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Evaluation of hematinic effects of aqueous leaf extract of hibiscus acetosella welw. Ex hiern on phenyl hydrazine-induced anemia in wistar rats

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ABSTRACT

Ethnopharmacological information indicates that the leaves of Hibiscus acetosella Welw. ex. Hiern are used in the treatment of anemia in western and central Uganda. In this study, the aqueous leaf extract of Hibiscus acetosella Welw. ex. Hiern was tested for its haematinic activity in Wistar rats. Phenylhydrazine (PHZ- 4 mg/kg, IP) was used to induce anemia in rats for a period of two weeks. Animals were grouped into six groups (1, 2, 3, 4, 5, and 6); each group had six rats. Group 1 (negative control), group 2 (positive control), group 3 were treated with FeSO4, and groups 4, 5, and 6 were treated with different doses of the extract (1000 mg/kg, 2000 mg/kg, and 4000 mg/kg, respectively). Screening of phytochemicals was performed, and acute toxicity study was carried out according to the Lorke's experiment 1993. Phytochemical analysis revealed that the aqueous leaf extract of Hibiscus acetosella Welw. ex. Hiern contains tannins, flavonoids, diterpenes, steroids, and saponins.The aqueous leaf extract of Hibiscus acetosella Welw. ex. Hiern exhibits haematinic effects.

Keywords: Hematinic effects**,** Aqueous leaf extract**,** Hibiscus acetosella Welw. ex Hiern**,** Phenyl hydrazine-induced anemia**,** and Wistar rats.

INTRODUCTION

Medicinal plants are nature's gift to human beings for a disease-free, healthy life. For ages, several million Ugandan households have been using nearly 8,000 species of medicinal plants for their healthcare needs. Over a million traditional healers employ a wide range of medicinal plants to treat ailments in both humans and livestock across the country [1–3].

Herbal and traditional medicines are widely used in Uganda. Many drugs used in modern medicine originate from plants, and there is no doubt that new drugs can still be discovered from plants, including those indigenous to Uganda. Therefore, there is a need for the government to provide adequate funds to institutions and universities to promote research in drug development, especially herbal medicine. Such research should be demonstrably relevant to the needs of society, with a high potential for immediate application [4–7]. Traditional herbal medicines are gaining significant attention in global health debates. In China, traditional herbal medicine played a prominent role in the strategy to contain and treat severe acute respiratory syndrome (SARS). Eighty percent of the African population uses some form of traditional herbal medicine as their primary means of healthcare. Some communities advise pregnant mothers to chew a special type of stones to help them add minerals and build blood [1, 8].

Anemia is a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiological needs and varies with age, sex, altitude, smoking, and pregnancy status[2]. Iron deficiency anemia is thought to be the most common cause of anemia globally; however, other conditions such as folate and vitamin B12 deficiencies, vitamin A deficiencies, chronic inflammation, parasitic infections, and inherited disorders can also cause anemia. In severe cases, anemia can be associated with fatigue, weakness, dizziness, and drowsiness[9]. Anemia generally results from acute blood loss, decreased red blood cell (RBC) production, poor RBC maturation, or increased RBC destruction. Pregnant women and children are particularly vulnerable to anemia. Females lose blood during menstruation and are at greater risk of iron deficiency anemia. Infants, especially those with low birth weight or born prematurely, who don't get enough iron from breast milk or formula, vegetarians, individuals with intestinal disorders, and frequent blood donors may also be at risk of iron deficiency [10].

Globally, anemia affects 1.62 billion people, corresponding to 24.8% of the population. The highest prevalence is in preschool-age children (47.4%), while the lowest prevalence is in men (12.7%) and women (95%) [11].

