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Original Article

Hydroalcoholic extract of *Psidium guajava* plant and bone marrow cells: examination and analysis of effects

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ABSTRACT

The purpose of the current study was to examine the effect of hydroalcoholic extract of *Psidium guajava* plant on bone marrow cells in rats and it will be extended to humans. Guava plant leaves were collected from Chabahar region in Sistan and Baluchistan province and dried. 40 adult male rats were assigned to one control group and three experimental groups (subjects that were administeredhydroalcoholic extract of *P. guajava* leaves with respective doses of 3000 mg/kg, 4000 mg/kg, or 5000 mg/kg, for 3 months, once daily). Following the intervention period, blood was taken from the heart and bone marrow was taken from the femur. Several parameters such as cell blood count, hemoglobin, and hematocrit, were examined in the blood sample. Also, in the bone marrow sample, a relative count was performed on five hundred bone marrow cells and the ratio of myeloid to erythroid was determined in both control and experimental groups. The results of this study indicated that the hydroalcoholic extract somewhat increased white blood cells and red blood cells, but no significant change was observed. The result of the study revealed the positive effects of guava leaf extract may be due to flavonoids, quercetin and triterpenes, which strong antioxidants that can prevent damage are caused by free radicals destroying cells. This study shows that guava leaf extract can have a positive effect on hematological parameters, as well as the lack of mutagenicity and cytotoxicity in high doses of this plant extract rather reflects its safe use in traditional medicine. Therefore, it is recommended that guava leaf extract be considered as a complementary and alternative treatment for many diseases, including the treatment of anemia.

1. Introduction

There has been a recent upsurge of interest in studying plants regarding bioactive chemical compounds, their effects on diseases and their use for human health as food supplements. As such, *Psidium guajava,* i.e., the guava plant, has traditionally been used to treat a host of diseases [1]. *P. guajava* is a plant from Myrtaceae family and Psidium genus. It is a medicinal plant and an important food crop in tropical and subtropical countries. Various pharmacological tests have been performed on the organisms, most of which have reflected valuable biological properties stemming from the presence of phenolic, flavonoid, carotenoid, and triterpene compounds. The extract and metabolites of this plant are deemed to be useful for medicinal uses [2]. Bone marrow is found in the central canals of long bones and cavities of

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spongy bones, and according to their appearance in macroscopic studies, two types of bone marrow have been described, namely, red and yellow bone marrow [3].

It is noteworthy that, there are cells in the bone marrow called multivalent stem cells, from which two types of cells are separated: 1) lymphoid cells and 2) myeloid cells [4]. Bone marrow biopsy can be used to diagnose infectious diseases. Many infectious diseases that remain elusive to routine tests can be diagnosed by microbial and fungal cultures using bone marrow obtained by aspiration [5, 6]. Therefore, in order to apply this diagnostic procedure for potential radioactive illnesses, it is necessary to first determine the tissue structure of the bone marrow in rats, i.e., the various cell types present in it in terms of form and morphology, percentage, and absolute quantity, among other factors [7, 8].

Researchers have previously reported that some extracts contain compounds that can readily stimulate the secretion of erythropoietin, hematopoietic growth factor, and bone marrow cells. In particular, the stimulation of blood growth factors and erythropoietin systems increases the rapid synthesis of blood cells [9-11]. In addition, the hematopoietic potential of *P. guajava* leaf extract can be attributed to its antioxidant functionality. A 2017 study titled "Active potential of *P. guajava* leaf extract and its anticancer activity" found that, with a dose of 78.7 micrograms, the extract had a favorable inhibitory effect on the growth of cancer cells [12].

Medicinal plants and their compounds have long been sought after for their potential effects on the treatment of various diseases. Today, despite the many advances in the field of synthetic drugs, the use of the medicinal properties of plants remains of utmost significance. One of the most important reasons for the significant and attention paid to plant compounds such as *P. guajava* is its minimal adverse effects compared to conventional drugs [13]. As well as the presence of compounds such as alkaloids, flavonoids, glycosides, and polyphenols in the extract of this plant. Despite the research that has been done on the properties of this plant, there is still little to no information about the effects of *P. guajava* on blood cells and bone marrow. Therefore, the purpose of the current research was to examine the effect of hydroalcoholic extract of *P. guajava* leaves on the blood cell count and bone marrow cells in rats.

