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Research Article

COMPARATIVE STUDY ON THE EFFECTS OF MATERNAL AND PRENATAL EXPOSURES TO *PILIOSTIGMA THONNINGII* ON HAEMATOLOGICAL PROFILES FOLLOWING ACETAMINOPHEN INDUCED-TOXICITY IN WISTAR RATS

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ABSTRACT

Anaemic condition is a challenge responsible for over 70% of morbidity and mortality rate in Africa and beyond during pregnancy. This present research compares the maternal and prenatal exposure to *P. thonningii* following acetaminophen induced toxicity. The leaves of *P. thonningii* were collected and air dried for 14 days until constant weight was obtained. Twenty-five (25) pregnant female rats (180-200g) were grouped on the bases of their weight to five (5) groups of 5 rats each. Animals in group A served as control while animal in group B-E served as the treated groups. Group B was administered with 200 mg/kgbwt of acetaminophen, Group C was administered with 200 mg/kgbwt of *P. thonningii*, Group D was administered with 100 mg/kgbwt of *P. thonningii* + 200 mg/kgbwt of acetaminophen, while group E was administered 200 mg/kgbwt of *P. thonningii* + 200 mg/kgbwt of acetaminophen. The administration was done for 28days consecutively. Thereafter, the animals were sacrificed and blood collected by cardiac puncture in an EDTA tube for haematological assessment. The result shows ($P<0.05$) increase in RBC, Hb, and HCT for groups administered with 200 mg/kgbwt *P. thonningii*, 100 mg/kgbwt *P. thonningii* + 200 mg/kgbwt acetaminophen and groups administered with 200 mg/kgbwt *P. thonningii* +200 mg/kgbwt of acetaminophen when compared with the control. Contrastingly groups administered with 200 mg/kgbwt acetaminophen shows significant ($P<0.05$) reduction on serum RBC, Hb and HCT when compared with the control. More so the extract produced a significant ($P<0.05$) increase in all the experimental groups when compared with the control with the exception of the groups administered with acetaminophen a lone on serum. The drugs and the extract also produced a significant ($P<0.05$) increase for serum neutrophil and groups administered with 200 mg/kgbwt of acetaminophen, 200 mg/kgbwt *P. thonningii* and 100 mg/kgbwt of *P. thonningii* + 200 mg/kgbwt of acetaminophen, except for groups co-administered with 200 mg/kgbwt *P. thonningii* and 200 mg/kgbwt of acetaminophen which shows a significant ($p<0.05$) decrease when compared with the control .The drug also showed significant ($P<0.05$) increase on the WBC of all the experimental groups with the exception of the groups administered with 200 mg/kgbwt acetaminophen a lone. Likewise, the prenatal exposure to ethanol extract of *P. thonningii* and acetaminophen shows similar trends with RBC, Hb, HCT, MCV, and PLT when compared with the control. The drugs rather produced a significant ($P<0.05$) increase on other experimental groups when compared with the control. More so the MXD produced a significant ($P<0.05$) increase on the groups administered with 200 mg/kgbwt of *P.thonningii* which compared with the control. The result also reviewed the other experimental groups produced no significant ($P<0.05$) difference. The spectrum of alterations from this results are indications that acetaminophen exhibits haematotoxic effect during early pregnancy and may compromise immunosuppressant and immunomodulation during pregnancy but the extract displayed haematopoietic and immunomodulatory effect on both maternal and prenatal exposure.

***Keywords**: Acetaminophen, anaemia , haematotoxic, immunosuppressant, immunomodulation.*

INTRODUCTION

Acetaminophen also known as (4'- Hydroxyacetanilide N-acetyl- p- aminophenol N Hydroxyphenyl acetamide) is a synthetic non-opiate derivative of p-aminophenol. Acetaminophen or paracetamol chemically named N-acetyl-p-aminophenol is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer) (Mckay *et al*.,2013). It is classified as a mild analgesic that is commonly used for the relief of headaches and other minor aches and pain and is a major ingredient in numerous cold and flu remedies (Imam and Yahaya). In combination with the opiod analgesics, paracetamol can be used in the management of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients (Oyedeji *et al*., 2013). The onset of analgesia is approximately 11 minutes after oral administration of paracetamol (Moller *et al*., 2005) and its half-life is 1-4 hours. Though paracetamol is used to treat inflammatory pain, it is not generally classified as an NSAID (Non-Steroidal Anti-Inflamatory Drugs) because it exhibits only weak anti-inflammatory activity.