With high prevalence worldwide, particularly in women and young children, anemia remains one of the leading causes of death in Africa and other developing countries. It complicates most tropical illnesses, with the highest proportion of affected individuals being women and children. In Africa, 57% of pregnant women, 48% of non-pregnant women, and 68% of preschool children are anemic

[12]. The prevalence of anemia in Uganda was 64% among children under 5 years, as noted in a subsequent study in 2006 [13], which indicated an increase to 72% in Uganda. The disease condition is multifactorial in etiology, but iron deficiency is thought to be the most common cause of anemia globally. Other factors such as lack of access to a balanced diet, folate and vitamin A deficiencies, chronic inflammation, parasitic infections, and inherited disorders can also cause anemia [14].

Experimental hemolytic anemia can be induced in rats using phenylhydrazine. Initially used as an antipyretic drug, phenylhydrazine is well known for its ability to produce hemolysis in rats and humans. Phenylhydrazine has been remarked as a potent drug for blood disorders [15–17]. Phenylhydrazine-induced toxicity is attributed to lipid peroxidation occurring in the membrane of RBCs, leading to the formation of methemoglobin and Heinz body formation. It is also known to decrease hemoglobin levels, RBC count, and PCV (packed cell volume) while inducing an increase in MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), and MCHC (mean corpuscular hemoglobin concentration)[17].

Anemia is considered one of the leading causes of mortality among women and children under five years in developing countries. Globally, anemia affects 1.62 billion people (24.8% of the population), with the highest prevalence (47.4%) in preschool-age children [18]. The use of Hacetosella Welw.ex. Hiern aqueous leaf extract in the treatment of anemia still raises questions about the correct dose, efficacy, and safety profile.

METHODOLOGY

Study Design

A short-term prospective-experimental study was conducted in which Wistar rats served as a model to predict the anti-anemic effects of Hibiscus acetosella Welw.ex. Hiem aqueous leaf extract, following phenylhydrazine-induced hemolytic anemia. The rats were orally treated with the leaf extract, and the positive and negative controls were analyzed.

Study Setting

The study was conducted in the Biopharmacy Lab at KIU Western Campus and the Lab at KIUTH Hospital.

Experimental Materials

Forty-five healthy, mature, non-pregnant Wistar rats were used. The materials included Hibiscus acetosella Welw.ex. Hiem aqueous leaf extract, beakers, air-tight storage containers, phytochemical screening reagents, analytical balances, oral cannula, phenylhydrazine, caliper, syringes (0.1 ml, 0.5 ml), conical flasks (250 ml), separating bottles, measuring cylinder, normal saline, blender, oven, fridge, Vacutainers, weighing scale, and filter papers.

Plant Material Collection and Extraction

The plant was collected from around a banana garden in Rwemirokora Ishaka town, Bushenyi district, and was identified by Dr. Eunice Olet, a botanist at Mbarara University of Science and Technology. The leaves were collected, sorted, and dried under shade in the KIU Pharmacy Laboratory for about two weeks, then ground with a blender. Two hundred grams of the powder was weighed in a beaker, submerged into 1 liter of distilled water in a conical flask, and shaken intermittently for 24 hours. The mixture was filtered using filter paper, and the filtrate was obtained. The residues were dried, and the filtrate was concentrated by evaporation at 40°C in an oven. The percentage yield was determined using the formula:

Percentage yield = (Weight of the dry extract (g) / Weight of the powder used) x 100.

Phytochemical Screening

Phytochemical parameters were screened following standard procedures[19].

Alkaloids (Picric Acid Test)

The reagent used was a saturated solution of picric acid in distilled water. Formation of a yellow precipitate indicated the presence of alkaloids.

Essential Oils

To 2 ml of the test sample, 0.1 ml of dilute sodium hydroxide (2M) was added and shaken, then a small quantity of dilute hydrochloric acid (2M). Formation of a white precipitate indicated the presence of essential oils (volatile oils).

Test for Saponins

Four milliliters of distilled water was added to 0.5 g of sample in a beaker and boiled for 5 minutes. The mixture was filtered while still hot, and 5 ml of sterile distilled water was added to a test tube containing an equal volume of cooled filtrate. The tube was stoppered and shaken vigorously for 30 seconds, then allowed to stand for 30 minutes. Formation of honeycomb froth indicated the presence of saponins.

