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Anti-fertility and Pro-fertility Activities of *Desplatsia dewevrei* (De Wild. & Th. Dur.) Burret on Wistar Rats

O.O. Godwin[1], M. Idu[2], E. Iyamah[3], K. Atoe[4], I. Obahiagbon[5], C. Imafidon[6] and O. Eguagie[6]

[1]Department of Biological Sciences, University of Medical Sciences, PMB 536, Ondo City, Ondo State, Nigeria
[2]Department of Plant Biology and Biotechnology, University of Benin, PMB 1154, Benin City, Edo State, Nigeria
[3]MLSCN Graduate Training School; University of Benin Teaching Hospital, Benin City, Edo State, Nigeria
[4]Department of Chemical Pathology, Edo State University, Uzairue, Edo State, Nigeria
[5]Department of Histopathology, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria
[6]Department of Science Laboratory Technology, University of Benin, Benin City, Edo State, Nigeria
.

*Corresponding author; Email: ooghale@unimed.edu.ng

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ABSTRACT: *Desplatsia dewevrei* (De Wild. & Th. Dur.) Burret fruits were investigated for possible anti-fertility and pro-fertility activities by hematological, biochemical and hormonal assays using Wistar rats of both sexes for 6 weeks. Methanol extract of *Desplatsia dewevrei* fruits was administered orally at 50 and 100 mg/kg. Results show that concentrations above 50 mg/kg interfered with the reproductive development of the liter (fetus) in female rats. While in male rats, doses above 50 mg/kg posed adverse effect on sperm count and sperm motility. Organ-to-body weight and temperature indices in pregnant female animals were not adversely affected by oral treatment with *Desplatsia dewevrei.* Thus, an EC_{50} of 50 mg/kg of *Desplatsia dewevrei* methanol extracts was observed to elicit pro-fertility effects. In conclusion, *Desplatsia dewevrei* from this research finding possesses potentials of a pro-fertility agent at doses lower than 50 mg/kg however, but can become an abortifacient at doses higher than 50 mg/ kg.

Keywords: Pro-fertility, Anti-fertility, *Desplatsia dewevrei*, Hematology, Biochemistry

Introduction

Infertility is of foremost concern to several people around the world (Raghuveer *et al*, 2010). Male potency with regards to sperm count is dwindling (Kumar and Singh, 2015). In South-Eastern Nigeria, infertility depending on disorders in men was found in 42.4% of married people and 25.8% of reproductive challenges in women amongst three hundred and fourteen (314) couples examined on the basis of sterility (Ikechebelu *et al.*, 2003). Sexual behaviour comprising mating, virility, conception and procreation forms the fundamentals of fertility while, countless substances have been reported to arouse sexual craving and performance including indigenous plants (Singh and Mukherjee, 1998; Chauhan *et al*., 2014). Several plant extracts have been reported to possess stimulatory activity on the reproductive sex hormones and organs which are known to control the reproductive physiognomies in male and female entities (Uboh *et al*., 2010).

Desplatsia dewevrei (De Wild. & Th. Dur.) Burret is an under-utilized medicinal plant used by indigenous people across West Africa as food and also in the management of several ailments and diseases (Ovuakporie-Uvo and Idu, 2017). Latham and Mbuta (2017), in their book entitled "Plants of Kongo Central Province, Democratic Republic of Congo", reported the leaves of *D. dewevrei* as medicinally useful in Equateur province. However, there are no documentations on the reproductive toxicity and fertility activities of the plant. Thus, this study was aimed at investigating the anti-fertility and pro-fertility activities of *D. dewevrei* fruits by hematological, biochemical and hormonal assays.

