RESEARCH ARTICLE

IMPACT OF AQUEOUS LEAF-EXTRACT OF *PSYCHOTRIA VOGELIANA (BENTH)* ON SERUM ELECTROLYTES CONCENTRATION IN WISTAR RATS WITH COMPLETE FREUND'S ADJUVANT-INDUCED RHEUMATOID ARTHRITIS

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ABSTRACT

Plant extracts can influence electrolytes concentration and potentially have implications for rheumatoid arthritis (RA) management. 48 female albino rats weighing between 100 and 200g were used in this study. RA was induced in the rats using 0.1ml of complete Freund's adjuvant (CFA). Arthritis index was tracked following the Chondrex technique, which only showed signs of inflammation such as redness, edema in the injected paw. Experimental animals were divided into six groups. Group 1 (control) received feeds and water only. Group 2 (toxic) was induced with RA and left untreated. Group 3 (Standard) was induced with RA and treated with standard drug (methotrexate at the dose of 0.225 mg/kg daily). Groups 4, 5 and 6 (treated groups) were induced with RA using CFA, 3 hours later, administered orally with *Psychotria vogeliana* aqueous leaf-extract at the doses of 200mg/kg, 400mg/kg and 600 mg/kg respectively. Standard methods were employed to determine serum electrolytes concentration. *Psychotria vogeliana* leaf extract at 200 mg/kg, 400 mg/kg, and 600 mg/kg significantly raised the levels of serum electrolytes of RA rats in a manner comparable to the group that was treated with standard drug and the normal control group. Our findings revealed that rheumatoid arthritis (RA) causes a notable decrease in the concentration of sodium, potassium, calcium, and bicarbonates, which can lead to a depletion of the serum electrolyte balance. Nonetheless, *Psychotria vogeliana* leaf extract showed a lot of potential for resupplying these vital bodily electrolytes.

Keywords: *Psychotria vogeliana*, Serum Electrolytes, Rheumatoid arthritis, Autoimmune Disease, Inflammation.

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1.0 INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory disease in which the synovial cells, bones and cartilage are progressively assaulted by autoimmune responses, causing joint destruction and long-term impairments (1). According to epidemiological research, RA affects roughly 1% of individuals worldwide and has a major influence on quality of life (2). It affects women more frequently than males in every demographic category (3). The prevalence of RA in Africa ranges from 0.1% to 2.5% in urban centres and from 0.07% to 0.4% among the rural dwellers (4). The frequency of RA, however, varies according to the hospital-based study conducted in Africa, with numbers as low as 2.2 percent and as high as 33 percent.

Rheumatoid arthritis presents systemic symptoms such as cardiovascular, pulmonary, physiological disorders, and skeletal abnormalities such as stiffness and lack of physical mobility (4). Due to insulin resistance and compromised beta-cell activity, chronic inflammation in RA results in decreased glucose metabolism. Additionally, people with RA seem more likely to develop moderate to severe atherosclerosis and heart failure (5).

Psychotria species has been reported to possess important therapeutic potentials, including antioxidant (6), anti-bacterial, anxiolytic, anti-depressive, anti-inflammatory, and antiepileptic activities(7). Major bioactive compounds found in *Psychotria species* are alkaloids, particularly monoterpene indole alkaloids (8). Alkaloids have demonstrated functional bioactivities, such as antimicrobial, antiviral, and antiparasitic activities (9). Additionally, *Psychotria species* alkaloids have been found to interact with sirtuins, which are promising targets for treating neurodegenerative conditions (10).

Studies have provided insights into the long-lasting inflammation and systemic changes associated with RA induced using Complete Freund's adjuvant (CFA) in wistar rats. They highlight the role of various factors in the pathogenesis of RA, including cytokines, cartilage destruction, bone erosion, and joint dysfunction. Jang and his research team in 2021 emphasized the significance of tumor necrosis factor α (TNFα) in RA, as it promotes cartilage and bone resorption, induces the release of inflammatory mediators, and facilitates inflammatory cell infiltration (11). In 2019, Jang and his team designed a procedure for creating an animal model of humanised synovitis that could be employed to study the function and processes of substances or cells that target RA fibroblast *In vivo*. Fibroblasts inflammation contribute to local production of cytokines, inflammatory mediators, and matrix metalloproteinases (MMPs), leading to cartilage destruction (12). Characteristics of RA, including chronic joint inflammation, synovial hyperplasia, leukocyte infiltration, and aggressive pannus formation that invades and erodes articular cartilage and subchondral bone (13)

