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Oxytocic and Abortifacient Potential of Ethanolic Extract of Date Fruit (*Phoenix Dactylifera*) in Albino Rats

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Abstract
This study aimedto evaluate the oxytocic and abortifacient potential of ethanolic extract of date fruit (*Phaenix dactylifera)* in albino rats. The phytochemical analysis of the extract was also evaluated using standard methods. For biochemical and hematological assay, a total of 30 wistar rats with body weight of 200 ± 50 g were used for this study. The animals were group into six groups of five rats each. Group 1 served as normal control and was administered only feed and water, while groups 2 and 3 were positive and negative control and were administered phenylhydrazine (PHZ), and PHZ + fero-hemoglobin, respectively. Groups 4, 5 and 6 were all administered PHZ, with co-administration of the extracts at 1000 mg/kg, 2000 mg/kg and 3000 mg/kg body weight respectively. This administration lasted for a period of 4 weeks, after which they were sacrificed and blood samples for hematological and biochemical analysis. Phytochemical analysis indicated the presence of tannins (3.30 mg/100 g) as compound with the highest concentration, while steroids (0.00 mg/100 g)) was absent. Others include alkaloids (0.34 mg/100 g), flavonoids (0.09 mg/100 g), and saponins (0.16 mg/100 g). From the results, hematological indices showed that results of platelets and white blood cells had significant ($p<0.05$) increase when the positive control was compared with the extract-treated groups, while hemoglobin, packed cell volume and red blood cells indicated significant ($p<0.05$) decrease when the positive control group was compared with the extract treated groups. From the oxytocic assay, results showed that the plant extract had significant ($p<0.05$) contraction at the highest dose which is not significantly different from the contraction of maximum dose of oxytocin. Also, salbutamol significantly ($p<0.05$) inhibited the contractile effects of both the extract and oxytocin. The

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pregnant rats littered completely following the administration of the extracts. With respect to the biochemical assays, results of catalase and glutathione peroxidase showed that the groups administered the extract of *P. dactylifera* at doses of 2000 mg/kg and 3000 mg/kg indicated significant ($p<0.05$) increases when compared with the positive control, while superoxide dismutase had no significant ($p>0.05$) effect. Malondialdehyde shows a marked significant ($p<0.05$) increase in the positive control when compared with other groups. Furthermore, it was observed that the results of albumin and total protein had significant ($p<0.05$) increase in all the extract-treated groups when compared with the positive control group. Results of this study indicate that the extract of *P. dactylifera* possesses some significant biochemical effects, oxytocic effects but no abortifacient effect and therefore further studies should be recommended to ascertain the active ingredientsresponsible and their possible mechanism(s) of action.

Keywords: *Phaenix dactylifera;oxytocic;abortifacient; hematology; catalase; glutathione peroxidase*

1. Introduction

In recent years, research efforts are underway on the possibilities of utilization of natural sources of bioactive compounds for the dietary management of certain chronic diseases such as anemia, cancer, diabetes, obesity, cardio-vascular diseases, etc. [1]. The use of herbal plants for curative purposes by the primitive man showed that some plants contain therapeutic agents and thus have necessitated scientific studies in order to explain the therapeutic potentials associated with traditional herbal remedies. Medicinal plant can be described as any plant which provides health promoting characteristics, temporary relief from symptomatic problems or has curative properties. It can also be defined as any plant containing substances that can be used for therapeutic purposes and could be used as a model to produce useful drug. There is increasing body of evidence that many of today's diseases are caused by the oxidative stress which is the result of imbalance between formation and neutralization of reactive free radicals. These free radicals are continuously produced and neutralized in our body so as to maintain the constant internal environment, that is vector state. Fruits and vegetables offer protection against oxidative due to the pressure of bioactive compounds such as polyphenolics, including flavonoids, vitamin C, E and carotenoid contents [2]. Flavonoids display some striking medicinal functions possibly due to their observed antioxidant properties.

