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Anti-inflammatory Activity of Ethanolic Leaf Extracts of Thaumatococus Danielli on Iodoacetamide Treated Rats

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Abstract
Anti-inflammatory drugs such as Non-steroidal anti-inflammatory drugs (NSAIDs) are used to reduce swellings and pains caused by inflammation but, long term use of these anti-inflammatory drugs results in the damage of human biological system such as the liver, gastrointestinal tract, etc. Hence, there is need for safer, potent, anti-inflammatory drugs. Hence, the anti-inflammatory activity of ethanol leaf extract of *Thaumatococcus danielli* on iodoacetamide treated rats was investigated. Forty-two (42) rats were divided into seven groups of six rats each. Group 1 (positive control) received 1ml of 1% CMC; Group 2 (negative control) received 1ml of 1% CMC and 1ml of 0.1% iodoacetamide; Group 3 received 50mg/kg of extract (low dose) and 1ml of 0.1% iodoacetamide; Group 4 received 100mg/kg of extract (high dose) and 1ml of 0.1% iodoacetamide; Group 5 received 50mg/kg of extract (high dose) and 1ml of 1% CMC; Group 6 received 100mg/kg of extract (high dose) and 1ml of 1% CMC; Group 7 received 1ml 1% iodoacetamide and 2.14mg/kg diclofenac. Treatment with *T. danielli* extract showed no significant difference ($p>0.05$) in all groups in lymphocyte, RBC, granulocyte, platelet, hemoglobin concentration, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin count but, a significant reduction in all groups was observed in ESR. Moreso, a significant decrease was observed in WBC in the high dose group, and a significant increase in group administered diclofenac. Ethanolic leaves extract of *Thaumaococcus danielli* possess an anti-inflammatory potential, possibly due to its embedded phytoconstituents.
Keywords: *Thaumatococcus danielli*, Anti-inflammatory activity, Hematological studies, Erythrocyte sedimentation rate, Nitric oxide concentration
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1. Introduction

Inflammations are the results of injuries or microbial infections, and are required in defense of animal cells as one of the most central processes. Acute and chronic are the two major phases in which inflammatory responses are triggered (Serhan et al., 2015). Acute inflammatory responses are defensive (Nguyen, 2012), but results in chronic inflammation and organ fibrosis due to untimely resolution. The chronic inflammation may also result from several different diseases such as cancer, cardiovascular diseases and even neurodegenerative disorders (Abdulkhaleq et al., 2018). Also, genomic changes in p53 have been strongly associated with the causes of many of these chronic inflammatory diseases (Kong, 2013, Ogrunc et al., 2014, Niederhuber et al., 2013). NSAIDs have long been the antidote for inflammations; unfortunately, these drugs have been associated with increased blood clotting risk which ultimately results in heart attacks, strokes, etc (Kumar et al., 2013, Mary et al., 2017, Vijayabaskar and Elango, 2018). Thus, the formulations of effective and non-toxic or less toxic anti-inflammatory drugs from natural source (plants) have been considered worldwide for more than a decade now.

Thaumatoccocus daniellii, belonging to the family of *Maranthaceae* and commonly called "sweet prayers plant" is widely known to impact color and flavor to most foods processed and wrapped with it when used to package food (Ayodeji et al., 2016). The flavor enhancing property is suggested to be impacted by the essential oil composition, as only food wrapped with the leaves of this plant gives this particular flavor. The leaves of this plant are commonly used to wrap food because they are believed to be safe, and also a source of herbal ingredients with potential health promoting properties (Dosumu and Akinnuoye, 2014). Secondary metabolites in *T. danielli* have been reported to include alkaloids, tannins, terpenoids, saponins, flavonoids, polyphenols, anthraquinones, cardiac glycosides, anthracene, glycosides (Ojekale et al., 2007, UKwubile et al., 2017, Hamid et al., 2017) with several biological activities such as antibacterial activity (Segun et al., 2015), antihyperglycemic activity (Ajayi et al., 2019), antioxidant activity (Ojekale et al., 2013, Adu et al., 2021) etc. Also, *T. danielli* have been traditionally claimed to possess anti-inflammatory activity, thus, the reason for this research to scientifically validate this claim on iodoacetamide treated rats.

2. Materials and Methods

2.1 Collection of Plant

Fresh leaves of *Thaumatococcus danielli* was purchased locally from Ile-Epo market, Lagos-Abeokuta

Expressway, Lagos State, Nigeria.

2.2 Preparation of plant extract

The leaves of *T. danielli* was cleaned and dried at room temperature for 3 weeks, and then grinded into powdery form using mechanical grinding machine. 100g of the powder was weighed and mixed with 600ml ethanol in a conical flask and left for 48hours with periodic shaking. The extract was later filtered using a white muslin cloth, concentrated in water bath at 40˚C and kept in the refrigerator at 4˚C prior to further analysis.

2.3 Experimental design

Forty-two (42) rats were divided into seven groups of six rats each. Group 1 (positive control) received 1ml of 1% CMC; Group 2 (negative control) received 1ml of 1% CMC and 1ml of 0.1% iodoacetamide; Group 3 received 50mg/kg of extract (low dose) and 1ml of 0.1% iodoacetamide; Group 4 received 100mg/kg of extract (high dose) and 1ml of 0.1% iodoacetamide; Group 5 received 50mg/kg of extract (high dose) and 1ml of 1% CMC; Group 6 received 100mg/kg of extract (high dose) and 1ml of 1% CMC; Group 7 received 1ml 1% iodoacetamide and 2.14mg/kg diclofenac. The process spanned for 12 days.

2.4 Collection of samples

The environment for dissection was properly disinfected with ethanol. The rats were then anaesthetized using diethyl ether and laid on a board covered with card board. The animal was cut from the lower abdominal region up to the neck using a pair of scissors and surgical blade and whole blood was collected from the heart into EDTA bottle. The stomach was also excised for the determination of nitric oxide concentration.