Many research findings have suggested that plant extracts can influence electrolyte levels and potentially have implications for RA management. Aqueous extract of *Uvaria chamae* leaves was reported to cause decrease in serum concentrations of certain electrolytes in rats (14). Alsaedi and Aljeddani in their studies demonstrated that ethanol extract of *Spilanthes*

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acmella leaves exhibited diuretic activity and increased electrolyte excretion in rats (15). Olorunnisola in 2015 showed that the ethanolic fruit-extract of *Lagenaria breviflora* stimulated erythropoiesis as well as caused electrolyte imbalances in rats (16). Lastly, Padzys revealed in his studies that the aqueous extracts of *Amaranthus rectroflexus* and *Gnetum africanum* leaves decreased plasma sodium concentration and affected urea and creatinine levels in rats (17). *Psychotria vogeliana aqueous leaf-extract* are usually offered for inflammations treatments and RA in many Nigerian traditional societies and has offered great healing effect to patients. Before now, many research outcomes have suggested that plant extracts can influence electrolyte levels that may potentially aggravate the clinical symptoms at various stages of RA pathogenesis. Additionally, there is no scientific literature on how *Psychotria vogeliana* aqueous leaf extract affects the blood electrolyte level of CFA induced RA in albino rats. Therefore, this study was done to provide useful scientific proof for this herbal medicine and further help to providing data for the development of therapeutic strategies that would provide a more affordable medicine for the management of RA.

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2.0 MATERIALS AND METHODS

Chemicals and reagents

Every chemical utilized in this investigation is of analytical standard.

Biological samples

The biological components employed in this study include *Psychotria vogeliana* leaf extract and female albino rats.

Collection and authentication of plant materials

In January 2022, *Psychotria vogeliana* leaves were obtained fresh in a bush located in Uburu, Ohaozara council area of Ebonyi state, Nigeria. Their authenticity was confirmed through the use of www.theplantlist.org and www.worldfloraonline.org. The leaf samples were stored with the code "EBSU/H/119" in the botanical library of the Applied Biology Department of Ebonyi State University in Nigeria.

Extraction of *Psychotria vogeliana* leaves materials

Psychotria vogeliana leaves were allowed to dry for four weeks at room temperature. Afterwards, they were crushed into a fine powder using an electric blender that had been sterilized with alcohol. The 700g of powdered leaf was soaked in 3200 mL of alcohol for 48 hours. The material used to make the filtering system was muslin. The resulting filtrate was concentrated by evaporation to dryness using a rotary evaporator **(18)**.

Ethyl acetate-based fractionation

The separation method used was chromatographic columns technique, which measured 50 centimetrs high and 2.5 centimetres in internal diameter. In order to preserve the silica gel within the column's structure, glass fibre was embedded into the bottom of the column. subsequently, 70 grammes of silica gel and 150 millilitres of ethyl acetate were combined and stirred to generate a gel-like solution. It was found that a

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packed bed column could rise up to 30 cm if its length-to-diameter proportion was more than 10. Our column is 12 centimetres long by 2.5 cm in diameter. A mixture of previously prepared specimens of reflux extracts of ethanol (Psychotria vogeliana) was added to the ethyl acetate solution. The resultant extract and ethyl acetate solution mixture was then added to the column. The sample was put above the compressed bed that was previously pierced **(19)**.

Acquisition and Care of Experimental Animals

48 female albino rats, weighting within 100 and 200g, were purchased from the University of Nigeria's Department of Veterinary Medicine and brought to the Department of Biochemistry, Ebonyi State University's animal house in metal cages. The rats were habituated for seven days in laboratory metal cages with sufficient air circulation and a 12-hour day/night cycle. The animals had unrestricted access to drinking water and commercial feed (Vital Feeds®, Ebonyi, Nigeria).