Materials and methods

Plant harvest and authentication: Desplatsia dewevrei fruits were harvested from a forest in Ugbogiobo village; Ovia North East Local Government Area of Edo State. Plant materials were identified and authenticated at the Department of Plant Biology and Biotechnology, University of Benin, Benin City (Voucher number UBHm0283).
Plant preparation and extraction: Fresh fruits were diced in bits before drying. Dried and blended plant materials were extracted using cold maceration method with methanol as solvent. Extracts were concentrated to fine powder using a rotary evaporator and freeze-drier (4 ℃) at the Biochemistry Laboratory, Adekunle Ajasin University, Akungba-Akoko, Ondo State.
Animals: Both sexes of inbred Wistar rats weighing 115-195 g, n= 40) got from the animal facility; Centre for Bio-computing and Drug Development Unit of Adekunle Ajasin University, Akoko-Akungba were used in this study. Ethical consent on the use of experimental animal in compliance with the National Institute of Health guide for the care and use of laboratory animals was obtained from the animal ethics committee of Centre for Research and Development (CRD), Adekunle Ajasin University, Akungba-Akoko.
Toxicity studies: A toxicity study based on OECD- guidelines 407 (OECD, 2008) was done to ascertain reproductive toxicity influenced by the administration of *Desplatsia dewevrei* extract (DDE). Adult male and female animals were housed in different cages after 7 days acclimatization period. Thereafter, they were grouped separately - four animals per treatment. Male animals; Group 1 received 50 mg/kg p.o DDE; Group 2 received 100 mg/kg p.o DDE; Group 3 served as negative control and received distilled water p.o; lastly, Group 4 were administered a single booster dose of testosterone i.m and co-administered DDE, served as positive control. For the female animals, Group 1 animals received 50 mg/kg p.o DDE; Group 2 received 100 mg/kg p.o DDE; Group 3 served as the positive control group and received a single dose of Clomid p.o and co-administered DDE while Group 4 served as negative control for a week. After the first week, animals were re-shuffled, 2 male animals were put together with 4 females in the same cage according to their dose regime for both treatment and control treatment for 2 weeks. Thereafter, male animals were withdrawn from the female cages and put in their original cages till the last day of the experiment. In the course of the experiment, animals were weighed on weekly basis and observed for clinical signs. After the experimental period, animals were sedated with 2% chloroform. Blood was collected by cardiac puncture for hematological, biochemical and hormonal analysis. Organ-to-body weight was calculated for the female animals following methods adopted by Ovuakporie-Uvo *et al*. (2015).
Pro-fertility and anti-fertility studies: *Desplatsia dewevrei* extract (DDE) was evaluated for the ability to modulate the expression of follicle-stimulating hormone receptor, luteinizing hormone receptor, steroid hormone receptor testes specific protein kinase 1 in the ovaries and testes of Wistar rats using methods adopted by Ukwenya *et al*. (2007); Sakpa *et al*. (2016).
Biochemical, hematological and hormonal studies: Biochemical and hematological tests were done using the blood of the laboratory animals collected from the heart and analyzed following methods described by Ovuakporie-Uvo *et al*. (2015). Serum testosterone, progesterone, prolactin, follicle stimulating hormone, estradiol, prolactin, leutinizing hormone concentrations were quantitatively analyzed using the Microplate Enzyme Immunoassay Kit Sigma-Aldrich® USA. The total testosterone, progesterone, estradiol, FSH, LH, and prolactin concentration in rat serum were estimated as described in the manufacturer's test procedure (Accu-Bind® Elisa Microwells). Absorbance was read using a microplate reader at 450 nm absorbance wavelength.
Statistical analysis: Data were expressed as Mean ± Standard Error of Mean (SEM). Variance between different treatments groups were analyzed using one-way ANOVA. For the haematology tests, multiple comparisons were done using Tukey's multiple range tests on Graph Pad prism 8 computer software packages. Significant levels were determined at $p< 0.05$.

Results

A 6-week fertility study using both sexes of Wistar rats showed no significant difference in all blood parameters except blood platelet count at 100 mg/kg of *Desplatsia dewevrei* methanol fruit extract as presented in Tables 1 and 2. Female animals in the group administered 100 mg/kg of the extract had thrombocytopenia; low platelet count (495.7 $\times 10^3$/ul) when compared with the control (906 $\times 10^3$/ul) and the positive control group (15620 $\times 10^3$/ul).

