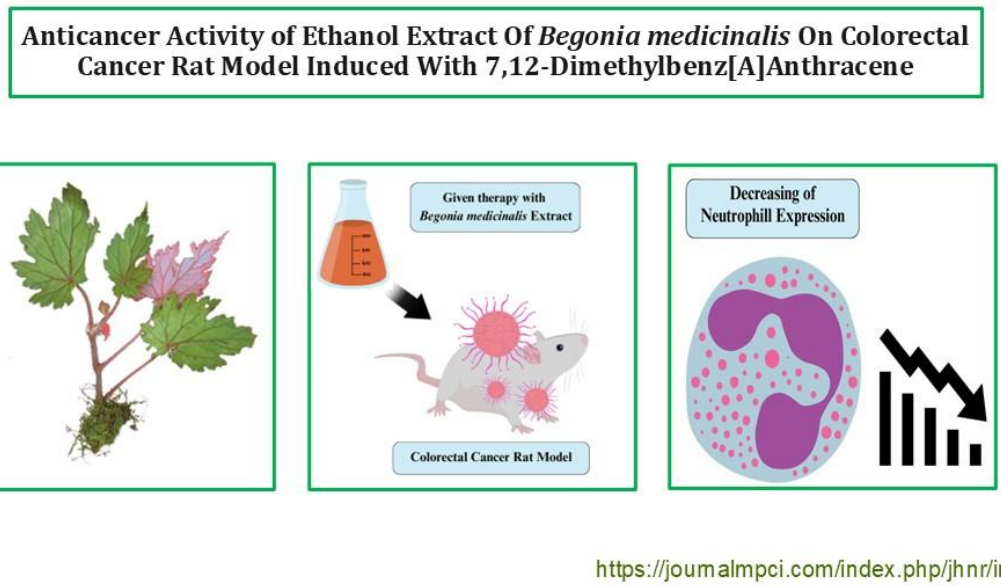
GRAPHICAL ABSTRACT



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INTRODUCTION

Colorectal cancer (CRC) remains a public health menace considering its ever-rising mortality rates, making it among the leading cancer causes of death after lung cancer (1,2). Apart from diet and nutritional status (3), one of the prominent factors for such high mortality rates is the presence of barriers to the effective management of this lethal disease (4). Even with the progress in medical technology and treatments, the standard therapies for CRC like chemotherapy and radiotherapy have significant drawbacks that affect their effectiveness and patient results (5,6).

The main limitation of CRC therapies is their inability to target cancer cells specifically. Both chemotherapy and radiotherapy work across a wide range, not effectively differentiating between cancerous and non-cancerous cells (7,8). Due to these difficulties, there is an increasing interest in investigating different treatment methods that provide improved selectivity and lower toxicity levels (9,10). Plant-based natural ingredients have become favorable options in this area of interest (11). Natural compounds can control different biological pathways through immunomodulation mechanisms, either through immunosuppression or immunostimulation, providing a more effective method for cancer treatment. The high specificity of natural ingredients offers a chance to create medicines that target cancer cells effectively with less impact on healthy tissues (12–14).

One way that natural ingredients work to fight cancer is by reducing inflammation. In cancer progression, inflammation is crucial, and neutrophils, a type of white blood cell, are vital indicators of this inflammatory reaction. Increased levels of neutrophils have been linked to a negative outcome in different cancer forms, including CRC (15,16). Natural substances have been shown to reduce the concentration of neutrophils, which could decrease the cancer-promoting impact of long-term inflammation. This adjustment of the inflammatory surroundings shows potential for precise cancer treatment (17).