Rheumatoid Arthritis Induction

Complete Freund's adjuvant (CFA) was purchased from Sigma Aldrich in Saint Louis, Missouri, and maintained at 2-4 °C away from direct sunlight. In the right hind leg footpad of female rats, 0.1 ml of CFA—a suspension of heat-killed Mycobacterium tuberculosis in 0.5 ml of mineral oil—was subcutaneously injected. The Arthritis Index (AI) has been tracked using Chondrex's methodology (35). The injected paw was the only one to exhibit signs of inflammation, including redness, swelling, and hypersensitivity to painful stimuli **(20)**.

Design of the study

48 female wistar albino rats weighting within 100 and 200 g were separated into eight groups for the purpose of this study: Group 1 (Control) was given standard chow and normal saline. Group 2 (Toxic) was subjected to CFA-induced RA in the absence of therapy. Group 3 (standard) received conventional treatment (methotrexate at a dose of 0.225 mg/kg daily) after RA was provoked by CFA (20). Group 4 (AE200) received treatment with 200 mg/kg of *Psychotria vogeliana* aqueous leaf extract after RA was induced by CFA. Group 5 (AE400) received treatment with 400 mg/kg of *Psychotria vogeliana* aqueous leaf extract after RA was induced with CFA. Rats in Group 6 (AE600) were given CFA to induce depression, and they were then given 600 mg/kg of *Psychotria vogeliana* aqueous leaf extract **(18,21–23)**. Isoflurane, an inhaled anaesthetic, was used to lightly sedate the rats following 28 days of oral treatment. (18). The drop jar technique was used to administer isoflurane before sacrifice.

Procedure for collecting blood samples, serum preparation and analysis

The rats' femoral veins were punctured to get blood, which was then placed into plain sample tubes. The clear, non-hemolyzed supernatant sera were removed from the whole blood within an hour after blood clotting by centrifuging the mixture at 3000 rpm for 15 minutes. The clear serum was then pipetted into plain tube samples and stored at -20°C until needed. Electrolytes including bicarbonate ion concentration,

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calcium ion, potassium ion, and sodium ion levels were examined in the serum.

2.9 Determination of serum electrolytes

Serum bicarbonate ion (HCO_3-) was measured using the standard test kit after back titration in accordance with (19) recommendations, serum potassium and sodium ions were determined by flame emission photometric method (410 flame photometer, Chiron diagnostics) in line with the manufacture's guidelines **(24)**. Serum calcium ion levels was measured using the colorimeter method **(25)**

2.10 Analytical Statistics.

The data underwent One way analysis of variance ANOVA and was presented as mean ± standard deviation, revealing a significant difference ($P<0.05$) using graph pad prism 5.0 software.

RESULTS

Impact of *Psychotria vogeliana* Aqueous Leaf Extract on Sera Electrolytes concentration

Figure 1, Figure 2, Figure 3 and Figure 4 below present the result of impacts of aqueous leaf-Extract of *Psychotria vogeliana* on sera electrolytes concentration (Serum Sodium ion, serum potassium ion, serum bicarbonate ion and serum calcium ion) levels in albino rats induced with RA respectively. Generally, there is notable ($p<0.05$) rise in serum levels of sodium ion, serum potassium ion, serum bicarbonate ion and serum calcium ion in all the groups that were given the leaf-extract of *Psychotria vogeliana* at the doses of 200 mg/kg, 400 mg/kg and 600 mg/kg relative to toxic group respectively. Whereas, the pattern of rise ($p<0.05$) in concentration of these serum electrolytes in the groups administered with leaf-extract of *Psychotria vogeliana* is comparable to those observed in the standard group in dose dependent manner thus, making the group that received 600 mg/kg show the highest effect

DISCUSSION

Medicinal plants are essential as first-line treatments for a wide range of ailments because they are readily available and reasonably affordable. In Nigerian traditional societies, herbalists have used *Psychotria vogeliana* as anti-inflammatory, antihypertensive, antiparasitic, anti-hyperglycemic and anti-arthritic medicine **(26)**.