2. Materials and methods

2.1. The effect of the extract on the studied groups section

Guava leaves from the Chabahar region in Sistan and Baluchistan province were collected and identified by a botanist from the Faculty of Pharmacy (SFPH-771). First, the leaves were cleaned and then placed in the shade to dry .After which they were grounded using electric mill. The resulting product was percolated using 70-degree ethanol. The extracts were concentrated by a desiccator at a temperature of 40 degrees (rotary) and then, the concentrated extracts were transferred to a freeze-dryer and finally, the leaf extract was lyophilized as powder.

2.2. Evaluation of antioxidant capacity by DPPH radical

DPPH (2, 2-diphenyl-1-picrylhydrazyl) is a stable, free radical whose methanolic solution has a purple color. This substance has an unpaired electron on one of the nitrogen bridge atoms. DPPH radical scavenging is the basis of antioxidant assay. The basis of this method is based on the reduction of DPPH free radicals by antioxidants in the absence of other free radicals in the environment. The DPPH radical acts as an electron acceptor from a donor molecule such as an antioxidant, as a result, the DPPH radical receives an electron. The violet color of the environment changes to yellow, so the intensity of absorption at 517 nm decreases, by measuring the decrease in intensity of absorption by spectroscopy, one can understand its antioxidant properties [14].

To evaluate the antioxidant capacity of the extract with DPPH, 270µL of quercetin was mixed with 30µL of DPPH in a test tube to produce a control with a concentration of 10µM. Different concentrations were produced to determine 50% rate inhibition of the extracts up to 4 times of dilution. 270 µL

of the dilutions prepared with 30 microliters of 100μM methanolic solution of freshly prepared DPPH mixture. Its volume reached 300 microliters. After 30 minutes of storage at room temperature and in the dark, the absorbance was read at 517 nm using a microplate reader. Each of the samples and controls was repeated 3 times and the average absorbance was calculated. Finally, it was calculated the inhibition percentage and IC50 [15-17].

2.3. Folin–Ciocalteu reagent assay

This method does not directly check the antioxidant capacity but always complements the methods of checking the antioxidant capacity. In fact, it determines the total phenolic compounds. Polyphenolic compounds include flavonoids, flavanols, flavanols, isoflavones, flavanone, and flavan, as well as lignin, tannin, and tocopherol, which are found in fruits, vegetables, oil seeds, nuts, medicinal plants, and plant parts. One of the methods for measuring the total content of phenolic compounds is the Folin-Ciocalteu method, which was proposed for the first time in 1982. Folin-Ciocalteu reagent is a mixture of phosphomolybdate and phosphotungstic acid, which is based on colorimetry, and can measure the total amount of phenolic compounds in the environment. The basis of this method is based on the principle that Folin–Ciocalteu is an oxidizing compound. Phenols and polyphenols, by transferring their single electron to it in an alkaline environment, regenerate this compound and create a blue color in the environment, which shows the highest absorption at 765 nm. In order to accurately control this method, it is necessary to use a control or standard solution, which is used as a standard in most researches [13].

Gallic acid standard curve and Folin–Ciocalteu method were used to determine the amount of total phenol in the extract of Psidium Guava. As reported in previous articles, 40 microliters (of 1mg/mL) of *Psidium Guava* extract or standard methanolic solution of gallic acid in different concentrations were mixed with 200 microliters of Folin-Ciocalteu reagent and its volume was diluted with distilled water. We deliver 3.16 ml. After 10 minutes, 600 microliters of 0.25% sodium carbonate solution is added to the reaction medium. Then it was kept for 2 hours at the temperature of the laboratory environment and its light absorption was read by a Polarstar spectrophotometer made in Germany at a wavelength of 765 nm. The amounts of total phenol in extract samples were expressed using a standard curve in terms of mg of gallic acid per gram of extract.

2.4. The effect of the extract on the blood cell count and bone marrow cells

This study was experimental. In this research, it was used 40 adult male Sprague Dawley rats (180-220 g and 10-12 weeks old). The animals were purchased from the animal shelter of Shiraz University of Medical Sciences and were kept at a temperature of 22±2 °C, 12 hours of light and 12 hours of darkness, and a relative humidity of 55±5% with free access to standard food and water.

The animals were randomly divided into four groups as follows: control and the first, second, and third experimental groups (n=10).

The research groups included the control group and the first, second and third test groups.