Paracetamol has been considered one of the safest analgesics, even for pregnant women (Bertolini *et al., 2006)*. It is known that paracetamol crosses the placenta and that paracetamol and its metabolites enter the foetal blood flow (Levy, 1981*)*. While it is generally safe for use at recommended doses (1000mg per single dose and up to 3000mg per day for adults human), acute overdoses of paracetamol can cause potentially fatal kidney, brain and liver damage, and in rare individuals, a normal dose can do the same; the risk is heightened by alcohol consumption. In the western world, paracetamol toxicity accounts for most causes of acute liver failure and for most drug overdoses (Daly *et al*., 2008, Khashab *et al*., 2007). It is the active metabolite of phenacetin, once popular as an anagelsic and antipyretic in its own right, but unlike phenacetin and its combinations, paracetamol is not considered carcinogenic at therapeutic doses (Bergman *et al*., 1996). The words acetaminophen and paracetamol both come from a chemical name for the compound: para-APAP, for acetyl-para-aminophenol (Khashab *et al*., 2007).

Acetaminophen possesses analgesic and antipyretic activity similar to aspirin (McEvoy, 2000). Unlike aspirin, acetaminophen does not possess anti-inflammatory activity or platelet function effects. Acetaminophen increases the pain threshold by inhibiting central cyclooxygenase and may inhibit chemical mediators that sensitize the pain receptors (Insel, 1996). Acetaminophen also inhibits the effects of pyrogen by blocking prostaglandin synthesis. Acetaminophen toxicity can result from a single toxic dose or repeated cumulative dosages which lead to methaemoglobinemia and hepatotoxicity. In dogs, acetaminophen is used therapeutically for analgesia at a dose of 10 mg/kg BID (Ficherederand and Jaffe, 1994). There have been several reports on the medicinal roles of different plants by researchers over the years, one of which is *Piliostigma thonningii* plant. The assemblage of different parts of this plant has been found traditionally useful. As a result, people have resulted to using parts of this plant in the management or treatment of different kinds of ailments due to its antimicrobial, aphrodisiac, haematopoietic, hepatoprotective properties among others (Dasofunjo *et al*., 2016; Dasofunjo *et al*., 2018).

Therefore, this present research determines the comparative study on effect of maternal and prenatal exposure to acetaminophen and *Piliostigma thonningii* on haematological profile.

MATERIALS AND METHODS

Materials

Plant material

Fresh *P.thonningii* leaves were obtained from Igoli/Okuku road, Cross River State, Nigeria in February, 2017.Identification and authentication was done at the Federal College of Forestry Jos, Plateau state, Nigeria, with the voucher number #25.

Experimental animals

Twenty five (25) virgin female Wistar rats were obtained from animal holding unit, Department of Medical Biochemistry Okuku. The animal was acclimatized for a period of seven (7) days. Each rat was housed in a woodened cage. The animal room were well ventilated and kept at room temperature and

relative humidity of 20±2c and 70% respectively with 12 hours natural light – dark cycle and were allowed free access to standard feed and water. Good hygiene was maintained by constant cleaning and removal of faeces and spilled feeds from cages daily. The animals were subcutaneously injected with 0.1mg/kg body weight of diethylstilbestrol in 0.5ml olive oil to ensure the female rats were in oestrous. The mature male rats were introduced in ratio 1:3 until they have been confirmed pregnant.

Preparation of ethanol extract of Piliostigma thonningii leaf

The leaves of *P. thonningii* were collected and air dried for 14 days until constant weight was obtained. The dried leaves were then pulverized after which 300g was extracted in 1000ml of ethanol for 72 hours with constant shaking using the electric shaker. This was later filtered using Whitman No.1 filter paper. The filtrates were concentrated in water bath at 45^{o}c. The resulting slurry was weighed and reconstituted in coil oil to administer the required dose.

Animal Grouping and Administration of Extract

Twenty five (25) pregnant female albino rats were picked at random and placed into wooden cages labeled A-E. Group A served as control while groups B -D were test groups. The animals in group A were administered orally with distilled water. Group B were administered 200mg/body weight of acetaminophen, Group C was administered 200 mg/body weight of the extract, Group D were administered 100 mg/kg body weight of *P. thonningii* + 200 mg/kg body weight of acetaminophen while group D was administered with 200 mg/kg body weight of acetaminophen and *P. thonningii* respectively. All experimental groups used corn oil as vehicle. The oral administration was done for 28 days (till parturition) i.e. till the dams gave birth. The offspring were carefully separated and cared for until they were weaned on day 21. The animals in each group were sacrificed after 24 hours by cardiac puncture procedure. The animals were handled humanely in accordance with the guidelines of European convention for the protection of vertebrate animals and other scientific purposes.