Test for Tannins

Exactly, 0.3 g of sample was boiled with 5 ml of distilled water on a hot plate. The mixture was filtered, and a portion of the filtrate was diluted with sterile distilled water in a ratio of 1:4, then 3 drops of 10% iron (III) chloride solution were added. Formation of a blue-green precipitate indicated the presence of tannins.

Test for Terpenoids

Five milliliters of the test sample was mixed with 2 ml of chloroform and concentrated sulfuric acid, then 3 ml was added carefully down the side of the test tube. Formation of a reddish-brown coloration of the interface indicated a positive test for terpenoids.

Test for Phenols

Two milliliters of the test sample was added to 2 ml of iron (III) chloride solution. Formation of a deep bluish-green solution indicated the presence of phenol in the extract solution.

Test for Glycosides (Molisch's Test)

One to two drops of the reagent was added to 0.5 ml of the test solution, then 10-15 drops of concentrated sulfuric acid were carefully added so that it formed a layer beneath the mixture. Formation of a purplish-colored interface indicated the presence of a carbohydrate.

Test for Flavonoids (Shinoda Assay)

One milliliter of the extract was diluted with 1 ml concentrated HCl, and a small strip of magnesium was added. After 5 minutes of the reaction, 1 ml of water and 1 ml of butyl or amyl alcohol were added. A dark-yellow, orange, red, or brown color indicated the presence of flavonoids.

Experimental Animal Models

Phenyl hydrazine-induced rat hemolytic anemia was used as the animal model of anemia [2]. Wistar rats of either sex were purchased from the Department of Pharmacology at KIU's animal research house. The animals were housed in clean wooden cages lined with sawdust and maintained at room temperature under cycles of 12 hours of light and 12 hours of darkness each day for one week before and during the experiments. The animals were fed standard laboratory rat pellets from NUVITA Uganda and provided drinking water ad libitum. Experimental animals were acquired and kept for one week prior to the beginning of the study to allow them to acclimatize in the study laboratory. Food was withheld with free access to water 12 hours before the experiments. Experiments were carried out according to the current guidelines for the care of laboratory animals and ethical guidelines (NIH, 1996).

Acute Toxicity Test

This was carried out using lorke's method [2].

Nine rats were randomly selected. The first group was administered with 5000 mg/kg of the extract and then monitored for signs of toxicity such as excitement, seizures, fever, skin hypersensitivity, and death at 1, 4, 8, and 12 hours within 24 hours. If the first group survived, the second group was given a higher dose of 7500 mg/kg. If no deaths occurred with the first group, the last group was treated with 10,000 mg/kg. Surviving animals were monitored for 2 weeks for delayed toxicities and death. The administered dose for each rat was calculated using the formula:

Administered dose = (Dose (mg/kg) x Animal weight (grams)) / (Concentration (mg/ml) x 1000).

Induction of Anemia

Thirty-six mature non-pregnant Wistar rats were weighed and grouped into six groups of six rats each. The animals were fasted for 12 hours before phenyl hydrazine treatment. Anemia was induced in the rats by daily intraperitoneal administration of phenylhydrazine (PHZ) at 4 mg/kg for 14 days[2] Rats that developed anemia with hemoglobin concentrations lower than 13 g/dl were recruited for the study.

Animals were administered phenylhydrazine as follows:

Group 1: Not induced with phenylhydrazine.

Group 2: Induced with phenylhydrazine (4 mg/kg) and treated with 200 mg/kg of $FeSO_4$.

Group 3: Induced with phenylhydrazine (4 mg/kg) but received no treatment (negative control).

Group 4: Phenylhydrazine-induced (4 mg/kg) with 1000 mg/kg of ALEHA.

Group 5: Phenylhydrazine-induced (4 mg/kg) with 2000 mg/kg of ALEHA.

Group 6: Phenylhydrazine-induced (4 mg/kg) with 4000 mg/kg of ALEHA.