Research in the field of ethnobotany has found that *Begonia medicinalis* has properties that can help fight cancer, indicating that it could be used to develop new treatments. Historically, *Begonia medicinalis* has been used in traditional medicine for treating a range of health issues, such as cancer, due to its bioactive properties (18). Furthermore, *Begonia medicinalis* was found by Zubair et al. (2021) to possess both antioxidant and antiviral properties (19). Prihardina and Fatmawati (2021) observed that the high flavonoid content of *Begonia medicinalis* contributes to its anti-cancer properties (20). Nevertheless, despite this encouraging ethnomedicinal history, there is a significant absence of in vivo research to confirm its effectiveness in cancer models. The lack of scientific evidence emphasizes the importance of thorough preclinical studies to understand the anticancer capabilities of *Begonia medicinalis*.

The objective of this study was to investigate anticancer properties of *Begonia medicinalis* extract by

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measuring neutrophil concentration in DMBA-induced rat model of colorectal cancer. The research focuses on observing changes in neutrophil levels as an initial step toward understanding the potential role of this plant in modulating inflammatory responses associated with colorectal cancer. The identification of these plant-based medicines shows potential for creating cancer treatments that are more targeted and safer, leading to better results and quality of life for patients in the end.

METHODS

The animal used in the study was Wistar rat (Rattus norvegicus). The animals were obtained from the Animal Testing Laboratory, Department of Pharmacy, Faculty of Natural Sciences and Mathematics, Tadulako University. The test subjects chosen for the study fulfilled the criteria, which included a weight of 100 - 200 grams, an age range of 8 – 12 weeks, good health, and displaying typical behavior and activity levels. Following this, the rats' cages and water containers were set up, given bedding, and allowed to adjust for two weeks. The sample size for each of the 5 treatment groups was determined using the Federer method (21), resulting in a sample size of 5 for each group.

This study is experimental lab research that employs a post-test-only group design. Animals were randomly assigned into 5 treatment groups (Figure 1), such as:

1. Group 1 = Induced with DMBA and treated with extract therapy at a dosage of 25 mg/kg body weight (dose I therapy).
2. Group 2 = Induced with DMBA and treated with extract therapy at a dosage of 50 mg/kg body weight (dose II therapy).
3. Group 3 = Induced with DMBA and treated with extract therapy at a dosage of 100 mg/kg body weight (dose III therapy).
4. Group 4 = Did not receive DMBA induction and was not treated with extract therapy (normal group).
5. Group 5 = Induced with DMBA and did not receive extract therapy (negative control).

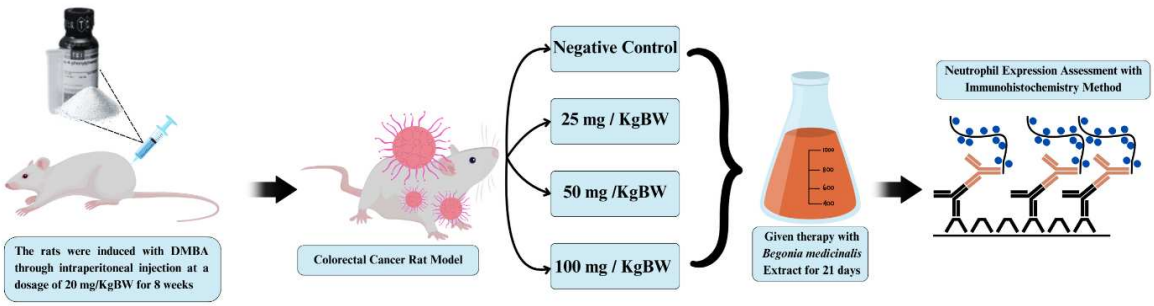

Figure 1. Design of Colorectal Cancer in Rat Model. A colorectal cancer rat model was developed using DMBA induction administered intraperitoneally at a dose of 20 mg/kg body weight for 8 weeks. The rats were subsequently treated with *Begonia medicinalis* extract, and neutrophil concentration was analyzed using immunohistochemical staining. The results were compared with neutrophil concentration in the normal and control groups.