The research groups consisted as follows:

- ✓ Control group: including animals that were not treated during the study.
- ✓ Experimental group 1: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000 mg/kg for 3 months (leave 3000).
- ✓ Experimental group 2: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 4000 mg/kg for 3 months (leave 4000).
- ✓ Experimental group 3: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 5000 mg/kg for 3 months (leave 5000).

At the end of the experimental period, the rats of all groups were anesthetized with ether, and blood was taken from the heart and femoral marrow samples. The blood samples were sent to the laboratory to measure parameters such as red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, average corpuscular volume, average cell hemoglobin, and average hemoglobin concentration. Also, to check bone marrow cells, a relative count was done on five hundred bone marrow cells and the ratio of myeloid to erythroid in both control and experimental groups was determined. Erythroid-type cells (rubriblast, prorubricyte, basophilic rubricyte, polychromatophilic rubricyte, metarubricyte) and myeloid-type cells (myeloblast, promyelocyte, myelocyte, metamyelocyte, and neutrophil) and it was counted other cells like: mitotically dividing cell, megakaryocyte, plasma cell, monocyte, and degenerate cell, lymphocyte and donor cell.

The research variables were recorded using an auto-analyzer and an optical microscope using an observational method, while the required outputs were extracted from the obtained curves.

2.5. Statistical analysis

The data was analyzed in SPSS using ANOVA and Tukey's post hoc test considering the significant level of P<0.05.

All the ethical principles of working with animals in this study were observed according to the ethical protocols of working with laboratory animals. This research was conducted under the supervision of the ethics committee of the Zabul University of Medical Sciences with the code of ethics IR.ZBMU.REC,1398.004.

3. Results

3.1. The effect of hydroalcoholic extract of guava leaf extract on erythroid cells in the bone marrow of male rats:

The average number of blast cells in the experimental groups increased compared to the control group, and this difference between these groups is not statistically significant (P<0.01)(Table 1). Also, the average number of pro-rubricyte and meta-rubricyte cells in the experimental groups receiving the extract with a dose of 4000 and 5000mg/kg increased compared to the control group, yet the difference between these groups is not statistically significant (p≤0.05) Also, the average number of polychromatophilic rubricyte cells in the test group receiving the extract with a dose of 5000 mg/kg increased compared to the control group, which also shows that the difference between the two groups is not statistically significant (P<0.01) (figure 1)(Chart 1).

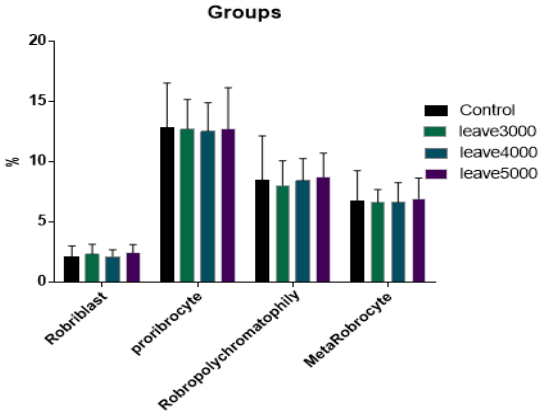

Fig. 1. The percentage of rat bone marrow erythroid cells in the studied groups (Mean±standard deviation). Control group: including animals that were not treated during the study;leave 3000:animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000mg/kg for 3 months; leave 4000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 4000mg/kg for 3 months; leave 5000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000 5000mg/kg for 3 months.

Table 1. The p value of bone marrow erythroid cells in the studied groups (p≤0.05)

Groups	Robriblast	Pro Robricyte	Robro polychromatophily	Meta Robrocyte
control	0.9	1	0.9	0.9
Test 3000	0.9	1	0.9	0.9
Test 4000	1	0.9	0.9	0.9
Test 5000	0.9	1	0.9	0.9

3.2. The effect of hydroalcoholic extract of guava leaf extract on myeloid cells in rat bone marrow

The average number of myeloblast cells in the experimental groups receiving the extract

with a dose of 3000, 4000 and 5000 mg/kg did not change compared to the control group (Table 2 and 3), so there is no significant difference between these groups (p≤0.05). Moreover, there is no significant difference in the average cells of promyelocyte, metamyelocyte and cell band between the experimental groups and the control group (P<0.01). Also, the average number of neutrophil cells in the experimental groups receiving the extract with a dose of 3000, 4000 and 5000 mg/kg were decreased compared to the control group, yet the difference is not statistically significant (p≤0.05)(Figures 2a and 2b).