Blood is a special type of connective tissue composed of formed elements (erythrocytes, leukocytes, and platelets) in a fluid matrix. Plasma is the fluid portion called serum when depleted to fibrinogen [3]. Blood analysis is a useful tool for the diagnosis and health monitoring of animals, as well as to distinguish pathogenic processes from those that might be purely physiological. The date palm (*Phoenix dactylifera* L.) is a palm extensively cultivated for its edible fruit belonging to the Palmae (Arecaceae) family [4]. The date pulp is rich in phytochemicals like sterols, phenolics, carotenoids, procyanidins, anthocyanins and flavonoids [5].

Dates are especially delicious as a fresh fruit. Beside direct consumption of the whole dates, the fruits are traditionally used to prepare a wide range of different products such as date juice concentrates (spread, syrup and liquid sugar), fermented date products (wine, bioethanol, vinegar,

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organic acids) and date pastes for different uses (e.g. bakery and confectionary) [5]. Minerals are critical for enzyme activation, gene expression, bone formation, hemoglobin composition and amino acid, lipid along with carbohydrate metabolism [6]. Minerals are also required for normal cellular functions [7]. Certain inorganic mineral elements (K, Zn, Ca and traces of Cr, etc) play an important role in the maintenance of normal glucose tolerance and in the release of insulin from beta islets of Langerhans. The reports on mineral composition of dates are based on non-representative samples or old methodology. The mineral compositions of fruit reflect the trace mineral contents of soils in any geographic region [6]. However, the oxytocic and abortifacient effects have not been sufficiently explored. Thus, this study aimed at investigating the oxytocic and abortifacient potential of the ethanolic extract of date fruit (*Phaenix dactylifera)* in albino rats.

2. Materials and Methods

Drugs and chemicals

Oxytocin from Himedia, Mumbia, phenylhydrazine from Sisco Research Laboratories Pvt. Ltd., Mumbai. Salbutamol from HimediaMumbia, glucose assay kits from Transasia Bio-Medicals Ltd. (Erba Manheim), Solan, Himachal Pradesh, India. Total protein kit from Transasia Bio-Medicals Ltd. (Erba Manheim), Solan, Himachal Pradesh, India. Bilirubin assay kit from Transasia Bio-Medicals Ltd (Erba Manheim), Solan Himachal Pradesh, India.All other chemicals and reagents used were of analytical grade.

Collection and identification of plant material

The fruits of date (*P. dactylifera*) used for this research were obtained from Sokoto Central Market Sokoto State Nigeria. The fruit was identified and authenticated by a Taxonomist, Dr. M. A. Jimoh. The fruit were shade dried for ten (10) days. The dried samples were grounded to pieces using grinding machine.

Plant extraction

150g of dried sample were weighed using electronic weighing balance (Gibertini, Italy). The fruits were shade dried and ground to fine particles with blender. The grounded samples were soaked in ethanol for a period of 72hrs. The extracts were then filtered with Whatman's number 1 filter paper and the filtrates concentrated at 40^{o}c using rotary evaporator. The standard extracts obtained were then stored and frozen at 4^{o}C until when required.

Animals

A total of Fifty-five rats (made up of 50 female and 5 male rats) weighing 200g ± 50g, and 30 – 35g mice, purchased from the Veterinary Department of University of Nigeria, Nsukka were used for the study. All animals were kept in the animal house at a temperature of 30 + 10^{o}C. They were fed with standard diets (Pfizer Feed Plc, Lagos) and water was supplied freely.

Experimental design

Thirty (30) female rats were grouped into 6 with five animals each, and used for biochemical assay as follows:

Group 1: received normal saline

Group 2: received phenyl hydraxine
Group 3: received phenyl hydraxine + fero-haemoglobin
Group 4: received phenyl hydraxine + 1000mg/kg of extracts
Group 5: received phenyl hydraxine + 2000mg/kg of extracts
Group 6: received phenyl hydraxine + 3000mg/kg of extracts

Phytochemical Analysis of the Ethanolic Extract of Date Fruit (*Phoenix Dactylifera*)

The preliminary phytochemical screening of the methanol extract of Datefruit **(***Phoenix dactylifera*)was carried out in order to ascertain the presence of some important phytochemicals and those detected were quantified. Both qualitative and quantitative analyses were done using standard methods described by [8].