Treatment of the animals:

On day 15, the anemic rats were randomly divided into six groups (6 rats per group) and were treated daily for 4 weeks as follows [21]:

Group one animals received (1 ml) 0.9% Normal saline (control).

Group two animals received $FeSO_4$ (DAWA Pharmaceutical Ltd, KENYA) 200 mg/kg.

Group 3 animals did not receive anything.

Animals in groups 4, 5, and 6 received 1000 mg/kg, 2000 mg/kg, and 4000 mg/kg of aqueous leaf extract. All administrations were done by oral intubation (using an oral cannula).

Analysis of hematological parameters:

Animals were anesthetized using chloroform and dissected following the National Institute of Health guide for the care and use of laboratory animals. Blood was collected by cardiac puncture using sterile needles, syringes, and Vacutainer tubes with EDTA, for hematological analysis including red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Hct), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC) count, and platelets, using an automated blood analyzer (Tokyo Symex).

Statistical analysis of data:

Data were analyzed using GraphPad Prism version 6.0. One-way analysis of variance (ANOVA) was used as a statistical test for variation across groups followed by multiple comparison tests. All values were reported as mean ± standard error of the mean (SEM). A p-value of <0.05 was considered significant.

Ethical considerations:

Approval for the current study was obtained from KIU-WC Research and Ethics Committee through the School of Pharmacy, KIU-WC. Animal experiments were conducted according to the National Institute of Health guide for the care and use of laboratory animals (NIH).

RESULTS

Percentage yield calculation.

Percentage yield of extraction from cold extraction was as follows:

% Yield= (weight of extract plus container) minus

weight of container alone multiply by 100 plus Weight of the initial powder. = (l 78.6-l 43.70) x 100+200=17.45

Table 1: To show phytochemical analysis and results

TEST	RESULTS
Anthroquinones	-
Reducing sugars (Benedict's test)	+++
Saponins (frothing test)	+
Tannins	+++
Steroids	+
Ninhydrin test	++
Test for arginine	
Flavonoids	+++
Cardiac glycosides	+++
Phlobatanins.	-
Resins	-
Alkaloids	-
Diterpenes copper acetate test	+++

KEY: + means present; - means absent.

The acute toxicity test results of *Hibiscus acetosella* Welw. ex. Hiern aqueous leaf extract showed that when orally administered to Wistar rats, even up to a dose of 10,000 mg/kg, no deaths occurred. However, some effects were noted.

Table 2 showing acute toxicity studies using Lorkes' Modified Method.

Dose	Signs after.		
	1-2 hrs	3hrs	24hrs
5000mg/kg of extract	Itching	Drowsiness	Loss of eye reflex.
7500mg/kg of extract	Drowsiness	Urination	None
10000mg/k of extract	Itching	Drowsiness	Itching

Thus, the LD_{50}, which is given by the formula:

$LD_{50} = \sqrt{}$ (Lowest dose × Highest non-lethal dose), was estimated/approximated to be greater than 10,000 mg/kg of body weight."

Table 3 Effects of ALEHA Welw.ex.Hiern on red blood cell count in rats with PHZ induced anemia

Treatment	Dose Mg/kg	RBC (10^6/µL)	P values P<0.005*
Control		8.58±0.37	<0.0001
PHZ	4	5.99±0.20	-
FeSO4	200	8.76±0.31	<0.0001
EXTl000	1000	8.57±0.27	<0.0001
EXT2000	2000	8.89±0.17	<0.0001
EXT4000	4000	9.16±0.15	<0.0001

The table shows that there are significant results between the control and tested extract of ALEHA, so we can conclude/say that the plant is efficient in the increase of RBC in anemic rats

Table 4 Effect of ALEHA Welw.ex.Hiern on Haemoglobin concentration in rats with PHZ induced anemia

Treatment	Dose Mg/kg	Hb (g/dL)	P values P<0.005*
Control		15.24±0.73	0.1160
PHZ	4	13.45±0.08	-
FeSO4	200	15.40±0.56	0.0710
EXTl 000	1000	16.76±0.52	0.0005
EXT2000	2000	16.35±0.50	0.0014
EXT4000	4000	16.63±0.32	0.0004

The table demonstrates significant effects for the extracts at doses of 1000mg/kg, 2000mg/kg, and 4000mg/kg compared to the control, while FeSO4 at a dose of 200mg/kg produced insignificant effects.