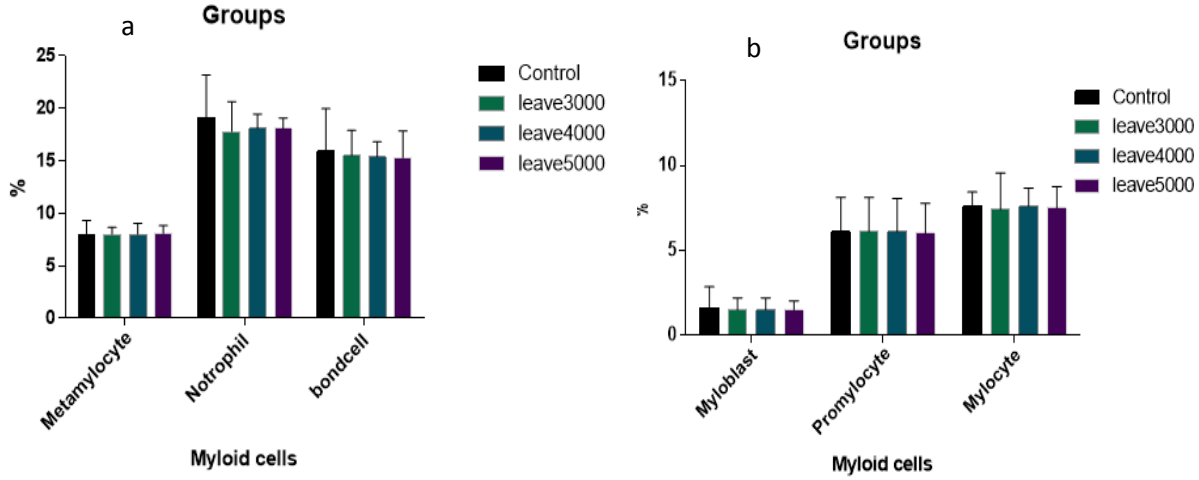

Fig. 2. a) The percentage of rat bone marrow myeloid cells in four groups (experimental and control) (P < 0.05); b) The percentage of rat bone marrow myeloid cells in the studied groups. (Mean±standard deviation). Control group: including animals that were not treated during the study; leave 3000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000mg/kg for 3 months; leave 4000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 4000 mg/kg for 3 months; leave 5000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000 to 5000mg/kg for 3 months.

Table 2. The p value of bone marrow myeloid cells in the studied groups (p≤0.05)

Groups	Bond cell	Metamylocyte	Notrophil
control	0.9	0.9	0.9
Test 3000	0.9	0.9	0.9
Test 4000	1	0.9	0.9
Test 5000	0.9	0.9	0.9

Table 3. The p value of bone marrow myeloid cells in the studied groups (p≤0.05).

Groups	Myloblast	Promylocyte	Mylocyte
control	0.9	0.9	0.9
Test 3000	1	0.9	0.9
Test 4000	1	0.9	0.9
Test 5000	1	0.9	0.9

3.3. The effect of guava leaf hydroalcoholic extract on cells of other types in the bone marrow of male rats

The results from Figures 4 and 5 reveal that the average of megakaryocyte, plasma cell, degenerate, and monocyte cells in the experimental groups receiving the extract with a daily dose of 3000, 4000 and 5000 mg/kg did not change compared to the control group, indicating that there is not statistically significant difference between the group regarding the aforementioned parameters (p≤0.05) (Table 4 and 5).

The average of the donut cells in the test groups receiving the extract with a dose of 3000, 4000 mg/kg decreased compared to the control group, yet the difference between these two groups is not statistically significant (p≤0.05). Also, the average of donut cells in the test group receiving the extract with a dose of 5000 mg/kg remains unchanged compared to the control group (p≤0.05)(Figures 3a and 3b).

The findings on the effect of guava hydroalcoholic extract on peripheral blood

cells and bone marrow in the current study indicate the non-toxicity of this extract in the experimental groups receiving daily doses of 3000, 4000, and 5000mg/kg of rat weight for a period of 3 months (Figures 3a and 3b).

3.4. The effect of guava leaf hydroalcoholic extract on the average number of red blood cells in male rats

Examining the average number of red blood cells in the control and experimental groups showed that there is an increase between the average of the experimental groups of 3000, 4000 and 5000 mg/kg compared to the control group, which is not statistically significant (P≤0.05; Figure 4a).