Acute Toxicity

The acute toxicity was tested using mice, the method and calculation proposed by [9] was employed Different doses of the plant extract based on body weight of the animals were divided into five groups and each received 1000mg /kg, 1500mg/kg, 2000mg/kg, 2500mg/kg and 3000mg/kg respectively. The animals were monitored for the first three hours and then examined after 24 hours. All doses were administered to the animals orally.

Uterine Tissue Experiment

Virgin female albino rats were injected with 0.2mg kg^{-1} diethyl/stilbestrol 24hours prior to the start of the experiments in order to induce estrus in the uterus. Once the vagina smear confirmed the rats in estrus phase, the rats were killed and the uterus was extracted out. Uterine strips (at approximately two centimeters threated and mounted in a 60ml organ bath containing Tyrode solution which aerated with 95% $O_2 5CO_2$ maintained at 37^{o}c. Organ bath then connected to a Power lab System (AD Instruments Pty. Ltd.). The uterine tissue was allowed to stabilize for 30mins before application of extracts or drugs of different doses (concentration), changes were registered using a Physiogram.

Preparation of rat uterine smooth muscle tissue for measurement of isometric contractions. The female rats used were primed with stilbesterol (0.1 mg/kg ip) 24 hours before experiment to induce estrous. The method used by [10] was adopted for this *in vitro* study. Briefly, each rat was euthanized by cervical dislocation and decapitation. The pelvic cavity was opened to expose and harvest the two uterine horns into a beaker containing De Jalon solution at 37^{o}C ± 5^{o}C and pH 7.4. About 3 cm of the tissue was suspended vertically by means of ligatures on a tissue holder in a 35ml organ bath also containing De Jalon solution and bubbled with air. The De Jalon solution was constituted such that each liter contains NaCl (9 g), KCl (0.42 g), $CaCl_2$ (0.06 g), $NaHCO_3$ (0.5 g) and Glucose (0.5 g). The isometric force displacement transducer was connected to PC-2004 physiopac® (Medicaid India), a digital physiological recorder and a screen for displaying responses. Resting tension in the muscle strip was readjusted to remove slack. The suspended tissue was allowed to equilibrate within 45 minutes. Basal rhythmic contractions were first recorded before dose-response relationships were established for the standard drugs and extract

and then repeated in the presence of salbutamol. For each application, a minimum time of 1 minute was allowed for tissue responses washing with De Jalon solution.

Hematological Analysis

The Automated Coulter Instrument Principle was used. The aspirated whole blood sample was diluted into two aliquots, and each was mixed with an isotonic aliquotes. The first dilution was delivered to the red blood cell (RBC) aperture chamber, and the second was delivered to the white blood cell (WBC) aperture chamber. In the RBC chamber, RBCs and platelets were counted and discriminated by electrical Impedance as the cells were pulled through each of three sensing apertures (50µm in diameter, 60µm in length). Particles 2 to 20ft were counted as platelets while particles greater than 36ft were counted as RBCs. In the WBC Chamber, a reagent was added to break RBCs and release hemoglobin before simultaneously counting the WBCs by Impedance on each of the three sensory apertures (100µm in diameter, 75µm in length). The white blood cell dilution was passed through the hemoglobin for the determination of hemoglobin concentration of a wavelength of 525nm.

Biochemical Analysis

Thiobarbituric acid (Malondialdehyde) reacting substances (TBARS) was determined by [11]. Reduced glutathione (GSH) was determined by [12]. Glutathione peroxidase (GPx) was determined by [13]. Superoxide dismutase (SOD) was determined by [14]. Estimation of catalase by [15].