From our present study, *Psychotria vogeliana* at the doses 200mg/kg, 400mg/kg and 600mg/kg doses notably increased ($P<0.05$) the serum sodium, potassium, calcium and bicarbonate ion concentrations in rats in comparison with the toxic group respectively (Figure 1, Figure 2, Figure 3 and Figure 4). Serum electrolytes levels were also significantly elevated in the group that received standard drug (methotrexate) ($p< 0.05$) in relation to untreated group, whereas significant decrease in serum electrolyte ($p< 0.05$) was observed in the untreated control group when compared to the group that was treated with methotrexate. The outcome of our present study has strong agreement with the findings that administration of certain plant extracts can lead to significant differences in serum electrolyte concentration in rats. Agbafor and Emmanuel in their studies found that the

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administration of *Acalypha wilkesiana* extract resulted in a noticeable rise in serum electrolyte levels in rats **(27)**. Changes in serum electrolyte levels, including a decrease in sodium and potassium concentrations in rats treated with *Aloe vera* extract was reported **(28)**. Additionally, electrolyte imbalances, such as a decrease in bicarbonate and calcium concentrations in rats administered with an extract of *Lagenaria breviflora* was also reported to show the same trend as recorded in the present study **(29)**. These results suggest that the administration of these herbal extracts may have an impact on rats' blood electrolytes concentration.

Literatures on precise cause of low serum electrolytes level as revealed in the present study in the untreated rat group is still very scarce. However, some insights into the potential causes of low serum potassium, sodium, calcium, and bicarbonate ions among rheumatoid arthritis (RA) patients were suggested; potassium deficiency may be a cause of RA **(30)**. RA patients were reported to have a decreased serum calcium/phosphorus ratio, indicating altered calcium and phosphorus metabolism **(31)**. It was observed that RA patients had lower mean calcium levels compared to healthy subjects, but differences in calcium concentration were not consistently traceable to disease activity **(32)**. In all, the present study suggests that potassium deficiency and altered calcium metabolism may be responsible for the low serum levels noticed in RA patients. Based on the pathophysiological processes in RA that may be connected to serum potassium ion, further possible reasons may be postulated. A higher metabolic rate and catabolic condition, which resulted in cachexia, poor muscle mass, an acid load, and an imbalanced pH, are characteristics of RA **(33)**. Neutral pH requires compensatory changes in cellular potassium and renal potassium excretion. The glycolytic pathways are highly active as a result of elevated demand on metabolic consumption of energy, and intensive immune cell activities. Numerous enzymes involved in the glycolytic process, including aldolase, the enolase, and glucose phosphate isomerase, depend on potassium ions **(34)**. It is possible that these metabolic events require excess electrolytes like potassium, and thus, there is an overutilization of potassium leading to low potassium level observed in untreated/toxic group. Rats in RA induced group (toxic), there may be a relative or absolute deficiency of body potassium which the aqueous leaf-extract of *Psychotria vogeliana* supplemented thus, the significant rise in serum potassium level observed in groups AE200, AE400 and AE600 (Fig. 2). The kind and severity of long-lasting aches associated with RA symptoms can be further suppressed by the increase in potassium levels.

In clinical settings , electrolytes including sodium, potassium, and bicarbonate ions are crucial indicators of renal function **(35)**. The importance of electrolytes in determining the osmolality of serum and the impact of hypertonic dehydration on cellular shrinkage was emphasized in their studies by **(36)**. Our findings in this study collectively suggest that in inflammatory diseases like RA, dehydration can deplete the serum electrolytes balance by decreasing sodium and potassium concentrations. Sodium ions helps to regulate the body fluid volume and aids the proper functioning of muscles and nervous system whereas, potassium ions help the heart and muscles work properly. It therefore implies that the

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reversal/increased concentrations of potassium and sodium ions observed in groups administered with 200 mg/Kg, 400 mg/Kg and 600 mg/Kg could enhance nerves and muscle functions while preventing attendant cardiovascular diseases that accompany RA. The increased concentration of bicarbonate ions as revealed among the rat groups treated with aqueous extracts of *Psychotria vogeliana* suggests that bicarbonate plays a crucial role in maintaining acid-base balance. Increase in concentration of serum calcium ion after treatment with leaf-extract of *Psychotria vogeliana* as observed in (Fig.4) could as well increases the strength of bones and teeth of RA patients and helps their muscles and nerve's function**(37)**.