3.6. The effect of guava leaf hydroalcoholic extract on the average number of white blood cells in male rats

Examining the average number of white blood cells in the control and experimental groups and comparing it at the level (P ≤ 0.05) showed that there is no statistically significant difference between the average of the experimental groups and the control group (Figure 4b).

3.5. The effect of guava leaf hydroalcoholic extract on blood hemoglobin MCV, MCH, MCHC of male rats

Examining mean blood hemoglobin, mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) Tukey's post hoc test showed that there was no significant difference in the experimental and control group (Figure 5).

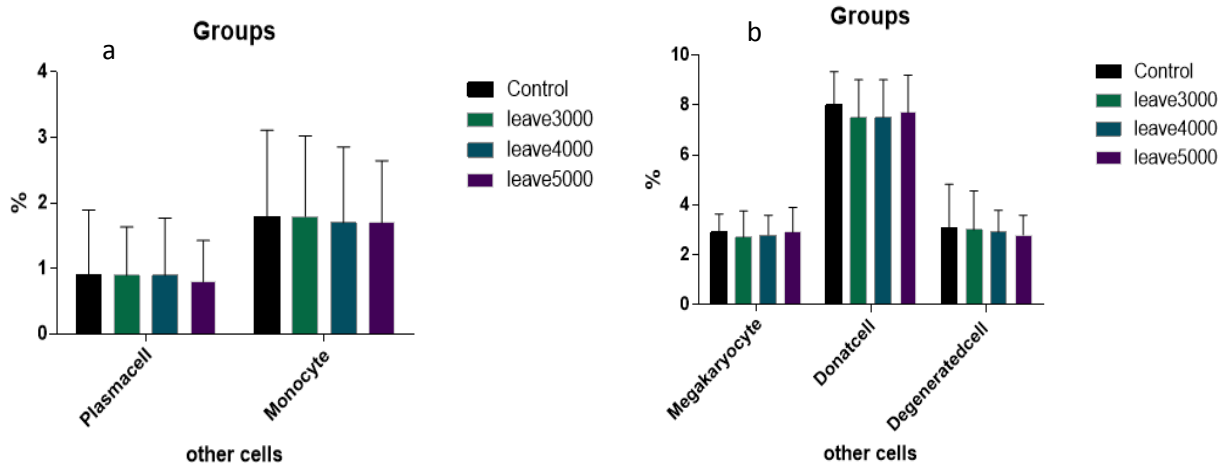

Fig. 3. a) The percentage of cells of other categories of rat bone marrow cells in the studied groups. (Mean±standard deviation). Control group: including animals that were not treated during the study; leave 3000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000mg/kg for 3 months; leave 4000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 4000mg/kg for 3 months; leave 5000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000 to 5000mg/kg for 3 months. b) Mean (standard deviation) of cells of other categories of rat bone marrow in four groups (experimental and control) (P < 0.05).

Table 4. The p value of bone marrow other cells in the studied groups (p≤0.05)

Groups	Plasma cell	Monocyte
control	0.9	0.9
Test 3000	0.9	0.9
Test 4000	0.9	0.9
Test 5000	0.9	0.9

Table 5. The p value of bone marrow other cells in the studied groups (p≤0.05)

Groups	Megakaryocyte	Donat cell	Degenerated cell
control	0.9	0.8	0.8
Test 3000	0.9	0.9	0.9
Test 4000	0.9	0.9	0.9
Test 5000	0.9	0.9	0.9