Blood Sample Collection

Blood was collected from all the test rats and control by cardiac puncture using disposable syringe and needle draw blood dispensed into tubes containing the anticoagulant ethylene diamine tetra acetic acid (EDTA). The specimens were labeled with the identification alphabets/ number. The EDTA samples were kept at room temperature until processing, which occurred within 30 minutes of collection.

Laboratory analysis

Full blood count was performed using a KN-21N Hematology Analyzer (Sysmex, Kobe, Japan), a three-part auto analyzer able to test 7 parameters per sample including Hb concentration, PCV, RBC concentration, MCH, MCV, MCHC, WBC count, and PLT count. Standardization, calibration of the instrument, and processing of the samples were done according to the manufacturer's instructions.

Procedures

Each blood sample was mixed well and then approximately 20 µL was aspirated by allowing the analyzer's sampling probe into the blood serum sample and depressing the start button. Results of the analysis were displayed after about 30 seconds, after which the analyzer generated a paper copy of the results on thermal printing paper.

Statistical analysis

Statistical analysis data used presentation as means ± SD of five determinations. Statement analysis was carved out using one way analysis of variances (ANOVA). Difference were statistically significant at $P<0.05$ (Mahajan, 1997).

RESULT

The result below shows the effect of maternal and prenatal exposure to the *P. thonningii* on haematological parameters following acetaminophen induced toxicity. The maternal haematological parameters reviews a significant ($p<0.05$) increase in RBC, Hb, and HCT. For groups administered with 200 mg/kgbwt *P. thonningii*, 100 mg/kgbwt *P. thonningii* + 200 mg/kgbwt acetaminophen and groups administered with 200 mg/kgbwt P. thonningii or 200 mg/kgbwt of acetaminophen when compared with

the control (Table 1). Contrastingly, groups administered with 200 mg/kgbwt acetaminophen shows significant ($p<0.05$) reduction on serum RBC, Hb and HCT when compared with the control. More so the extract produced a significant ($p<0.05$) increase in all the experimental groups when compared with the control with the exception of the groups administered with acetaminophen a lone on serum WBC's when compared with the control (Table 1-2, Fig 1).

The drugs and the extract also produce a significant ($P<0.05$) increase for serum neutrophil of groups administered with 200 mg/kgbwt of acetaminophen, 200 mg/kgbwt *P. thonningii* and 100 mg/kgbwt 0f *P. thonningii* + 200 mg/kgbwt of acetaminophen. Except for groups co-administered with 200 mg/kgbwt *P. thonningii* and 200 mg/kgbwt of acetaminophen which shows a significant ($p<0.05$) decrease when compared with the control (Table 1).

The effect of prenatal exposure to *P. thonningii* following acetaminophen toxicity shows a significant ($p<0.05$) increase on the WBC of all the experimental groups with the except of the group administered with 200 mg/kgbwt acetaminophen a lone, likewise the prenatal exposure to ethanol extract of *P. thonningii* and acetaminophen shows similar trait with RBC, Hb, HCT, MCV, and PLT when compared with the control (Table 3, Fig 2).

Though, the drugs and the extract produced more significant ($p<0.05$) difference on the lymphocyte of the groups administered with 200 mg/kgbwt of acetaminophen when compared with the control (Table 2).

The drugs rather produced a significant ($p<0.05$) increase on other experimental groups when compared with the control. More so the M×D only produced a significant ($p<0.05$) increase on the groups administered with 200 mg/kgbwt of *P. thonningii* which compared with the control. The result also reviewed the other experimental groups produced low significant ($p<0.05$) difference.