2.5 Biochemical assay

2.5.1 Haematological studies

Five mililitre of whole blood were collected from the heart into EDTA vacutainer bottle. It was then mixed by gentle inversion, and the roller mixer put on for proper mixing. Then, 13µL was analyzed using Mind Ray BC 300 Plus Autoanalyzer.

2. 6 Determination of erythrocyte sedimentation rate

Starrsed analysis using StaRRsed Auto-Compact instrument was based on the Westergren sedimentation technique although the method was slightly modified. Routinely, 3ml of K_2-EDTA-blood was taken for the ESR determination. The instrument uses a vacuum pump to aspirate 1.6 ml of the sample diluted with 0.4 ml of 3.8% (105 mM) Na_3-citrate solution. The diluted sample was then aspirated to the westergren pipette and the sedimentation was measured using the optical density at 950nm after exactly 30 minutes. A correlation curve was then used to transform the results into 60 minutes measurement time. Finally, results were given in mm/h at 18˚C using the temperature correction equation in the instrument according to the manufacturer (Horsti et al., 2010).

2.7 Determination of nitric oxide concentration

A chunk of stomach tissues was weighed with a weighing balance (ALE-223, India). 2ml of 0.1M phosphate buffer (pH 6.8) was added to it, homogenized and then centrifuged at 4000rpm for 30 minutes. The supernatant was collected and used for this assay. A 50µL portion of the sample was measured and diluted with 75µL of distilled water. 125µL of 0.3N NaOH was then added and incubated at room temperature for 5 minutes. 62.5µL of $ZnSO_4$ was added to deprotenise and centrifuged at 4000rpm for 30 minutes. Two hundred microlitre of the supernatant was added to equal volume of Griess reagent. Absorbance was then read at 540nm after 30 minutes of incubation (Giustarini et al., 2008).

3. Results

Figure 1 shows the effect of ethanolic leaf extract of *T. danielli* on white blood cell (WBC) count. A statistically significant increase ($p<0.05$) was observed in WBC count in rats administered with iodoacetamide and diclofenac compared to the controls and other groups. Rats administered with high dose ethanolic extract of *T. danielli* have the lowest WBC count compared to all groups. However, there was no significant difference between other rat groups.

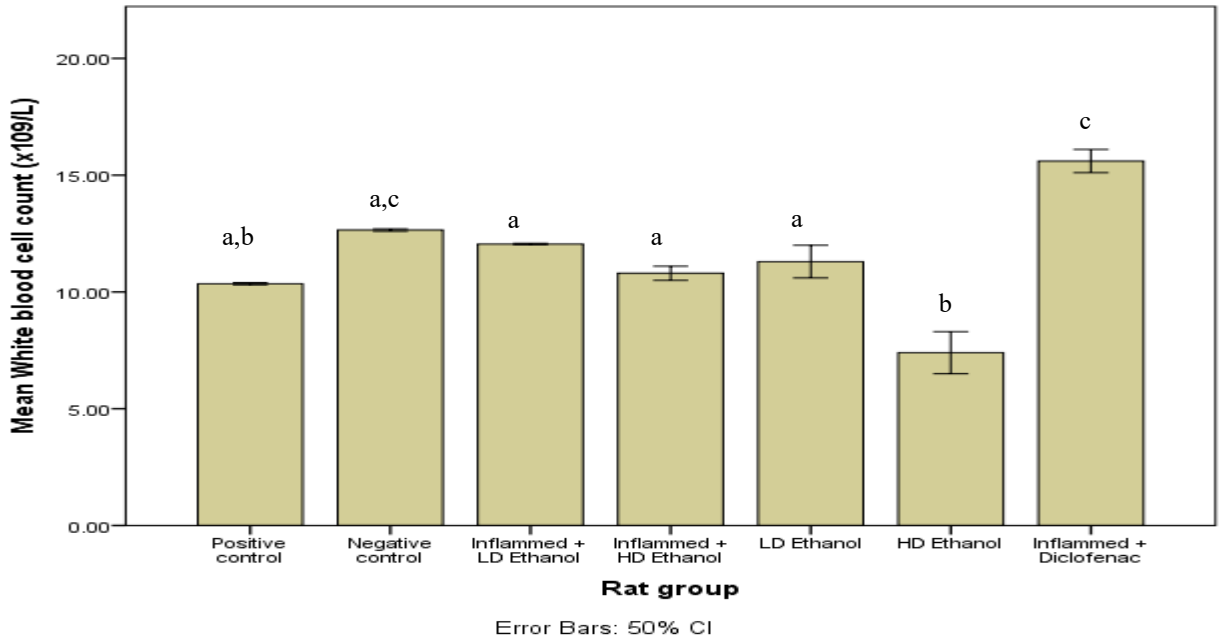

Figure 1: Effect of ethanolic leaf extract of *T. danielli* on white blood cell count in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 2 shows the effect of ethanolic leaf extract of *T. danielli* on red blood cell (RBC) count. There was no significant difference between all the rat groups.