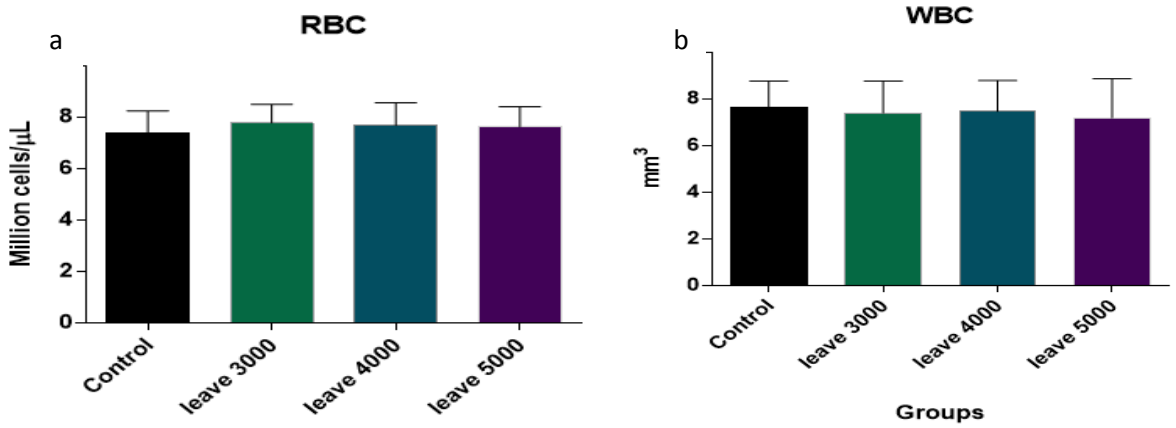

Fig. 4. a) The number of red blood cells of rats in the studied groups. (Mean±standard deviation). Control group: including animals that were not treated during the study; leave 3000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000mg/kg for 3 months; leave 4000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 4000mg/kg for 3 months; leave 5000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000 to 5000mg/kg for 3 months. b) The number of white blood cells of rats in the studied groups. (Mean±standard deviation). Control group: including animals that were not treated during the study; leave 3000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000mg/kg for 3 months; leave 4000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 4000 mg/kg for 3 months; leave 5000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000 5000 mg/kg for 3 months).

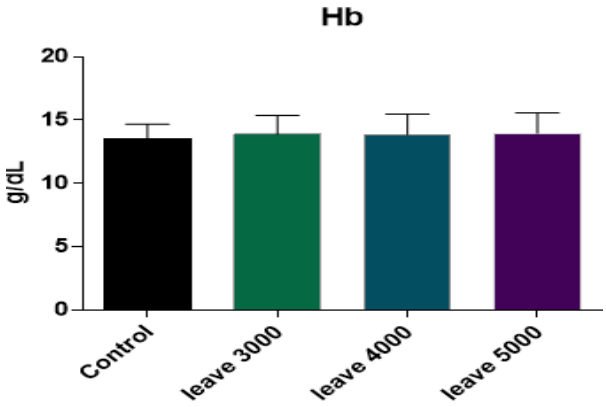

Fig. 5. The hemoglobinconcentration in the blood of rats of the studied groups. (Mean±standard deviation). Control group: including animals that were not treated during the study; leave 3000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000 mg/kg for 3 months; leave 4000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 4000mg/kg for 3 months; leave 5000: animals that were administered the hydroalcoholic extract of *P. guajava* leaves at a daily dose of 3000 to 5000mg/kg for 3 months

3.7. Findings on antioxidant activity

Phenolic constituents react with reactive oxygen species such as hydroxyl radical, superoxide and lipid peroxyl radical. These compounds have a broad spectrum of chemical and biological activities including radical scavenging properties. The total polyphenol content was 252.67 ± 2.71 mg GAE/g of dry extract. In agreement with the animal study reports it can be seen IC_{50} = 172± 3.592 ng/mL is active against DPPH° radical.

The findings on the antioxidant activity of guava leaf extract, which was iterated 3 times, illustrate that the hydroalcoholic extract has an extraordinary activity in trapping free radicals. The total amount of phenolic compounds in this extract is 252.67 ± 2.71mg GAE/g of dry extract. The obtained results show that the MIC of guava leaf extract is 3.592 ± 172ng/ml.

4. Discussion

The purpose of the present study was to investigate the effect of hydroalcoholic extract of *P. guajava* leaves on the number of bone marrow cells in rats. Herbal plants, guava being no exception, have been used for decades to treat several human diseases given the inhibitory effect of this extract on the growth of cancer cells, anti-proliferative activity of guava on fibroblast cells in MCF-7 and Caco3 medium [18], treatment of

gastroenteritis, dysentery, its effect on Escherichia coli [19], streptococcus inhibitor [20], anti-inflammatory and strong antioxidant [21]. Since anemia is a major public health problem. Iron deficiency anemia is the most common form of anemia, the main cause of which is malnutrition in developing countries. Teenagers are one of the main groups at risk of getting anemia. This condition can lead to brain dysfunction and as a result, reduce the ability to learn and decrease academic performance. Also, in order to reduce the side effects of drugs, it is suggested to use herbal drugs, one of these medicinal plants is guava, which is rich in polyphenolic compounds such as: flavonoids, tannins, ellagic acid, Triterpenes and quercetin, all of which are presumed to have strong antioxidant properties. Medicinal plants, specifically, guava (since guava fruit contains coumarin compounds [22-24].