Table 1: Effect of maternal exposure to extract of *P. thonningii* on erythrocyte level following acetaminophen induced toxicity

Parameters	RBC $\times10^6$(µL)	Hb (g/dL^{-1})	HCT (%)	MCV (fl)	MCH (pg)	MCHC (g/dL)
Control	5.7± 0.7	8.7 ±1.3	27.4±3.5	35.5±2.2	20.5±0.4	31.4±0.1
200mg/kg acetaminophen	0.5± 0.5	5.7± 1.3^{b}	20.0±5.7^{b}	35.3±4.2^{a}	20.5±0.5^{a}	31.5±376.7^{a}
200mg/kg *P. thonningii*	6.1±0.4^{bc}	11.9±0.8^{bc}	36.9±3.2^{bc}	61.5±1.5^{bc}	19.9±0.1^{a}	32.3± 0.7^{bc}
100mg/kg *P. thonningii*+ 200mg/kg acetaminophen	6.7±0.4^{bc}	14.0±0.2^{bc}	44.3±0.8^{bc}	63.0±0.9^{bc}	19.1±0.4^{a}	31.7± 0.2^{a}
200mg/kg acetaminophen +200mg/kg *P. thonningii*	6.5±0.7^{bc}	12.1±1.9^{bc}	32.9±6.2^{bc}	61.6±2.0^{bc}	19.5±0.8^{a}	31.5± 0.4^{a}

Result expressed as mean ± SEM (n =5). [a] Non-significant (P>0.05) compared to the normal control. [b] Significant (P<0.05) compare to test groups. [c] Significant (P<0.05) compared to the standard

Table 2: Effect of maternal exposure to extract of *P. thonningii* on Leucocyte level following acetaminophen induced toxicity

Parameters	WBC $\times10^3$(µL)	LYMP (%)	NEUT (%)
Control	3.7±1.3	5.6± 39.6	49.1±40.5
200mg/kg acetaminophen	2.3± 1.9^{b}	9.2± 1.5^{b}	66.0± 0.8^{b}
200mg/kg *P. thonningii*	5.7± 1.8^{bc}	5.3± 0.9^{ac}	80.0 ±0.3^{bc}
100mg/kg of *P.thonningii* +200mg/kg acetaminophen	4.8± 1.8^{bc}	14.0± 0.7^{bc}	78.0± 0.3^{bc}
200mg/kg acetaminophen + 200mg/kg *P.thonningii*	3.6± 4.1^{ac}	3.1± 1.1^{bc}	43.3± 0.7^{ac}

Result expressed as mean ± SEM (n =5). [a] Non-significant (P>0.05) compared to the normal control. [b] Significant (P<0.05) compare to test groups. [c] Significant (P<0.05) compared to the standard