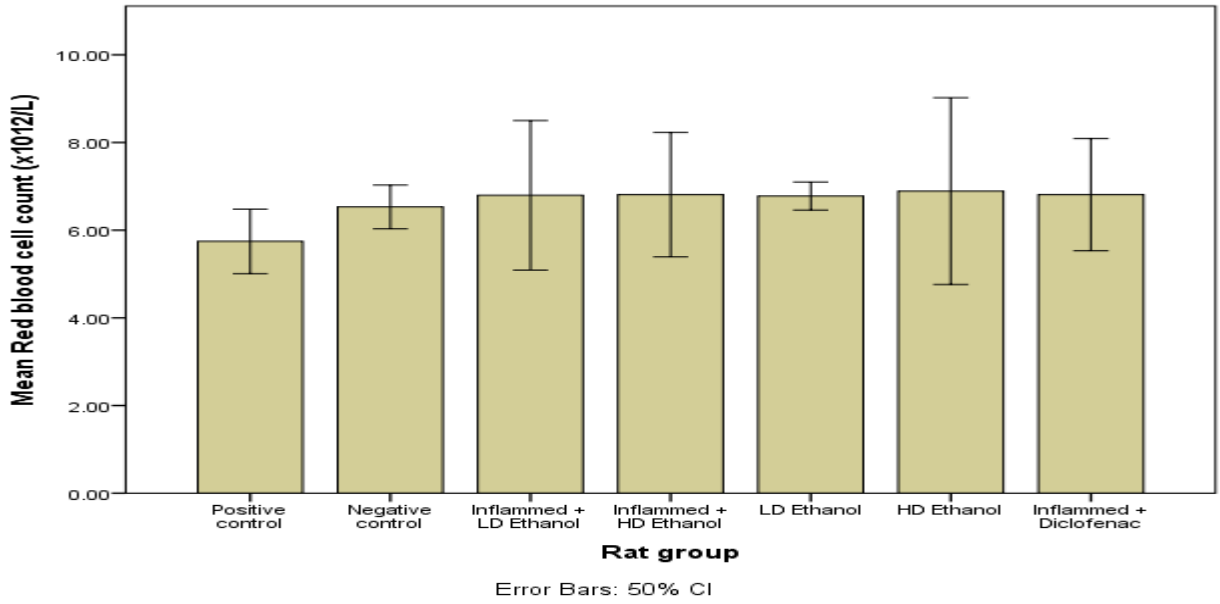

Figure 2: Effect of ethanolic extract of *T. danielli* on red blood cell count in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 3 shows the effect of ethanolic leaf extract of *T. danielli* on lymphocyte. There was no significant difference between all the rat groups.

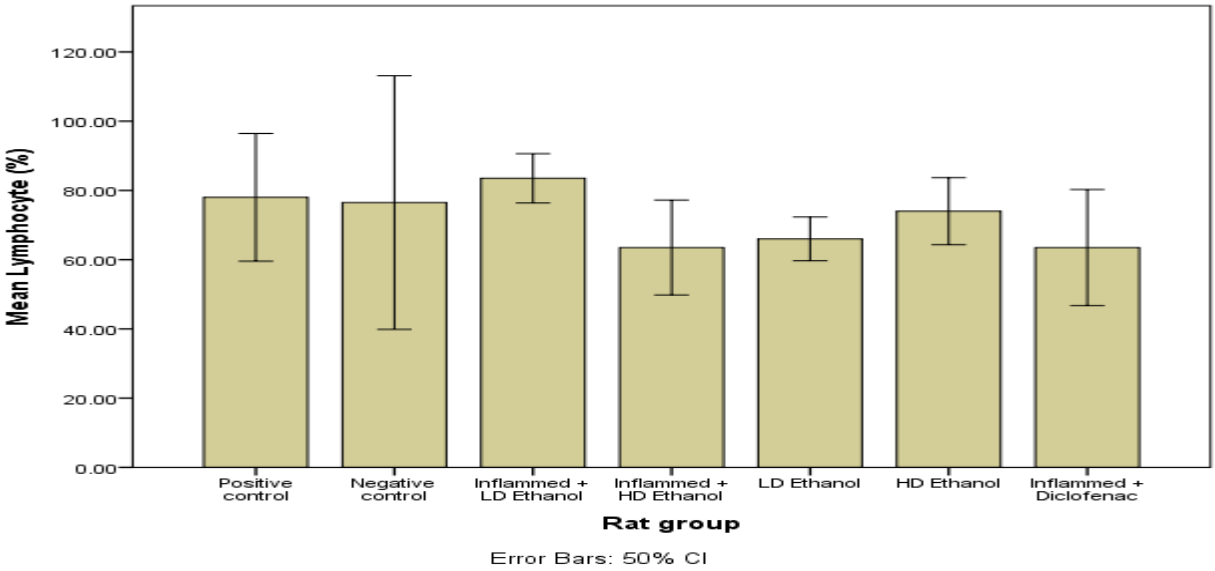

Figure 3: Effect of ethanolic extract of *T. danielli* on lympholyte in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 4 shows the effect of ethanolic leaf extract of *T. danielli* on granulocyte. There was no significant difference between all the rat groups.