Table 1: Hematology of 6 weeks anti-fertility studies of *D. dewevrei* fruit extract in female rats

Hematological Parameters	Group 1 (50 mg/kg)	Group 2 (100 mg/kg)	Group 3 (50 mg/kg Clomid)	Group 4 (Basal Control)
WBC (10^3/ul)	7.10 ± 0.00	5.17 ± 1.54	6.15 ± 1.05	8.35 ± 0.85
LY ($\times10^3$/ul)	5.30 ± 0.01	4.20 ± 1.99	5.65 ± 0.95	6.10 ± 0.42
MO ($\times10^3$/ul)	0.90 ± 0.02	0.30 ± 0.15	0.20 ± 0.10	0.70 ± 0.27
GR ($\times10^3$/ul)	0.90 ± 0.01	0.67 ± 0.37	0.35 ± 0.50	1.53 ± 0.58
RBC ($\times10^6$/ul)	6.68 ± 0.00	7.14 ± 1.49	9.02 ± 0.97	9.19 ± 0.36
HGB (g/dl)	13.70 ± 0.00	14.14 ± 1.52	11.75 ± 2.43	17.73 ± 1.07
HCT (%)	41.00 ± 0.01	44.57 ± 0.67	54.50 ± 0.80	54.05 ± 1.28
MCV (fl)	61.30 ± 0.01	62.50 ± 1.26	60.25 ± 1.05	58.83 ± 0.97
MCHC (g/dl)	33.40 ± 0.02	33.00 ± 0.47	23.00 ± 1.80	32.70 ± 1.45
PLT ($\times10^3$/ul)	1510.0 ± 0.00^b	495.7 ± 108.99^a	1562.00 ± 52.00^b	906.00 ± 132.63^a
PCT (%)	1.04 ± 0.00^b	0.38 ± 0.95^a	0.93 ± 0.07^b	0.57 ± 0.10^a

n=4; Values are Mean ± S.E.M, where; values with same alphabet are significantly different from each other at P< 0.05.

Table 2: Hematology of 6 weeks anti-fertility studies of *D. dewevrei* fruit extract in male rats

Hematological Parameters	Group 1 (50 mg/kg)	Group 2 (100 mg/kg)	Group 3 (Basal Control)	Group 4 (20 ng/kg Testosterone)
WBC ($\times10^3$/ul)	14.40 ± 1.16	15.75 ± 1.15	13.20 ± 3.35	11.37 ± 0.69
LY ($\times10^3$/ul)	12.17 ± 1.39	11.55 ± 2.35	9.77 ± 1.77	10.13 ± 0.47
MO ($\times10^3$/ul)	0.80 ± 0.06	1.50 ± 0.40	1.33 ± 1.08	0.57 ± 0.12
GR (%)	1.43 ± 0.20	2.70 ± 0.80	2.17 ± 1.92	0.67 ± 0.22
RBC ($\times10^6$/ul)	8.74 ± 0.26	8.70 ± 0.11	10.09 ± 1.43	9.01 ± 0.06
HGB (g/l)	17.03 ± 0.12	17.55 ± 0.25	16.70 ± 1.12	17.47 ± 0.63
HCT (%)	51.13 ± 0.74	51.30 ± 0.80	60.17 ± 3.68	51.73 ± 1.69
MCV (fl)	58.57 ± 2.03	58.90 ± 0.20	59.53 ± 0.71	57.37 ± 1.87
MCHC (g/dl)	33.27 ± 0.32	34.15 ± 0.05	29.23 ± 5.27	33.70 ± 0.36
PLT ($\times10^3$/ul)	1239.0 ± 81.99	1331.5 ± 122.5	1472.0 ± 286.20	1300.33 ± 139.91
PCT (%)	0.91 ± 0.06	0.90 ± 0.06	0.96 ± 0.15	0.87 ± 0.12

n=4; Values are Mean ± S.E.M, where; values are not significantly different from each other at P< 0.05

Figure 1 shows the results of the serum biochemistry carried out on the male rats. Animals administered 50 mg/kg of *D. dewevrei* extract elicited comparable measures of urea, Na^+, K^+, HCO_3 and Creatinine with those in the testosterone (standard) group. This was obvious in the physical observations of uncontrolled bleeding, failed pregnancy and whiteness of the dissected animals as presented in Figure 2.