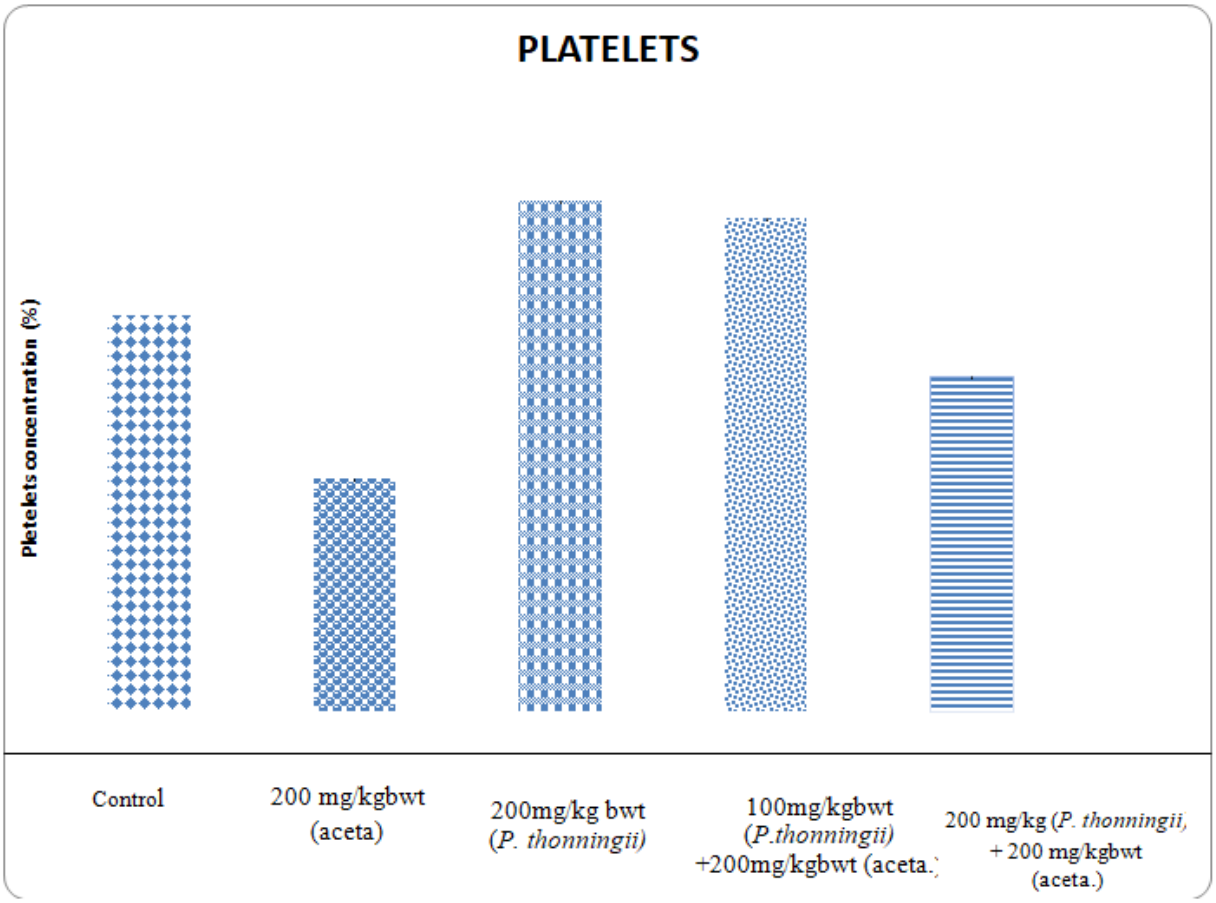

Figure 1: Effect of maternal exposure to extract of *P. thonningii* on platelets level following acetaminophen induced toxicity.

Table 3: Effect of prenatal exposure to extract of *P. thonningii* on Leucocyte level following acetaminophen induced toxicity

Groups	**WBC**10^3(µL)	**LYMP** (%)	**NEUT** (%)
Control	4.4± 3.7	18.3 ±5.5	10.5± 4.7
200 mg/kgbwt acetaminophen	3.7 ±0.3	18.2±82.4	11.6± 4.3
200mg/kgbwt *P. thonningii*	6.0± 0.6	73.7± 6.6	10.1 ±6.6
100mg/kgbwt *P.thonningii* +200mg/kgbwt acetaminophen	5.6± 3.5	51.1± 44.6	10.1± 10.6
200mg/kgbwt acetaminophen+ 200 mg/kgbwt *P. thonningii*	5.3± 3.1	76.4 ±8.2	10.3 ±14.6

Result expressed as mean ± SEM (n =5). [a] Non-significant (P>0.05) compared to the normal control. [b] Significant (P<0.05) compare to test groups. [c] Significant (P<0.05) compared to the standard

Table 4: Effect of prenatal exposure to extract of *P.thonningii* on Erythrocyte level following acetaminophen induced toxicity

Groups	RBC $\times 10^6$(µL)	Hb (g/dL^{-1})	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
Control	4.1± 1.3	9.5± 2.1	29.7± 8.8	7.4 ±1.4	23.4±0.0	31.9 ±0.6
200 mg/kgbwt acetaminophen	3.3 ±0.2^{b}	11.4±0.3^{b}	15.0±2.1	60.7±8.0^{bc}	19.8±0.2	29.5± 1.2
200 mg/kgbwt *P.thonningii*	5.6±0.2^{bc}	15.7±0.5^{bc}	38.9 ±2.9^{bc}	69.1±2.5^{bc}	20.7±0.2^{a}	30.0±1.1^{a}
100 mg/kgbwt (*P.thonningii*+200 mg/kgbwt acetaminophen	6.1±0.2^{bc}	14.3±1.0^{bc}	40.5± 1.1^{bc}	66.7±1.3^{bc}	20.3± 1.9	30.4±3.2^{a}
200mg/kg *P.thonningii* +200 mg/kg acetaminophen	6.9±4.9^{bc}	13.7 ±8.2^{b}	37.1±34.4^{bc}	68.2±2.1^{bc}	24.4±34.9^{ac}	34.1±19.9^{bc}

Result expressed as mean ± SEM (n =5). [a] Non-significant (P>0.05) compared to the normal control. [b] Significant (P<0.05) compare to test groups. [c] Significant (P<0.05) compared to the standard