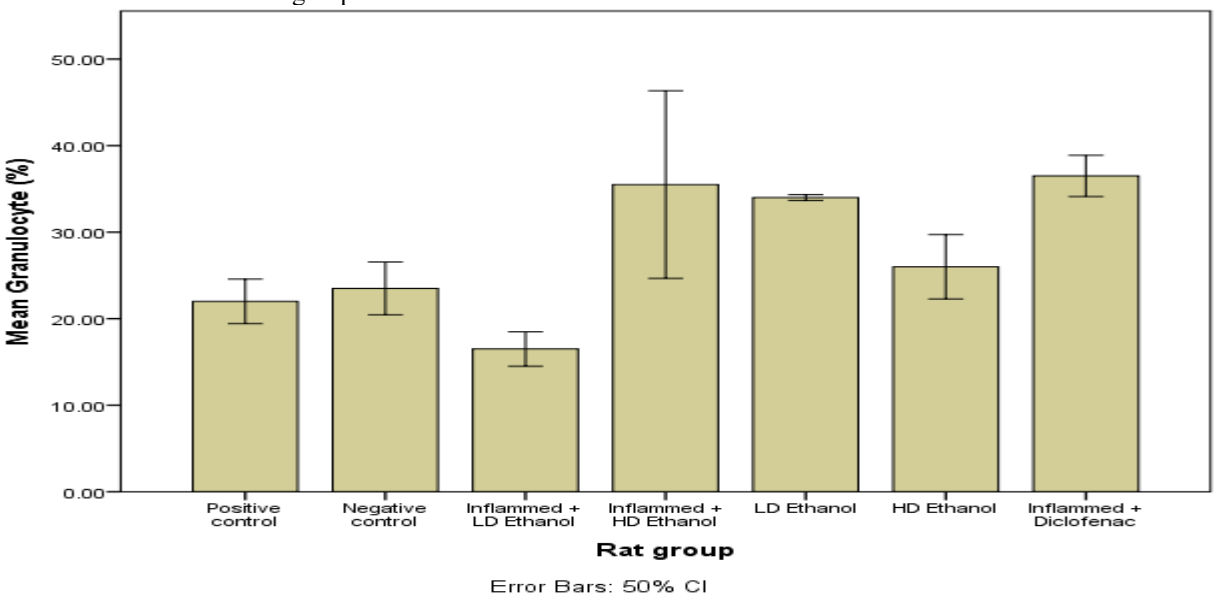

Figure 4: Effect of ethanolic extract of *T. danielli* on granulocyte in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 5 shows the effect of ethanolic leaf extract of *T. danielli* on hemoglobin concentration. There was no significant difference between all the rat groups.

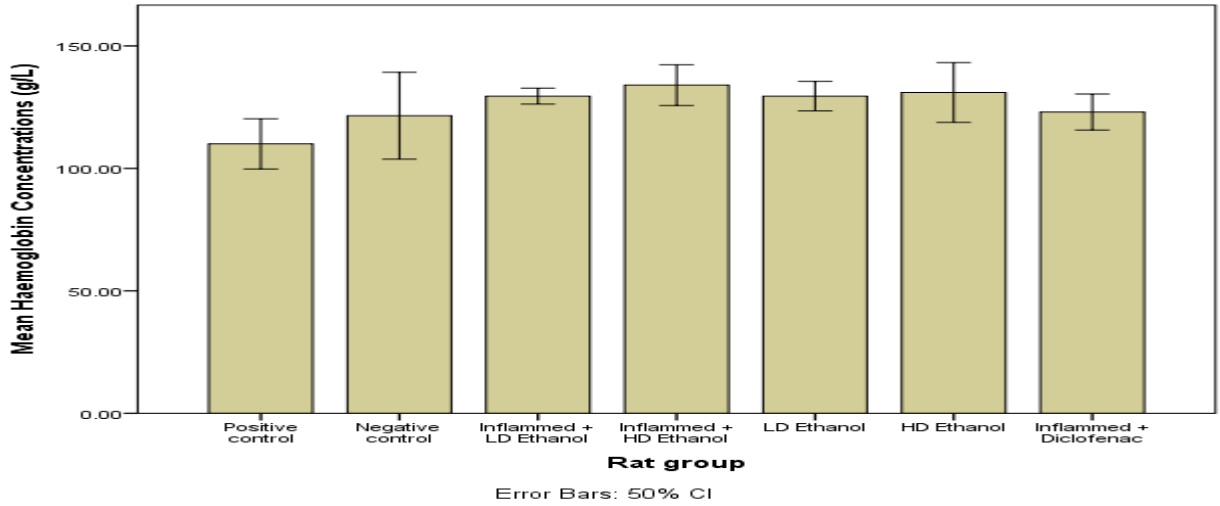

Figure 5: Effect of ethanolic extract of *T. danielli* on hemoglobin concentration in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 6 shows the effect of ethanolic leaf extract of *T. danielli* on platelet. There was no significant difference between all the rat groups.

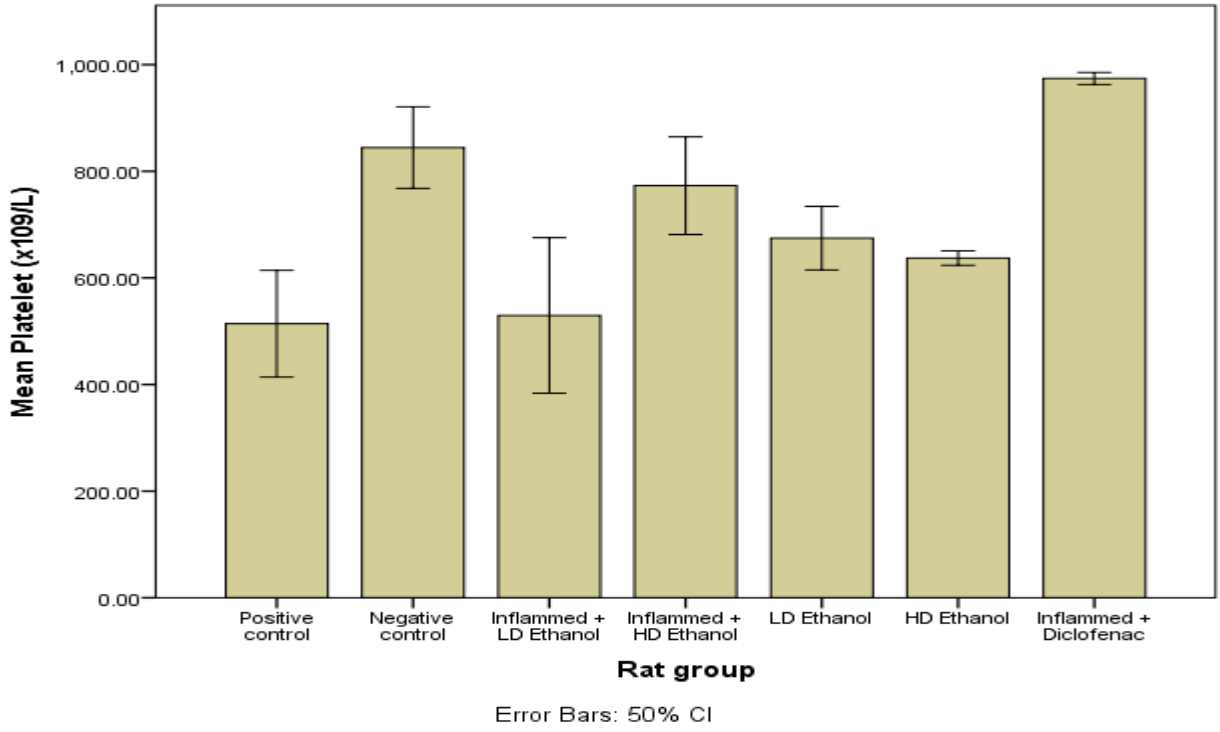

Figure 6: Effect of ethanolic extract of *T. danielli* on platelet in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 7 shows the effect of ethanolic leaf extract of *T. danielli* on hematocrit. There was no significant difference between all the rat groups.