Table 5 Effect of *Hibiscus acetosella* Welw.ex.Hiern on Haematocrit level in rats with PHZ induced anemia.

Treatment	Dose Mg/kg	HCT (%)	P values P<0.005*
Control		15.24±0.73	0.0602
PHZ	4	13.45±0.09	-
FeSO4	200	15.40±0.56	0.0955
EXTl000	1000	16.76±0.52	0.0007
EXT2000	2000	16.35±0.50	0.0052
EXT4000	4000	16.63±0.32	0.0036

*Significant changes. The table shows significant effect for extract 1000mg/kg, 2000mg/kg and 4000mg/kg dose in comparison to the control whereas $FeSO_4$ in a dose of 200mg/kg produced insignificant effects.

Table 6 Effect of *Hibiscus acetosella* Welw.ex.Hiern on Mean cell volume in rats with PHZ induced anemia

Treatment	Dose Mg/kg	MCV (fL)	P values P<0.005*
Control		54.24±0.86	<0.0001
PHZ	4	68.28±2.58	-
FeSO4	200	52.82±0.57	<0.0001
EXTl000	1000	58.70±1.62	0.0061
EXT2000	2000	54.42±1.70	<0.0001
EXT4000	4000	53.15±1.58	<0.0001

*Significant changes. The table shows that there are significant results between the control and tested extract of ALEHA, so we can conclude/say that the plant is efficient in the increase of MCV in anemic rats. However, for a dose of 1000mg/kg the results were insignificant. Hence the data suggested that the effects are dose dependent.

MCHC Vs Extract

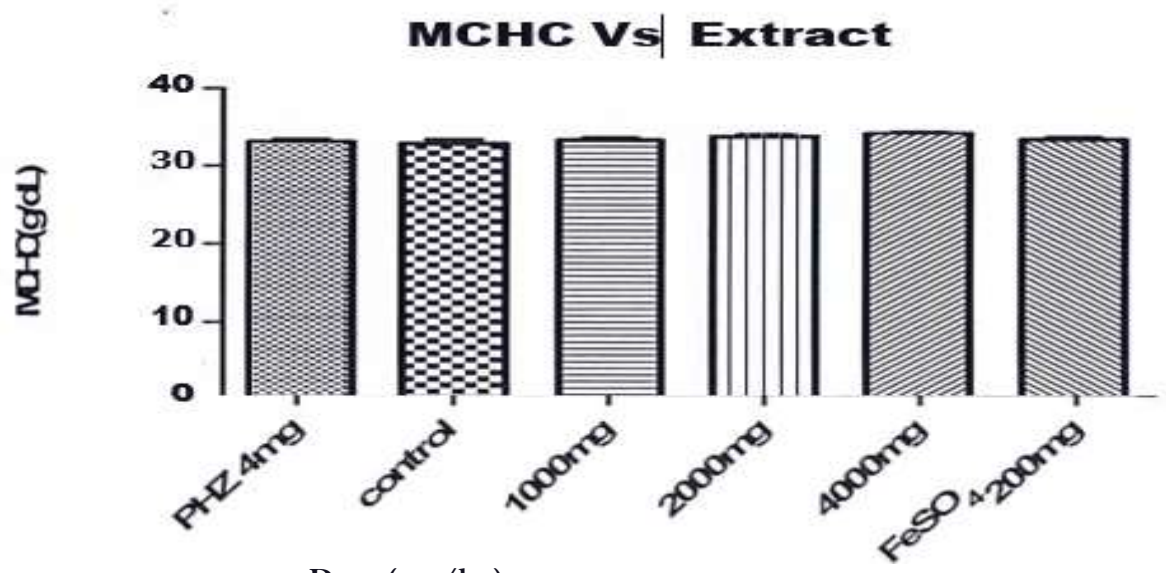

Figure 1: A graph of average MCHC level against treatment at different doses of ALEHA.