It has been examined in their study the effect of aqueous extract of *P. guajava* leaves on hematological indicators in rat, where male and female rats were administered a daily oral dose of 200mg/kg body weight of aqueous extract of guava leaves for a period of 30 days. The results indicated that the frequency of red blood cells, hematocrit and hemoglobin concentration increased significantly with the administration of the extract in male and female rats ($P<0.05$). The findings of this study also revealed that *P. guajava* leaf extract may be used as a blood properties enhancer in anemia conditions or for preventive purposes[25].

Although the specific mechanism(s) through which the extract increases these hematological indices was not determined in this study, it is assumed that it is a direct effect of the extract on hematopoietic systems. It is possible that this extract contains compounds that can stimulate the synthesis and secretion of erythropoietin, hematopoietic growth factors and committed stem cells. Stimulation of hematopoietic growth factors and erythropoietin synthesis can increase the rapid synthesis of blood cells [25]. The results of this study are consistent with the results of the related study.

It has been evidenced that exposure of stem cells extracted from bone marrow to different doses of hemp extract affects the growth process of the cells, in that low doses caused more growth while higher doses had a lethal effect thereon. Daily exposure of bone marrow stem cells to cannabis extract has been shown to increase apoptosis over time. Furthermore, bone marrow stem cells of mice retain their mesenchymal properties after exposure to non-lethal cannabis [26]. As such, the results of this study are in line with those of the current study regarding its effect on stem cells and maintaining the properties of cells.

It has been examined in their study the effects of *P. guajava* aqueous extracts on hematological parameters in Albino rats, in which the subjects were orally administered daily doses of 250mg/kg and 500mg/kg of body weight. The results showed that the concentration of hemoglobin, red blood cells, MCH, MCHC, MCV and the number of platelets in the dose of 250mg/kg and 500mg of body weight increased significantly compared to the control group. This study shows that the studied *P. guajava* extract can have a positive effect on hematological parameters in mice is recommended for further study in the treatment of anemia [27-29].

The findings of the current study are consistent with those of others, in that the use of *P. guajava* plant does not have any side effects on the hematological parameters of the body, while it can strengthen the immune system by increasing the number of white blood cells. Moreover, it is perceived to be effective in hematopoiesis through increasing the number of red blood cells and bone marrow erythroid cells. Examining the antioxidant activity of guava hydroalcoholic extract shows that this extract plays a great role in trapping free radicals and preventing anemia[30-32].

Evidence suggests that, since guava leaf hydroalcoholic extract is rife with flavonoids, tannins, ellagic acid, triterpenes and quercetin, it can provide favorable conditions for the growth and differentiation of stem cells into hematopoietic cells and help in the regeneration of blood tissue. These

compounds can protect cell membranes, including red blood cell membranes, from damage caused by free radicals, prevent their destruction, and hence increase their count in the blood [30-32].

Based on past studies and the results of this research, it can be suggested that the positive effects of guava leaf extract are caused by flavonoids, quercetin and triterpenes. These strong antioxidants can prevent damage caused by free radicals that destroy cells. This study shows that guava leaf extract can have a positive effect on hematological parameters, as well as the lack of mutagenicity and cytotoxicity with high doses of this plant extract means its safe use in traditional medicine[33, 34]. Therefore, it is recommended that guava leaf extract can be considered as a complementary and alternative treatment for many diseases, including the treatment of anemia. Of course, more studies are needed to confirm these results using other experimental models such as rabbits and pigs.

5. Conclusion

The results of the effect of guava hydroalcoholic extract on peripheral blood cells and bone marrow in the current research revealed the non-toxicity of this extract in the experimental groups receiving daily doses of 3000, 4000, and 5000 mg/kg for a period of 3 months. More researches are needed to understand the metabolism, mechanism of action, effectiveness, safety and effective components of guava hydroalcoholic extract. Even though, the present study showed that this plant extract is not toxic and has no harmful effects, but according to the results of previous studies, it may be useful for the treatment of anemia.

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publications

All authors read and approved the final manuscript for publication.

Informed Consent

The authors declare not used any patients in this research.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors had equal role in study design, work, statistical analysis and manuscript writing.

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