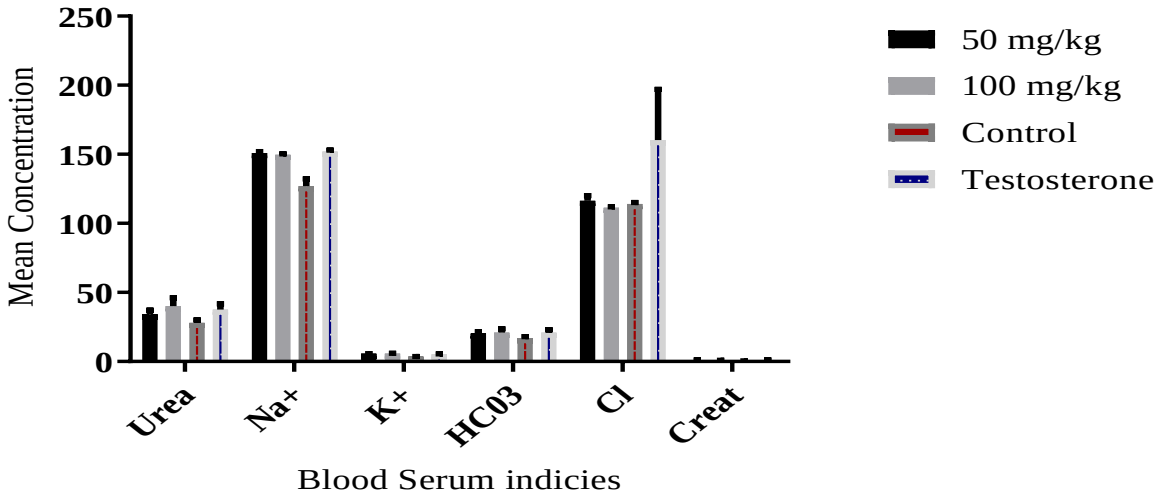

Figure 1: Serum biochemistry of male animals

Figure 2 shows the dissected female animals administered 50 and 100 mg/kg of *Desplatsia dewevrei* methanol leaf extract. The internal structures show that above 50 mg/kg, animals experienced failed pregnancy and abnormal development of the fetus depicting an adverse response to treatment.

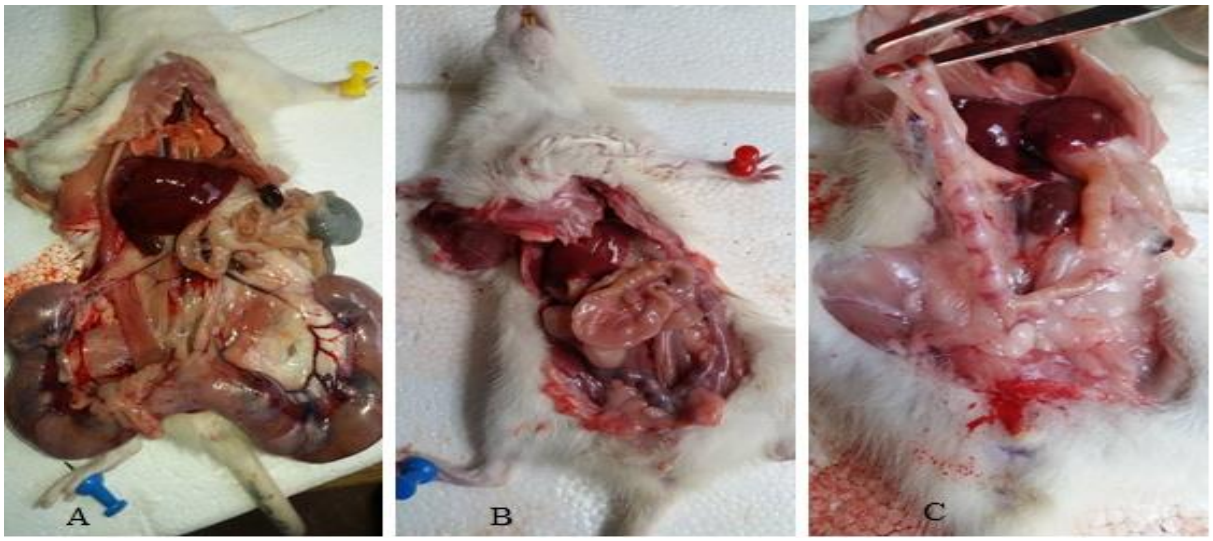

Figure 2: Internal structure of female Rats showing different responses to treatment with *D. dewevrei*; Animal treated with "A" Control, "B" 50 mg/kg extract and "C" 100 mg/kg extract

An elevated progesterone and estradiol level with reduced testosterone level in the hormonal profile of male rats administered 100 mg/kg of *D. dewevrei* methanol fruit extract was observed (Table 3). This trend of response to treatment suggests that *Desplatsia dewevrei* methanol fruit extract at 100 mg/kg or beyond can serve as an anti-fertility agent in male animals and an abortifacient in female animals.
There was an overall weight loss in rats in the experimental group administered 100 mg/kg of *D. deweverei* methanol fruit extract. However, no statistical differences in the organ to body weight indices were recorded in the treatment groups when compared with the control group (Table 4).