The figure shows that there are significant results between the control and tested extract of ALEHA, so we conclude that the plant is efficient in the increase of MCHC in anemic rats. However, for rats which were not treated with the extract were able to recover by themselves. Hence the effect shows dose independent.

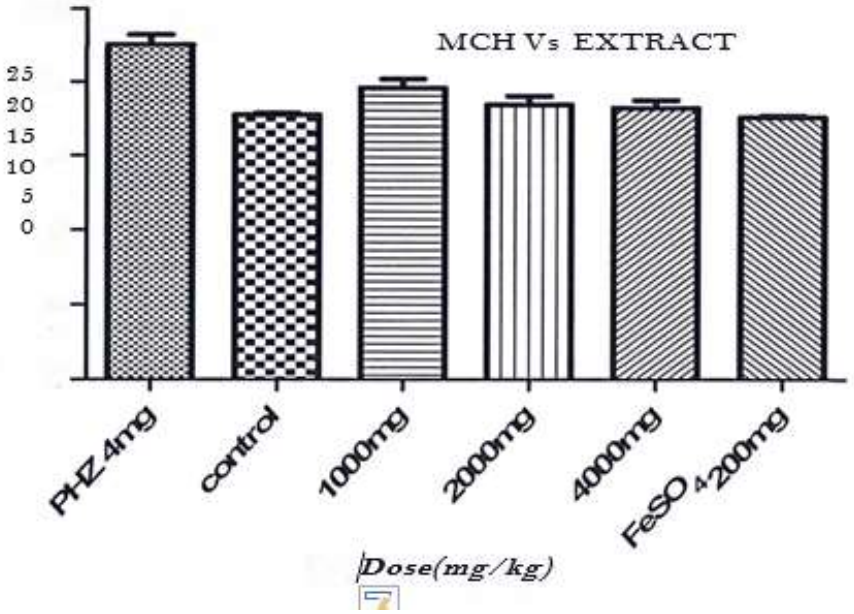

Figure 2: A graph of average MCH level against treatment at different doses of ALEHA The figure shows significant effect for extract 2000mg/kg,4000mg/kg dose in comparison to the control whereas FeSO4 in a dose of 200mg/kg produce significant effect, while extract I 000mg/kg produced insignificant effect. Animal treated with PHZ 4m/kg showed a higher level of MCH.

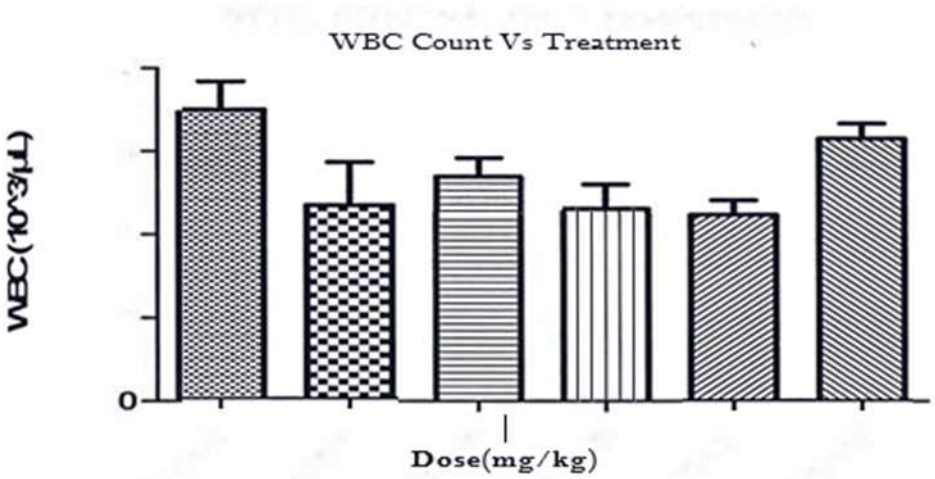

Figure 3: A graph of average WBC level against treatment at different doses of ALEHA

The figure shows that there are insignificant results between the control and tested extract of ALEHA, so we conclude that the plant has no effect on WBC in anemic rats. However, rats which were treated with PHZ had higher level of WBC.