The samples of *Begonia medicinalis*, consisting of leaves, stems, and roots, were obtained from North Morowali Regency, Central Sulawesi, using a purposive sampling method. The samples were identified at the Plant Biosystematics Laboratory, Department of Biology, Faculty of Science and Mathematics, Tadulako University. After collection, the samples were dried in an oven at a temperature of 60 °C for 24 hours and then pulverized into simplicia using a blender. The simplicia was soaked in 70% ethanol as the solvent for a duration of 24 hours. Following this, the liquid from the maceration process was evaporated using a vacuum rotary evaporator set at a temperature of 40 °C and a speed of 75 rpm to effectively remove the solvent. The concentrated substance was then further evaporated using a heat source and stored in a refrigerator to preserve its integrity (22–24).

A qualitative test was performed to screen for phytochemicals like flavonoids, alkaloids, saponins, tannins, and terpenoids in the extract of *Begonia medicinalis*. Screening for flavonoids, alkaloids, saponins,

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tannins, and terpenoids was conducted using Shinoda's Test, Mayer's Test, Foam Test, Ferric Chloride ($FeCl_3$) Test, and Liebermann-Burchard Test, respectively (25,26).

DMBA (DO677 TCI, Japan), a substance used to cause colorectal cancer, was prepared by dissolving it in 40 ml of sesame oil and administrated through intraperitoneal injection at a dosage of 20 mg/kg body weight per 3 days for 8 weeks. DMBA was administered to groups 1, 2, 3, and 5. Following 4 weeks of induction, where the model developed cancer, they received *Begonia medicinalis* extract through intraperitoneal injection at dosages of 25 mg/kg body weight for group 1, 50 mg/kg body weight for group 2, and 100 mg/kg body weight for group 3. The test substance was administered once a day for a total of 21 days. Following the treatment, the rats were not fed for one day and were then dissected to obtain their colorectal organs.

Neutrophil concentration was assessed using the immunohistochemistry technique. The immunohistochemical method employed was the indirect method with diaminobenzidine as the chromogen. The procedure began with embedding, and preparation of colorectal tissue samples, followed by deparaffinization and rehydration, cell permeabilization, cell blocking, incubation with the primary antibody anti-CD15, incubation with the secondary antibody, and finally mounting. Observation was conducted at 100 fields of view under a magnification of 4 x 10.

The data analysis in this study employed statistical techniques to determine the differences and effects of treatments across each group. Statistical methods included the Kolmogorov-Smirnov Test for normality, Bartlett's Test for homogeneity, and one-way ANOVA with an alpha level of 0.05 for variance analysis, followed by Tukey's HSD for post hoc testing. Statistical analysis and graph creation were performed using GraphPad Prism 8.0.1 by GraphPad Software, Inc., California, USA.

CODE OF HEALTH ETHICS

The ethics committee of the Faculty of Medicine, Tadulako University gave a letter of approval for research ethics through the Ethics Committee statement number 6586/UN 28.1.10/KL/2024.

RESULTS

Preliminary phytochemical screening tests show that *Begonia medicinalis* extract contains secondary metabolites such as flavonoid, alkaloid, saponin, tannin, and terpenoid (Figure 2). In the Shinoda test, the sample turned a reddish-brown color after being treated with ethanol, concentrated HCl, and magnesium powder, indicating the presence of bioactive flavonoids in the extract. For Mayer's test, a yellow precipitate formed when chloroform, ammonia, H2SO4, and Mayer's reagent were added, confirming the presence of bioactive alkaloids. In the foam test, a layer of foam appeared after the sample was mixed with distilled water, revealing that the extract contained bioactive saponins. During the Ferric Chloride test, the sample shifted to a green-violet color when treated with distilled water and FeCl3, indicating the presence of tannins. Lastly, in the Liebermann-Burchard test, the sample turned blue-green after being treated with acetic acid and H2SO4, suggesting that bioactive terpenoids were present in the extract (Table 1) (25,26).