Table 3: Hormonal assay of male rats treated with *Desplatsia dewevrei* for 6 weeks
n=4; Values are Mean ± S.E.M, where values are not significantly different from each other at P< 0.05.

Hormones	**Control**	**20 ng/kg Testosterone**	**50 mg/kg**	**100 mg/kg**
Progesterone (ng/ml)	0.11 ± 0.09	1.83 ± 0.90	0.43 ± 0.06	4.89 ± 1.31*
Testosterone (ng/ml)	0.80 ± 0.52	2.75 ± 0.63	2.01 ± 1.62	0.63 ± 0.09
Estradiol (pg/ml)	18.96 ± 1.21	13.59 ± 1.90	30.85 ± 2.37	47.49 ± 3.67
FSH (mlu/ml)	0.63 ± 0.17	0.50 ± 0.07	0.51 ± 0.01	0.54 ± 0.03
LH (mlu/ml)	2.16 ± 0.05	2.28 ± 0.03	2.16 ± 0.05	2.33 ± 0.07
Prolactin (ng/ml)	2.71 ± 0.06	3.29 ± 0.40	3.06 ± 0.16	2.40 ± 0.00

Key: FSH=Follicle Stimulating Hormone; LH=Luteinizing Hormone

Table 4: Organ-body weight ratios of female Wistar rats

Conc (mg/kg)	**Average B.W (g)**	**Organ-to-body Weight Indices**					
		H:BW	**K:BW**	**Li:BW**	**L:BW**	**S:BW**	**O:BW**
0	160	0.0039±0.0002	0.0036±0.0003	0.031±0.0004	0.0103±0.0006	0.0046±0.0003	0.0005±0.0001
50	160	0.0036±0.0003	0.0033±0.0004	0.035±0.0002	0.0098±0.0011	0.0062±0.0006	0.0004±0.0000
100	150	0.0040±0.0001	0.0038±0.004	0.020±0.0010	0.0164±0.0054	0.0061±0.0007	0.0005±0.0000
Clomid	150	0.0040±0.0001	0.0036±0.0001	0.0294±0.0005	0.0105±0.0004	0.0045±0.0001	0.0007±0.0030

Values are Mean ± SEM where, n=4. (No statistical difference between control and treatment groups).
Key: H=Heart; K=Kidney; Li=Liver; L=Lungs; S=Spleen; O=Ovaries; BW=Body Weight

Expected elevated body temperature; an occurrence associated with pregnancy in females did not occur. Temperature was observed to be within the normal body temperature range (in the third trimester) for Wistar rats treated with 50 and 100 mg/kg of *Desplatsia dewevrei* methanol fruit extract (Table 5). Estimation of sperm

count, motility and morphology in male rats reported in Table 6 shows that percentage total motility, progressive motility (%) and total sperm count (cells/mm^3) of animals treated with 50 mg/kg of *Desplatsia dewevrei* methanol fruit extract was comparable to the findings in those administered 20 ng/ml of testosterone as a positive control (standard drug) group

Table 5: Effect of daily oral administration of *D. dewevrei* on body temperature of female Wistar rats

Conc (mg/kg)	Temperature indices in 3rd Trimester (°C)					
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**
0	37.60 ± 0.15	37.47 ± 0.13	36.30 ± 0.21	37.10 ± 0.22	38.20 ± 0.40	36.53 ± 0.02
50	35.83 ± 0.23*	36.77 ± 0.13	36.90 ± 0.10	37.77 ± 0.13	37.50 ± 0.10	35.97 ± 0.07
100	38.07 ± 0.55	36.77 ± 0.55	36.77 ± 0.20	36.37 ± 0.52	37.33 ± 1.01	34.67 ± 1.09
Clomid	38.10 ± 0.32	37.43 ± 0.13	36.30 ± 0.16	37.33 ± 0.14	37.63 ± 0.18	35.57 ± 0.30

Values are Mean ± SEM. n= 4. Significant mean differences are determined at $p<0.05$
(**N.B:** Normal body temperature of rat is between 35.9-37.5 °C).