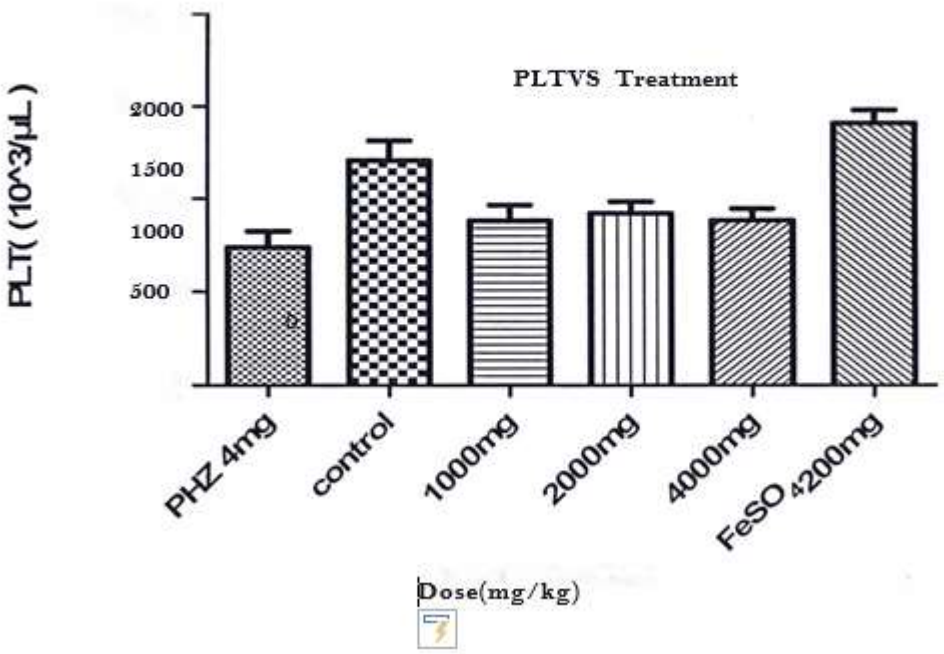

Figure 4: A graph of average Platelets level against treatment at different doses of ALEHA

The figure shows that there are insignificant results between the control but there is significant results between extract of dose of 1000mg/kg,2000mg/kg and 4000mg/kg ALEHA, while rats treated with $FeSO_4$ it results were insignificant, we conclude that the plant has no effect on PLT in anemic rats. However, rats which were treated with PHZ had lower level of platelets.

DISCUSSION

Anemia, a condition characterized by reduced oxygen-carrying ability of the blood, regardless of its cause, is more a sign of an underlying disorder than a disease [22]. In vertebrates, anemia is a common hematological condition associated with various factors such as drug toxicity, parasites, genetic defects, and blood loss [23]. The hallmark of anemia is inadequate levels of oxygen in the blood, leading to symptoms like easy fatigue, paleness, shortness of breath, edema, and chills often experienced by anemic individuals.

The diagnosis of anemia typically begins with spectroscopic measurement of blood hemoglobin levels. Reduction in hemoglobin is usually accompanied by a decrease in red cell count and packed cell volume. Phenylhydrazine may cause damage to red blood cells, potentially resulting in anemia and secondary involvement of other tissues such as the spleen and liver [2] Phenylhydrazine induces the destruction of red blood cells through oxidative stress and various cellular changes, resulting in hemolytic anemia. It also reduces hemoglobin levels, red blood cell concentration, packed cell volume, and impairs erythrocyte deformability. Intraperitoneal administration of Phenylhydrazine at a dose of 4mg/kg for two weeks reduced hematological indices by 50% [2]. However, these parameters were restored to normal ranges after treatment with aqueous leaf extract of Hibiscus acetosella Welw.ex. Hiern, suggesting that the leaf extract has a hematinic effect. Under normal conditions, the body can generate new red blood cells to replace those lost [24].