Table 1. Phytochemicals Screening of *Begonia medicinalis*

Phytochemicals	Method	Observation	Inference
Flavonoid	Shinoda's Test	Reddish-brown colored solutions	+++
Alkaloid	Mayer's Test	Yellow precipitate	++
Saponin	Foam Test	Presence of foam	+
Tanin	Ferric Chloride (FeCl3) Test	Green-violet colored solutions	+
Terpenoid	Liebermann-Burchard Test	Blue-green colored solutions	++

(+): Indicates a low presence or a small quantity; (++): Represents a moderate presence or a medium quantity; (+++): Denotes a high presence or a large quantity; (-): Signifies the absence of the characteristic or substance.

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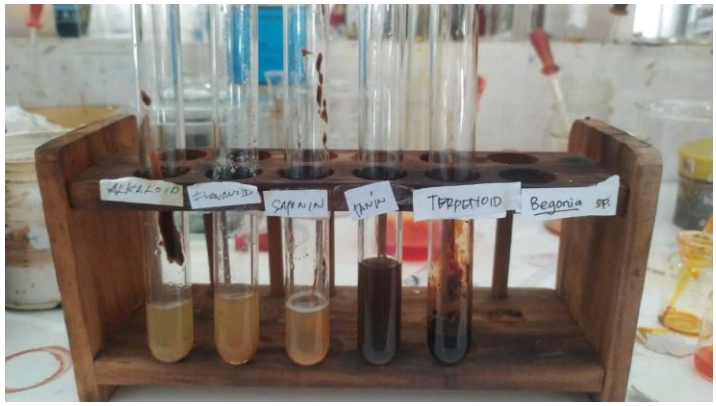

Figure 2. Qualitative analysis of *Begonia medicinalis* extract demonstrating the presence of key phytochemicals, including alkaloids, flavonoids, saponins, tannins, and terpenoids.

Histopathological observations of colorectal tumors using immunohistochemistry revealed a reduction in neutrophil concentration in the group that received the extract treatment. As the therapy dose increased, tissue slides from the therapy group showed progressively less brown, suggesting a decrease in neutrophil concentration (Figure 3).

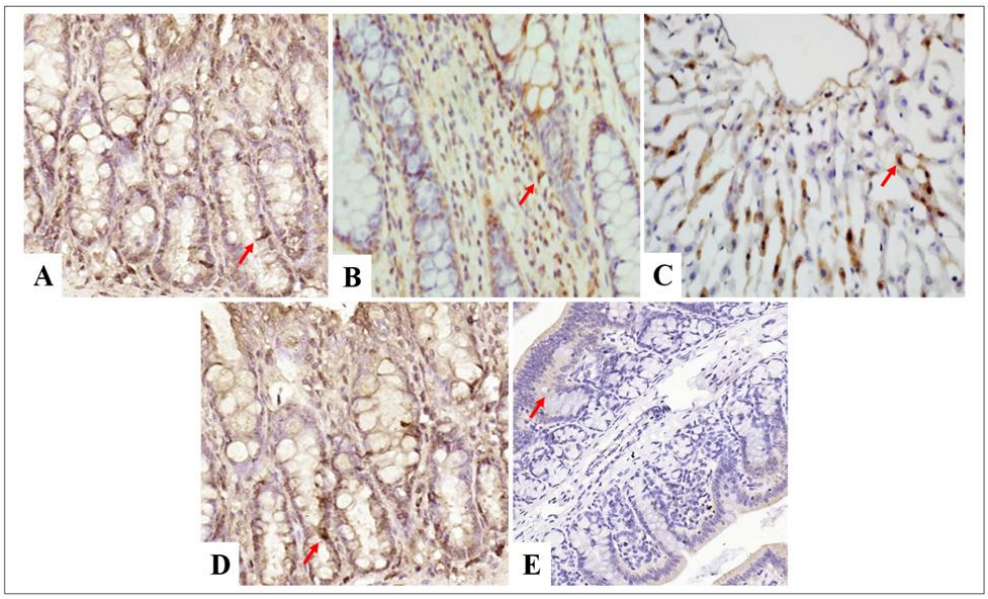

Figure 3. Histological sections of colon tissue from experimental animal groups, stained to visualize neutrophil concentrations (indicated by arrows), as an indicator of inflammation and cancer severity. Images were captured at 4 × 10 magnification. Panel A shows tissue from animals induced with DMBA and treated with extract therapy at 25 mg/kg body weight; Panel B, at 50 mg/kg; and Panel C, at 100 mg/kg. Panel D represents the normal group with no DMBA induction or therapy, while Panel E depicts the negative control group induced with DMBA but without extract treatment.