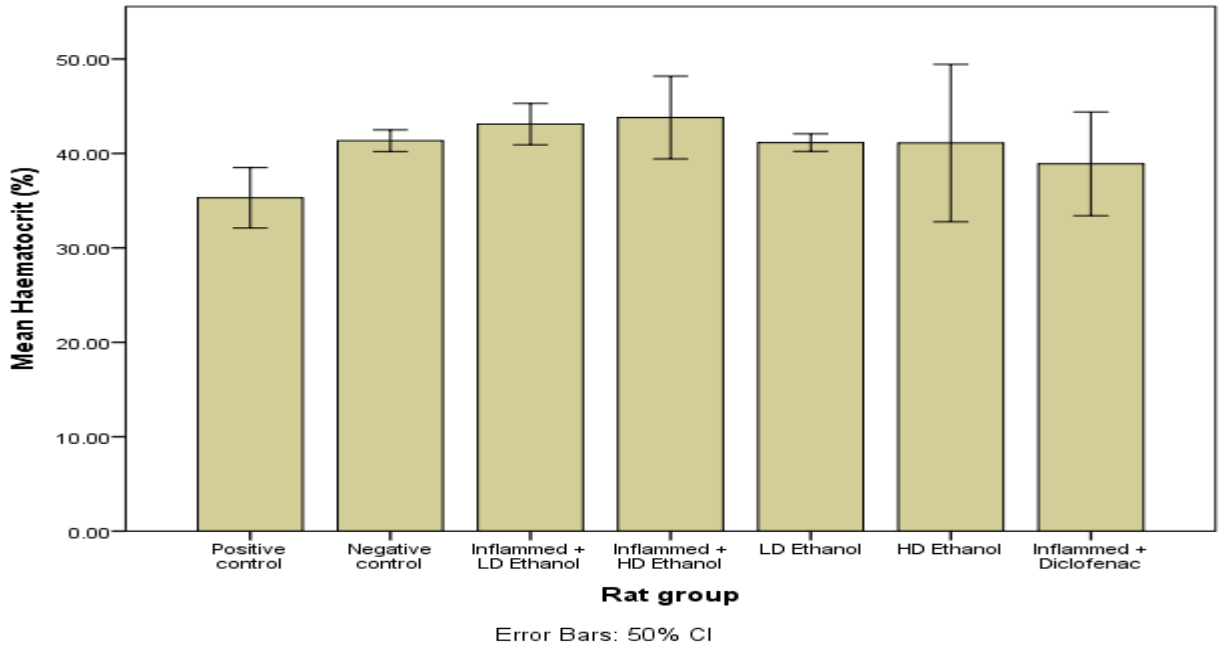

Figure 7: Effect of ethanolic extract of *T. danielli* on hematocrit in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 8 shows the effect of ethanolic leaf extract of *T. danielli* on mean corpuscular volume. There was no significant difference between all the rat groups.