The presence of phytochemicals such as flavonoids, saponins, tannins, diterpenes, and steroids in the aqueous leaf extract of Hibiscus acetosella Welw.ex. Hiern has been reported to have hematinic effects. These agents inhibit known cyclic adenosine monophosphate (cAMP) phosphodiesterase, thereby accumulating cAMP [2, 25]. This effect stimulates phosphorylation of proteins and synthesis of protein, thereby enhancing erythropoiesis. This indicates that the aqueous leaf extract of Hibiscus acetosella Welw.ex. Hiern contains bioactive agents that may promote erythrocyte formation by stimulating the kidney to release renal erythropoietin factor, thereby causing the conversion of blood protein to erythropoietin which stimulates the red bone marrow to produce more red blood cells, replacing those denatured by Phenyl hydrazine. The effect of the extract on hematological indices showed a significant increase ($P<0.05$) in hemoglobin

concentration, red blood cell count, hematocrit, mean cell hemoglobin, mean cell hemoglobin concentration, and mean cell volume. There were significant results between the control and tested extract of ALEHA Welw.ex. Hiern, suggesting that the plant is efficient in increasing red blood cells in anemic rats. There was a significant effect for extract doses of 1000mg/kg, 2000mg/kg, and 4000mg/kg compared to the control, while FeSO4 at a dose of 200mg/kg produced an insignificant effect on hemoglobin level. There was a significant effect for extract doses of 1000mg/kg, 2000mg/kg, and 4000mg/kg compared to the control, while FeSO4 at a dose of 200mg/kg produced an insignificant effect on hematocrit. There were significant results between the control and tested extract of ALEHA Welw.ex. Hiern in the increase of mean corpuscular volume in anemic rats. However, for a dose of 1000mg/kg, the results were insignificant, suggesting that the effects are dose-dependent. There were significant results between the control and tested extract of ALEHA Welw.ex. Hiern in the increase of mean corpuscular hemoglobin concentration in anemic rats. However, untreated rats were able to recover by themselves, indicating that the effect shows dose independence. Significant effects were seen for doses of 2000mg/kg and 4000mg/kg compared to the control, while FeSO4 at a dose of 200mg/kg produced a significant effect, while extract at 1000mg/kg produced an insignificant effect. Animals treated with PHZ showed a higher level of Mean Corpuscular Hemoglobin. There were insignificant results between the control and tested extract of ALEHA Welw.ex. Hiern; animals treated with PHZ had a higher level of White Blood Cells. Significant results were seen between extract doses of 1000mg/kg, 2000mg/kg, and 4000mg/kg, while rats treated with FeSO4 showed insignificant results. However, rats treated with PHZ had lower levels of platelets, indicating that the plant has no effect on platelets. The optimum dose of the ALEHA Welw.ex. Hiern was 1000mg/kg. This shows that the extract had an ameliorating effect, which may have reduced the intravascular hemolysis caused by Phenylhydrazine. No animals died during the acute toxicity study because Hibiscus acetosella Welw.ex. Hiern aqueous leaf extract is safe and non-toxic at an LD50 of 10000mg/kg, indicating a very high safety margin. The percentage yield of the aqueous leaf extract of Hibiscus acetosella Welw.ex. Hiern is 17.45%. These results support, at least partially, the folk use of aqueous leaf extract Hibiscus acetosella Welw.ex. Hiern in the treatment of anemia.

CONCLUSION

The extract contains polyphenols i.e., saponins, glycosides, diterpenes, phenols, and steroids which contribute to its efficacy in the treatment of anemia. The effect of the extract was comparable to animals treated with FeSO4. Therefore, we can propose the use of the aqueous leaf extract of Hibiscus acetosella Welw.ex. Hiern in the treatment of anemia because the plant was also found to be safe even up to doses of 10000mg/kg.

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