Treatment with *Begonia medicinalis* extract greatly decreased neutrophil concentration. Treatment with 50 mg/kg body weight and 100 mg/kg body weight doses successfully reduced neutrophil concentration in the experimental subjects, with the best results seen at the 100 mg/kg body weight dosage.

Groups 1, 2, 3, 4, and 5 had average neutrophil cell densities of 41.80, 26.46, 15.68, 36.17, and 5.62, in that order. The findings from the One-Way ANOVA test showed that the use of *Begonia medicinalis* extract had a significant impact in decreasing neutrophil concentration (p=0.0001). Prior to conducting the ANOVA test, the Shapiro-Wilk test was performed to assess the normality of the data distribution, ensuring the validity of the ANOVA results. The posthoc test findings showed that the average neutrophil cell density in

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group 1 was not notably distinct from group 4 (p=0.4013), but it was notably distinct from groups 2 (p=0.0007), 3 (p=<0.0001), and 5 (p=<0.0001). There was a significant difference in neutrophil cell density between group 2 and groups 3 (p=0.0193), 4 (p=0.0398), and 5 (p=<0.0001). Group 3 had a notably different neutrophil cell density compared to groups 4 (p=<0.0001) and 5 (p=0.0316). Group 4 had a markedly distinct neutrophil cell density compared to group 5 (p=<0.0001). The results indicate that treatment with *Begonia medicinalis* extracts at 50 mg/kg body weight and 100 mg/kg body weight doses can decrease neutrophil cell count, with the best therapeutic outcome seen at 100 mg/kg body weight dose (Figure 4).

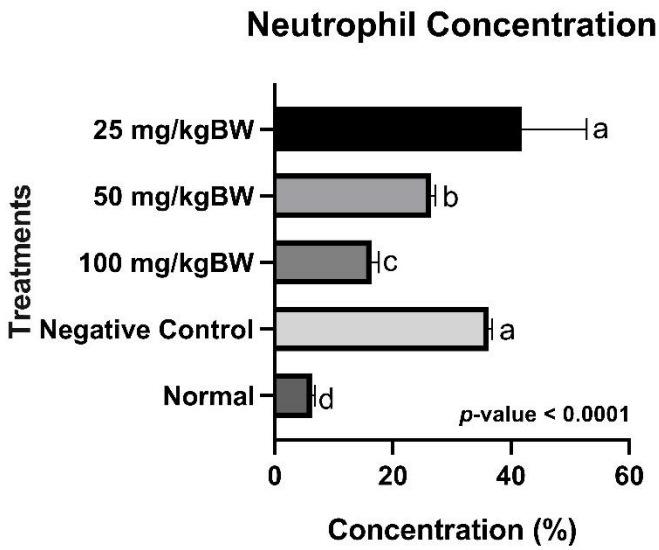

Figure 4. Neutrophil concentration. The information shows the typical neutrophil concentration. Experimental animals were administered DMBA and exposed to increasing amounts of the extract: 25 mg/kg body weight (Group 1), 50 mg/kg body weight (Group 2), and 100 mg/kg body weight (Group 3). Animals that were treated with DMBA but did not receive the extract therapy (Group 4) were included, as well as animals that were neither treated with DMBA nor given the extract therapy (Group 5). The values displayed represent the mean ± SD. Bars in the graph with different notations indicate significantly different mean values. *p*-value *<0.0001*