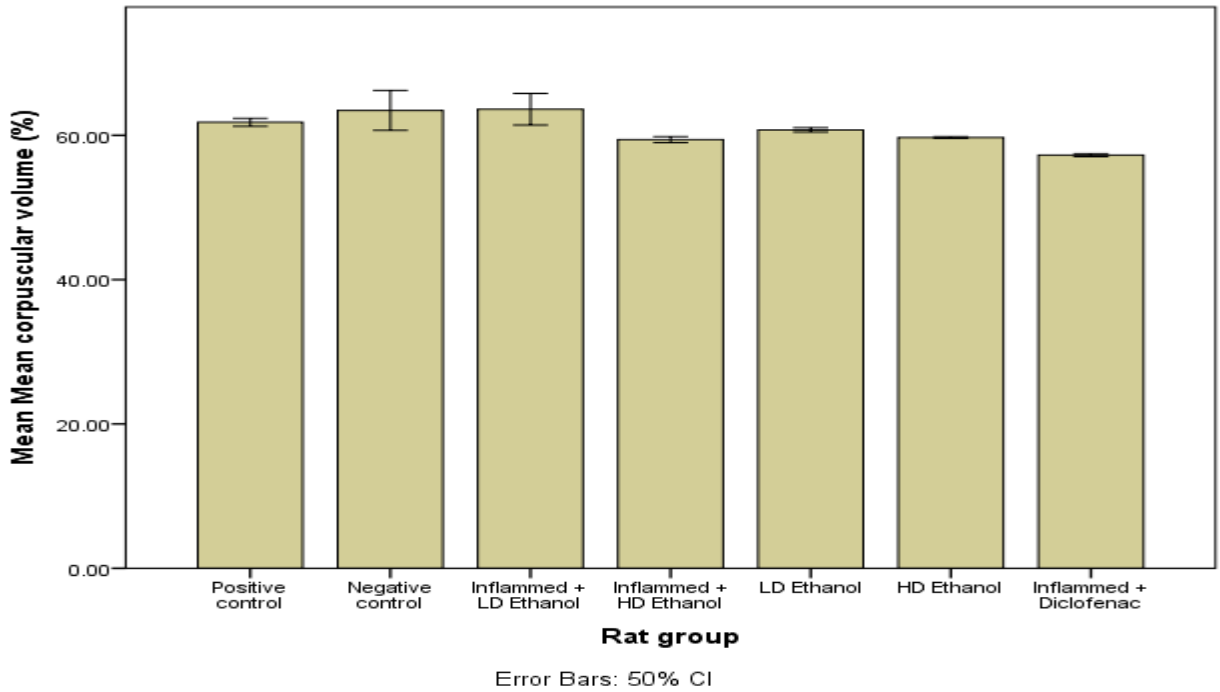

Figure 8: Effect of ethanolic extract of *T. danielli* on mean corpuscular volume in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 9 shows the effect of ethanolic leaf extract of *T. danielli* on red blood cell mean corpuscular hemoglobin count. There was no significant difference between all the rat groups.

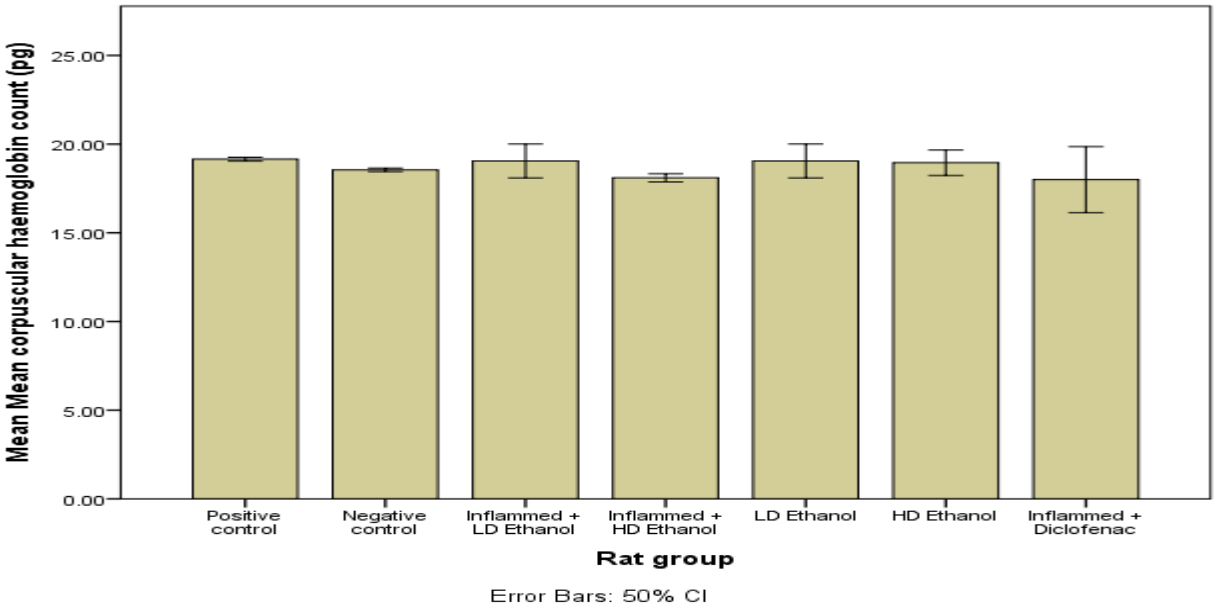

Figure 9: Effect of ethanolic extract of *T. danielli* on mean corpuscular hemoglobin count in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 10 shows the effect of ethanolic leaf extract of *T. danielli* on mean corpuscular hemoglobin concentration (MCHC). A significant decrease ($p<0.05$) was observed in MCHC in rats administered with iodoacetamide and low dose ethanolic extract of *T. danielli* compared to all groups. However, a significant increase was observed in rat groups administered with only low and high doses of the extract, which are comparable with rat group treated with iodoacetamide + diclofenac and positive control compared to other rat groups.