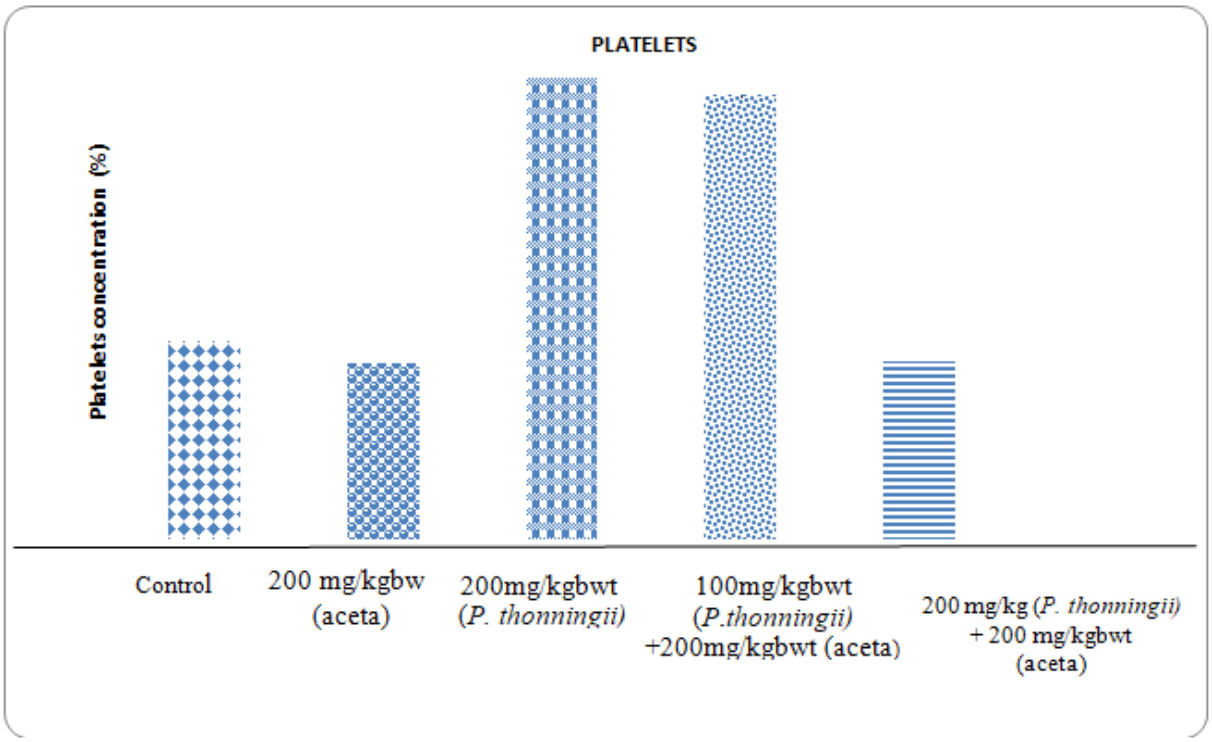

Figure 2: Effect of prenatal exposure to extract of *P. thonningii* on platelets level following acetaminophen induced toxicity

DISCUSSION

Haematological parameters are good indicators of the physiological and pathological changes in the animals and are also an excellent medium for the measurement of potential biomarkers. The blood consisting of blood cells and plasma fulfills the transport, regulatory, protective and homeostatic

functions. Blood parameters are indispensible in the diagnosis, treatment or prognosis of many diseases (Roy *et al*., 2010). Pregnancy on the other hand is associated with physiological and biochemical changes that are relevant in the nurturing and survival of the foetus (Dasofunjo *et al*., 2017). The lives of eight million women are threatened, and more than 500,000 women are estimated to have died as a result of causes related to pregnancy and childbirth complications (Chandra *et al*., 2012). In fact, anaemia is the most common haematological problem in pregnancy, followed by thrombocytopenia and leukocytosis accordingly (Roy *et al*., 2010; Eyers *et al*., 201l).

In this present research ,the increase in haemoglobin concentration and PCV for both maternal and prenatal exposure may be due to increase in plasma volume during pregnancy causing haemodilution, hormonal changes that increases fluid retention and iron deficiency (Wahed *et al*., 2008, Sembulingan, 2010). Likewise, HB concentration was found to decrease significantly in maternal and prenatal exposure to acetaminophen which may be attributed to an increased demand for iron as pregnancy progresses. More iron is requirement for iron to meet the expansion of maternal HB and the needs for foetal growth. During pregnancy, an increased plasma volume with the lack of an adequate increase in erythrocytes mass results in a decrease in haemoglobin level and the development of anaemia, which is defined as dilution anemia (Roy *et al*., 2010).