DISCUSSION

This study identified that *Begonia medicinalis* contains various bioactive compounds, including flavonoids, saponins, tannins, terpenoids, and alkaloids. According to Prihardina and Fatmawati (2021), the flavonoids in *Begonia medicinalis* extract exhibit significant anticancer properties (20). Similarly, Ardiputra et al. reported the presence of flavonoids, alkaloids, and saponins in *Begonia medicinalis*, highlighting its potential as a therapeutic agent against colorectal cancer. These compounds exert curative and chemopreventive effects on colorectal cancer by inhibiting cyclin-dependent kinase (CDK) activity and mitigating oxidative stress and intestinal inflammation (27).

This study shows that the *Begonia medicinalis* extract effectively suppresses neutrophil concentration in a DMBA-induced colorectal cancer rat model. The results demonstrate that both treatment groups 2 and 3 effectively reduce neutrophil cell counts. Notably, group 3 exhibits the most significant therapeutic outcome, achieving a statistically greater reduction in neutrophil concentration compared to group 2. This reduction in neutrophil levels suggests a corresponding decrease in inflammation, which may contribute to a slower growth rate of tumors in the treated subjects. A study by Zhang et al. (2020) found that some natural substances may have the ability to act as a treatment option for cancer and inflammation by blocking neutrophil activity (28). A study by Amirova demonstrates that certain natural plant extracts have the potential to reduce neutrophil activity in inflammation by modulating cyclooxygenase-2 (COX-2) activity (29).

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In CRC, secondary metabolites can affect neutrophil function and concentration, which may slow the growth of the tumor. By altering neutrophil polarization and reducing neutrophil recruitment, some secondary metabolites inhibit the growth and metastasis of colorectal cancer. By targeting important pathways in neutrophil recruitment, activation, and maintenance, the extract disrupts their involvement in the tumor microenvironment (30,31).

The presence of neutrophils in the tumor microenvironment indicates the severity of cancer. Tumors frequently use chronic inflammation to grow, with neutrophils playing a crucial role in this mechanism. This includes the activation of pro-inflammatory cytokines like IL-6 and IL-1β, initiating inflammation within the tumor microenvironment. A study by Lee et al. (2021) reveals that natural elements can prevent the release of cytokines IL-6 and IL-1β (32).

The inflammatory response is regulated by NF-κB, an inflammatory mediator that controls the release of pro-inflammatory cytokines. Moreover, activation of NF-κB also triggers the upregulation of adhesion molecules (ICAM-1 and VCAM-1) on endothelial cells, which helps in the recruitment of neutrophils to tumor sites. Numerous natural substances have been shown to reduce NF-κB levels, allowing them to function as cancer-fighting and tumor-inhibiting agents (33,34).

This study provides new insights into the effects of plant-based therapies, *Begonia medicinalis* extract, in modulating the immune system by decreasing neutrophil concentration in a colorectal cancer rat model. The current study employs a fundamental methodology that does not adequately address the underlying mechanisms by which *Begonia medicinalis* extract may suppress neutrophil concentration. To enhance our understanding, further research is necessary to explore additional pathways through which *Begonia medicinalis* extract influences the immune system. Additionally, conducting toxicological assessments of the extract is essential to evaluate its safety and potential therapeutic applications.

CONCLUSION

This study shows that the *Begonia medicinalis* extract effectively decreasing neutrophil concentration in a DMBA-induced colorectal cancer rat model. Treatment with *Begonia medicinalis* extract greatly decreased neutrophil cell presence. Treatment with 50 mg/kg body weight and 100 mg/kg body weight doses successfully reduced neutrophil cell levels in the experimental subjects, with the best results seen at the 100 mg/kg body weight dosage. This research offers possible understanding for clinical application of *Begonia medicinalis*, as well as for the development of phytopharmaceuticals.

FUNDING

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CONFLICTS OF INTEREST

The authors declare that they have no known competing financial or non-financial interests that could have influenced the work reported in this paper.

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