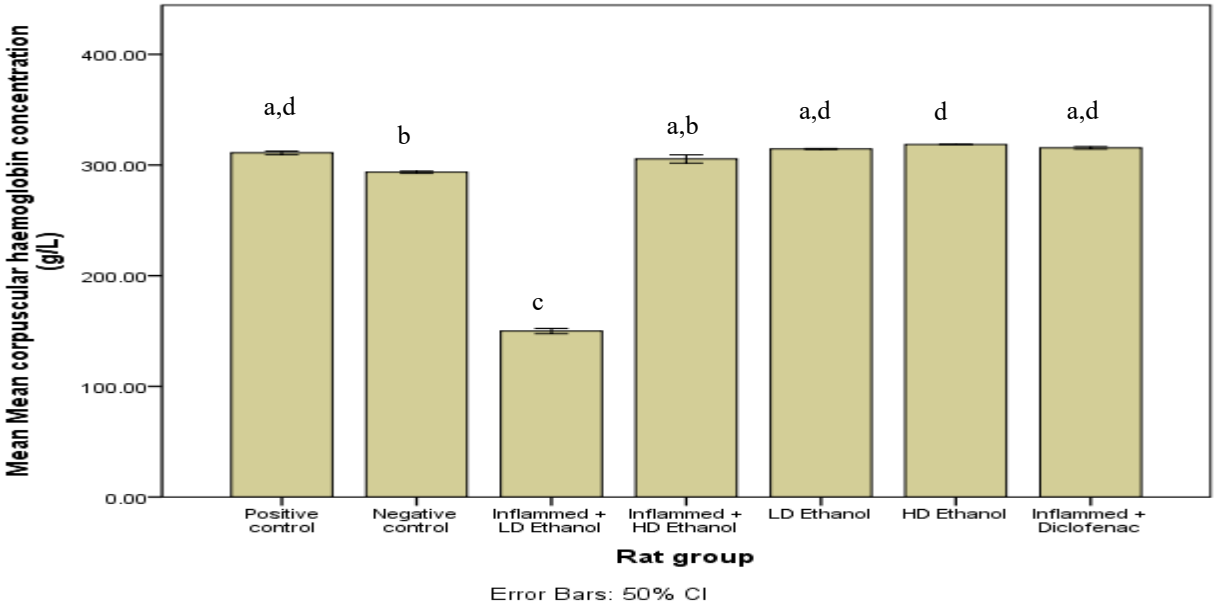

Figure 10: Effect of ethanolic extract of *T. danielli* on mean corpuscular hemoglobin concentration in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 11 shows the effect of ethanolic leaf extract of *T. danielli* on mean erythrocyte sedimentation rate (ESR). A significant decrease ($p<0.05$) was observed in ESR in all the rat groups treated with the ethanolic extract of *T. danielli*, with or without iodoacetamide administration compared to the controls. However, group treated with iodoacetamide + high dose of the extract decreased ESR more compared to other rat groups.

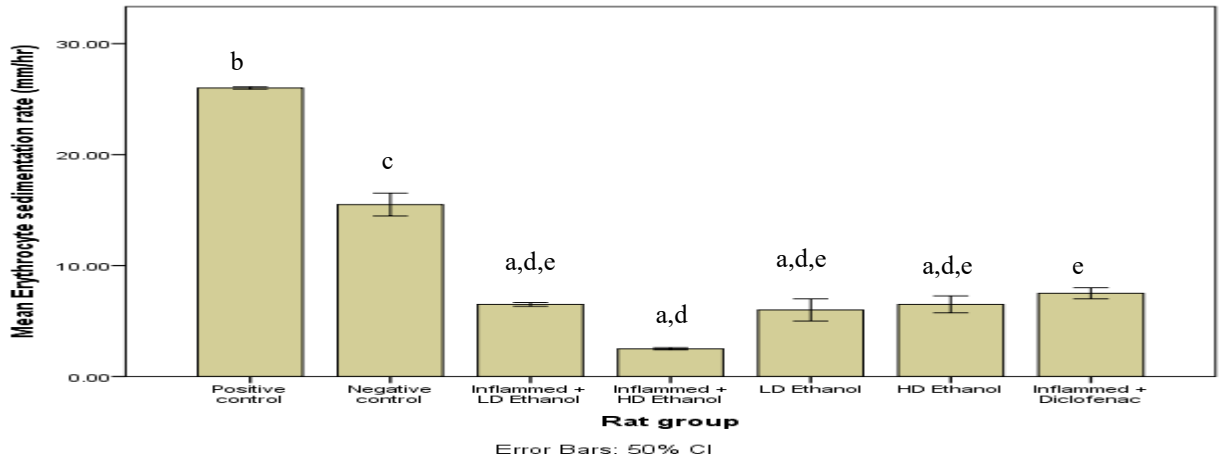

Figure 11: Effect of ethanolic extract of *T. danielli* on erythrocyte sedimentation rate in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

Figure 12 shows the effect of ethanolic leaf extract of *T. danielli* on nitric oxide (NO) concentration. A significant decrease ($p<0.05$) was observed in NO in all the rat groups treated with only high dose ethanolic extract of *T. danielli* without iodoacetamide administration compared to the controls and all other groups. However, groups treated with iodoacetamide + high dose of the extract, low dose of the extract only, and iodoacetate + diclofenac increased NO concentration towards the negative control.

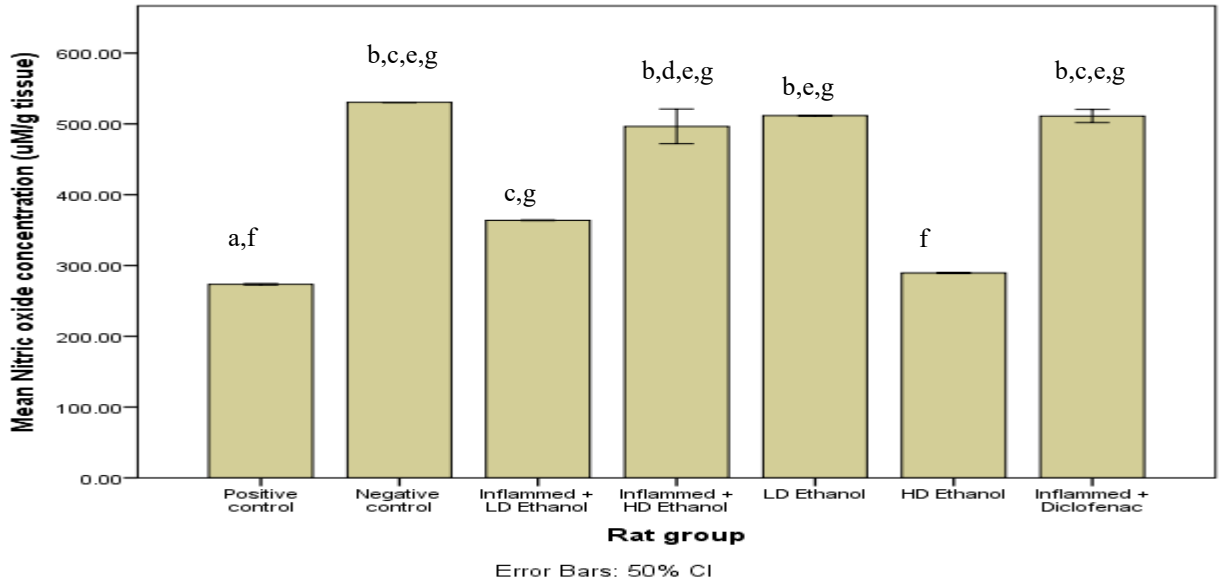

Figure 12: Effect of ethanolic extract of *T. danielli* on nitric oxide concentration in the blood following treatment with iodoacetamide. Data are presented as Error bars showing mean±SEM. Bars with different alphabets are statistically significant ($p<0.05$) from each other.