In addition, the general decrease in the other blood indices is more likely explained by increased needs during pregnancy. Therefore, the increase in these blood indices could be a reflection of adequate iron metabolism resulting in increased haemoglobin production following the administration of the extract. Also, the additional progesterone and estrogen that are secreted by the placenta during pregnancy cause a release of renin from the kidneys. Renin stimulates the aldosterone-renin-angiotensin mechanism, leading to sodium retention and increased plasma volume. The increase in plasma volume is relatively greater than the increase in red cell mass, which results in a fall in maternal Hb in groups administered with acetaminophen resulting in physiological anaemia that occurs in pregnancy, Contrastingly, the treated groups co-administered with acetaminophen and *P.thonningii* mitigate this effect suggesting that the extract contain some bioactive substances possibly saponin, flavonoid or alkaloid which synergistically enhances hematopoietic or hematopoietic system during pregnancy. Likewise, the significant increase observed on the Red blood cells (RBC following the administration of the extract may be an indication that it improve the rate of production of red blood corpuscles (erythropoietin). This may imply that the extract was capable to release erythropoietin in the kidney, which is the hum oral regulator of RBC production. Since MCHC, MCH and MCV relate to individual red blood cells while HB, RBC, PCV are linked to the total population of red blood cells, the significant increase following the administration of the extract of the extract on these indices may imply the incorporation of haemoglobin into red blood cells or the morphology and osmotic fragility of the red blood cells was increased this is in accordance with our earlier report (Dasofunjo *et al*., 2013). Therefore, it is likely that the drug(acetaminophen) affect the oxygen-carrying capacity both on the maternal and prenatal exposure of each of the RBC and the total population of Wistar rat, it may be logical to infer that the extract had effect on the average size of RBC (microcytes) as well as the weight of haemoglobin per RBC but a contrary effect was observed in the acetaminophen group which displayed a dishaematopoietic effect, hence exhibiting an evidence of physiological anaemia associated with pregnancy this is similar to the report of Dasofunjo *et al*., (2017). White blood cell differentials are indicators of the ability of an organism to protect itself against infection. A rising WBC count in pregnancy is not a reliable indicator of infection in subclinical chorioamnionitis; rather, clinical methods of detection such as maternal pyrexia, offensive vaginal discharge, and foetal tachycardia are better indicators, especially of preterm labour and membrane rupture (Akingbola *et al.*, 2006).Leukocytosis occurring during pregnancy may be due to the physiologic stress induced by the pregnant state. In this context, Pilsczek *et al* ., (2008) explained this change as a result of the body building the immunity of the foetus and it is achieved by a state of selective immune tolerance, immunosuppressant and immunomodulation in the presence of a strong antimicrobial immunity. There is also down-regulation of potentially dangerous T-cell-mediated immune responses, while activating

certain components of the innate immune system, such as neutrophils which are the major type of leukocyte on differential count (Guyton *et al.*, 2011, Gatti *et al.*, 1994). Therefore, the decrease of WBC count in all the treated groups following the administration of the extract suggests that the extract might not enhance systemic immunity or prevents predisposition to opportunistic diseases and infections during pregnancy. Neutrophilia observed following the administration of acetaminophen alone may be due to impaired neutrophilic apoptosis in pregnancy (Jessica *et al*., 2007, Jensen *et al*., 2011). Neutrophil chemo taxis and phagocytic activity are depressed, especially due to inhibitory factors present in the serum of a pregnant female (Margarat *et al*., 2010). The above unique deregulation between different components of the immune system plays a central role in the maternal adaptation to pregnancy or help in preventing foetal allograft rejection by infiltrating the decidua tissue possibly, through Prostaglandin E2 mediated immunosuppressant. It appears that the groups administered with acetaminophen alone compromised the immunosuppressant and immune modulatory effect following both maternal and prenatal exposure hence resulting in the observed decrease.

Conclusion

The spectrum of alterations from this results are indications that acetaminophen exhibits an haematotoxic and may compromise immunosuppressant and immunomodulation during pregnancy but the extract displayed haematopoietic and immunomodulatory effect on both maternal and prenatal exposure.

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