Phytochemicals like flavonoids, flavones, catechins, polyphenols, and phytoestrogens are some of the antioxidants reported in *Psychotria vogeliana* leaf-extract that could boost electrolyte level in the body **(38)**. Therefore, the observed increased levels of serum electrolytes in groups administered AE200, AE400 and AE600 in Fig. 1, Fig. 2 and Fig. 3 relative to the untreated groups could be due to the presence of these bioactive compounds which could boost serum electrolytes concentration.

Our findings in this study collectively suggest that RA can deplete the serum electrolytes balance by decreasing sodium, potassium, calcium and bicarbonates concentrations. However, treatment of RA rats with the leaf extract of *Psychotria vogeliana* holds great promise for replenishing the rheumatoid arthritis rats with these essential body electrolytes. Further studies should be carried out to unravel the biochemical events that leads to the reduction of serum electrolytes in RA rats models using the *in silico* molecular docking analysis and how the positive effects of *Psychotria vogeliana* on serum electrolytes level in RA models will be exploited to design effective supplements for RA patients.

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FIGURES

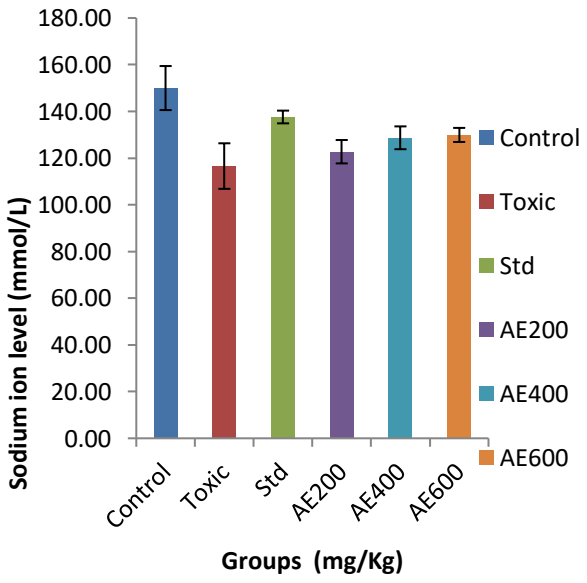

Figure 1. Presents the impacts of aqueous leaf-extract of *Psychotria vogeliana* on serum sodium ion level in albino rats induced with R.A. Data are shown in bar charts as Mean ± S.D, (n=8). The toxic group revealed a significant (P<0.05) decrease in sodium ion level when compared to the control, standard, AE200, AE400 and AE600 groups respectively. Conversely, the standard group (treated with methotrexate) showed noticeable (P<0.05) rise in sodium ion level when compared to the level in groups AE200, AE400 and AE600 respectively.

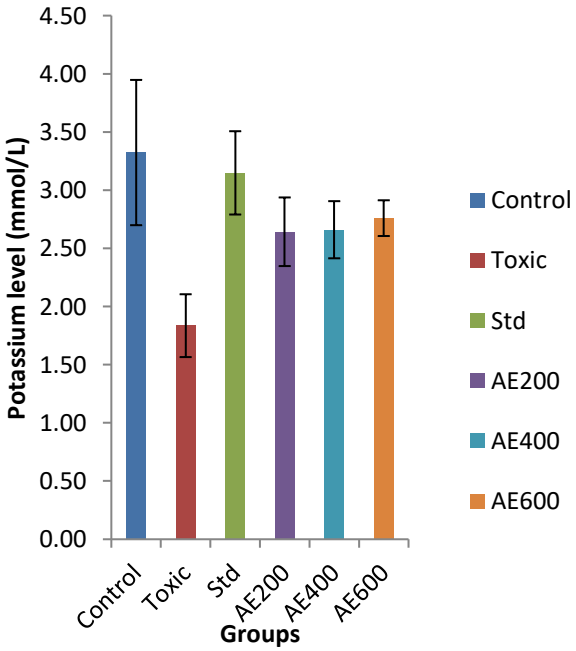

Figure 2. Presents the impact of aqueous leaf-extract of *Psychotria vogeliana* on serum potassium ion level (mmol/L) in albino rats induced with R.A. Data are shown in bar charts as Mean ± S.D, (n=8). The toxic group revealed a noticeable (P<0.05) rise in sodium ion concentration when compared to the control, standard, AE200, AE400 and AE600 groups respectively. Conversely, the standard group (treated with methotrexate) revealed notable (P<0.05) rise in sodium ion level relative to the level observed in groups AE200,

https://kjhs.kiu.ac.ug https://doi.org/10.59568/KJHS-2024-4-1-06 KJHS 4(1); 2024. Page (56-67)

AE400 and AE600 respectively.