4. Discussion

Thaumatococcus danielli is widely used to package food but have also been reported with various biological potentials such as antibacterial activity against some human pathogens (Segun et al., 2015), antihyperglycemic activity (Ajayi et al., 2019), and antioxidant activity (Ojekale et al., 2013, Adu et al., 2021). Several phytochemical components of the plant extracts such as, alkaloids, tannins, terpenoids, saponins, flavonoids, polyphenols, anthraquinones, cardiac glycosides, anthracene, glycosides (Ojekale et al., 2007, UKwubile et al., 2017, Hamid et al., 2017) have been suggested to be responsible for these biological activities, and there could also be a possible anti-inflammatory health benefit. Thus, in the present study, the anti-inflammatory activity of ethanolic leaf extract of *T. danielli* on iodoacetamide treated rats was investigated.

Hematological changes in animal studies have a high predictive value for human, as the estimation of blood parameters is crucial to evaluating health status and toxicity of drugs (Olson et al., 2000, Hayes and Kruger, 2014, Esch et al., 2015). In contrast with the report of Aniagu et al. (2008), our result showed no appreciable

difference in white blood cell and platelet of groups treated with iodoacetamide and the plant extracts. However, a statistically significant increase was observed in WBC count in rats administered with iodoacetamide and diclofenac compared to the control and other groups while, a non-significant increase was seen also seen in platelet count. These may be as a result of diclofenac which also causes inflammation. It was also noticed from the results that group administered iodoacetamide and low dose of the extract showed reduced WBC (although not significantly) compared to negative control, while a further reduction was observed in those administered iodoacetamide and high dose of the extract. Also, the platelet count of group administered iodoacetamide and low dose of the extract showed reduction (not significant) compared to the negative control but was almost at similar level with the positive control. This may suggest a possible and potential anti-inflammatory of *T. danielli* extracts. In comparison to the positive control, slight increases were noticed in RBC, WBC, platelets and hematocrit groups treated with iodoacetamide and the extract. Generally, from our results, RBC, lymphocyte, granulocyte, platelet, hemoglobin concentration, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin count showed no appreciable differences.

The determination of ESR is neither sensitive nor specific when used as a general screening test (Sox Jr and Liang, 1986) such that, the ESR may be elevated in the presence of infectious disease, other inflammatory or destructive processes, collagen vascular disease or malignancy (Saadeh, 1998), and may also not be increased in a number of infectious diseases (e.g., typhoid fever, malaria, mononucleosis), allergic processes, angina (as opposed to myocardial infarction) or peptic ulcer disease (as opposed to active inflammatory bowel disease) (Brigden, 1999). The elevated level of ESR have also been linked to age (more in elderly), gender (more in females) and in obese (Böttiger and Svedberg, 1967, Sox Jr and Liang, 1986, Brigden, 1999). The measurement of erythrocyte sedimentation rate (ESR) is a simple and inexpensive laboratory test, and the amount of blood fibrinogen directly correlates with ESR. A process of systemic inflammation and immune disorders results in increased blood fibrinogen and immunoglobulins proportion which binds to cause increased RBC aggregation. These RBCs form masses and settles fast, and results in increased erythrocyte sedimentation rate (ESR), and an increase in ESR indicates the presence of high plasma fibrinogen (Cheesbrough, 2005, Duvoix et al., 2013). Similar to the findings of Koffuor et al. (2014), a significant decrease (p,0.05) was observed in ESR in all the rat groups treated with the ethanolic extract of *T. danielli*, with or without iodoacetamide administration compared to the controls. However, group treated with iodoacetamide and high dose of the extract decreased ESR more compared to other rat groups. It have been reported that drug therapy with aspirin or other nonsteroidal anti-inflammatory agents such as phenolic components of plant extracts may decrease ESR (Hmidani et al., 2020). Although, there is an enormous body of literature concerning the elevated value of ESR (Bray et al., 2016, Brigden, 1999), but a decrease in ESR have been associated with a number of blood diseases as a result of irregular or smaller shape of red blood cells that causes slower settling. The phytoconstituents, such as alkaloids, tannins, sterols, terpenoids, saponins, flavonoids, polyphenols, anthraquinones, cardiac glycosides present in the extracts of *T. danielli* (Ojekale et al., 2007, UKwubile et al., 2017, Hamid et al., 2017) reported in literatures may be responsible for this anti-inflammatory activity observed in this study. The anti-inflammatory activities of these phytoconstituents (saponins, glycosides, tannins, sterols, etc) with their respective mechanism of actions have been documented in literatures (Koffuor et al., 2014, Alemu et al., 2018, Jeffers, 2006).

Nitric oxide (NO) is one of the key local mediator of inflammation used as an important target exploited for the screening and development of anti-inflammatory drugs (Salvemini et al., 2013). Oxidation of terminal guanidino nitrogen of L-arginine produces NO, in a reaction catalyzed by nitric oxide synthase (NOS), and the conjugation of NO with superoxide anion ($O_2^{\cdot-}$, SO) produces an effective proinflammatory and cytotoxic agent (peroxynitrite) that also modulates cyclooxygenase (COX) enzymes (Salvemini et al., 2013). In the present study, a significant decrease was observed in NO in all the rat groups treated with only high dose ethanolic extract of *T. danielli* without iodoacetamide administration compared to the controls and all other groups. This situation is indicative of inflammation. The results showed that in the absence of iodoacetamide, HD of extract did not cause inflammation, but in the presence of iodoacetamide, LD of extract lowered inflammation. This strengthens the position of the probability of low dose *T. danielli* having a counter effect to inflammation.

5. Conclusion

In conclusion, *Thaumaococcus danielli* leaf have a potential anti-inflammatory property, possibly due to its embedded phytoconstituents.

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