Table 6: Estimation of sperm count, motility and morphology in male Wistar rats

Groups	Total Motility (%)	Progressive Motility (%)	Total Count (Cells/mm^3)
Control	75	70	16
50 mg/kg	50	45	10
100 mg/kg	-	-	23
Testosterone (ng/ml)	50	45	19

Values are Mean ± SEM. significance between control and treated group were determined at $P<0.05$.
N.B: Animals in the group administered 100 mg/kg showed no motile sperm cells at the time they got to the hospital. However, the total sperm count was determined.

Discussion and conclusion

Several dynamics including nutrition affect the fertility status of animals and man. Foods rich in arginine, for example, have been implicated in stimulating sexual performance because they are aphrodisiac (Sumalantha *et al*., 2010). Diet shaving minerals like zinc help to stimulate the secretion and action of testosterone which can lead to increased efficiency of spermatogenic machinery and increased number of germ cells in the seminiferous tubules (Pizent *et al*, 2003 and Abdella *et al.*, 2011). According to earlier studies, *Desplatsia dewevrei* fruits (0.1359 g/100 g) contain trace quantities of zinc (Ovuakporie-Uvo *et al.,* 2019). This may be a contributing factor to the fertility activities the plant potentiates.

Production of reactive oxygen species exceeding critical levels can override all antioxidant defense lines of spermatozoa and seminal plasma which can result to damages in the testes membranes. This may cause degeneration of the spermatogenic and Leydig cells, which disrupts spermatogenesis and reduces sperm counts (Latchoumycandane *et al*., 2002). However, the competitive total phenolic and flavonoid content alongside the remarkable quantity of Vitamin C in *D. dewevrei* gives it an antioxidant scavenging edge over free radicals that peroxidase leydig and other cells that promote fertility (Ovuakporie-Uvo *et al*., 2019).

Testosterone shortage has an adverse effect on erectile nerves and the structure of penile tissues (Grahl *et al*, 2007). The results of the hormonal assay in male animals revealed a statistical decrease in serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin. At 50 mg/kg dose of *D. dewevrei* methanol fruit extract, pro-fertility activities were recorded but at 100 mg/kg, *D. dewevrei* caused infertility as evidenced by elevated progesterone and estradiol in male Wistar rats (Table 3).

In the female animals, there were no organ to body weight changes or temperature changes in all treatment groups in comparison with the control group (Table 4). However, hematology results (Table 1) and cut sections of animals (Figure 2) show that at 100 mg/kg dose, thrombocytopenia (low platelet concentration) and contraction of uterine horn resulting in whiteness of animal interior and failed pregnancies was observed. Platelets also called thrombocytes are a component of blood whose function along with the coagulation factors is to stop bleeding by clumping and clotting blood vessel injuries (Laki, 1972). Some drugs used to treat inflammation have unwanted side effects of suppressing normal platelet functions (Rao *et al*., 1983). However, hemotoxicity was not observed in all blood parameters tested in male animals (Table 2).

Testosterone is absolutely required for meiotic prophase and entry into the final meiotic division. Without testosterone, no haploid spermatids are formed. The progression of haploid spermatids through spermiogenesis also relies on testosterone and in the absence of androgens, the spermatogenic arrest occurs. The final release of spermatids during the process of spermiation is also sensitive to androgen and gonadotropin inhibition (O'Donnel *et al*., 1999; De Gendt *et al*., 2004; Chang *et al*., 2004; Holdcraft and Braun, 2004; Abel *et al*., 2008; Lim *et al*., 2009; O'Donnel *et al*., 2011). Results from the present study showed that the administration of methanol fruit extract of *D. dewevrei* at 50 mg/kg for 6 weeks progressively boost testosterone in male rats (Table 3). It can, therefore, be concluded that *D. dewevrei* at 50 mg/kg have pro-fertility potentials but administration of the extract at doses above 50 mg/kg can result in reduced spermatogenesis.

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Note: O.O. Godwin (Mrs.) is the same person as O.O. Ovuakporie-Uvo (Miss). The general public should please take note for future correspondence.

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