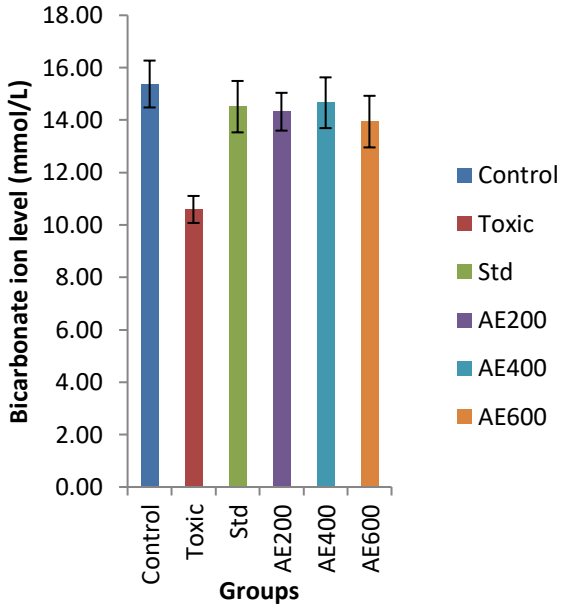

Figure 3. Presents the impacts of aqueous leaf-extract of *Psychotria vogeliana* on serum bicarbonate ion level (mmol/L) in albino rats induced with R.A. Data are shown in bar charts as Mean ± S.D, (n=8). The toxic group revealed a noticeable (P<0.05) decline in sodium ion concentration when compared to the control, standard, AE200, AE400 and AE600 groups respectively. Conversely, the standard group (treated with methotrexate) showed insignificant (P<0.05) rise in sodium ion level when compared to the level in groups AE200, AE400 and AE600 respectively.

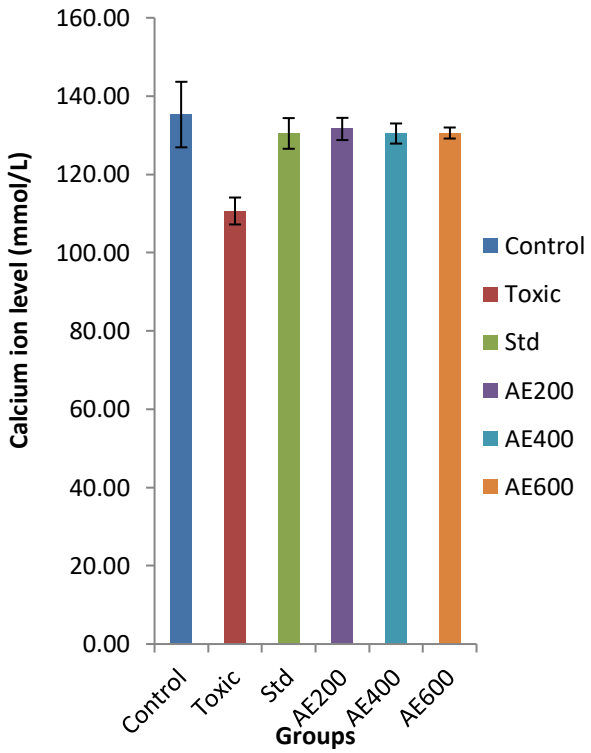

Figure 4. Presents the impact of aqueous leaf-extract of *Psychotria vogeliana* on serum calcium ion level in albino rats induced with R.A. Data are shown in bar charts as Mean ± S.D, (n=8). The toxic group revealed a noticeablet (P<0.05) fall in sodium ion level when compared to the control, standard, AE200, AE400 and AE600 groups respectively. Conversely, the standard group (treated with methotrexate) showed insignificant (P<0.05) increase in sodium ion level when compared to the level in groups AE200, AE400 and AE600 respectively.

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