Abortificient Effect of Date Fruits on Pregnant Rats

A total of 25 rats, made up of 5 males and 20 females, were used for this test. After acclimatization period, the female rats were separated from the male rats into four different cages (containing 5 female rats each) and their estrus was synchronized using diethyl stilbestrol dissolved in paraffin oil in the dosage of 1mg/kg body weight. One male rat was introduced into each female cage for mating. After 7 days, a cotton swab moistened with normal saline was carefully inserted into the vaginal cavity of the rats to make a smear. The smear was made on a clean glass slide and stained with Giemsa. The slide was then observed under the microscope to know if there is presence of protein coagulates. Some were pregnant while others were not, the pregnant rats were then regrouped into four and treated as follows:

Group 1: Normal saline ad libitum
Group 2: Concentrated date fruits Extract ad libitum for a day (24hrs)
Group 3: Concentrated date fruits Extract ad libitum for 2 days (48hrs)
Group 4: Concentrated date fruits extract ad libitum 3 days (72hrs)

The animals were monitored daily till they littered [16].

Statistical Analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 26. The data obtained were analyzed using one-way analysis of variance (ANOVA), and result subjected to post hoc test using Duncan. The data were expressed as mean ± standard error of mean. Statistical significance of the difference of the means was evaluated and values of $p < 0.05$ were considered significant.

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3. Results

Table 3.1: Qualitative Phytochemical Characteristics of *P. dactylifera* extracts

Phytochemical	Aqueous extract	Ethanol
Alkaloid	+	+
Flavonoids	+	+
Saponins	+	+
Tannins	+	+
Steroids	-	-
Reducing sugar	-	-
Phenol	-	-

Result of the qualitative phytochemical characteristics of *P. dactylifera* extracts revealed presence of alkaloid, flavonoids, saponins and tannins, while steroid, reducing sugar and phenols were found to be absent.

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Table 3.2: Quantitative phytochemical constituents of *P. dactylifera*

Phytochemical	***P. dactylifera* (mg/100 g)**
Alkaloids	0.34[a]
Tannins	3.30[b]
Flavonoids	0.09[c]
Saponins	0.16[c]

Results with different superscripts are significantly different ($p<0.05$) when compared along the columns.

Like oxytocin, the activity of *P. dactilyfera* leaf extract on the piece of isolated uterine tissue was excitatory and dose dependent as higher doses of the extract produced higher effect and verse versa. All doses applied significantly increased both amplitude and frequency of contraction when compared with basal values ($p<0.05$). The application of 0.017 and 0.068 iu of oxytocin increased the amplitude of contraction from 6.00±0.00 mm in the basal to 21.67±0.88 mm and 25.33±0.33 respectively, representing a percentage contractile activity of 261.17±0.00% and 316.67±0.00% respectively (Table 3.3).

Table 3.3: Contractile effect of oxytocin on an isolated uterine tissue

Dose Applied (iu)	**Basal amplitude of contraction (mm)**	**Response amplitude (mm)**	**Percentage contractile activity**
0.017	6.00±0.00	21.67±0.88[a]	261.17±0.00[a]
0.034	6.00±0.00	24.00±0.58[b]	300.00±0.00[b]
0.068	6.00±0.00	25.33±0.33[b]	316.67±0.00[b]

Results with different superscripts are significantly different ($p<0.05$) when compared along the columns

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Table 3.4: Contractile effect of *P. dactylifera* on an isolated uterine tissue

Dose Applied (µg/ml)	Basal amplitude of contraction (mm)	Response amplitude (mm)	Percentage contractile activity
333.33	6.00±0.00	10.67±0.67[a]	77.83±0.00[a]
666.66	6.00±0.00	19.33±0.33[b]	222.17±0.00[b]
1333.33	6.00±0.00	22.00±0.58[c]	266.67±0.00[c]

Results with different superscripts are significantly different ($p<0.05$) when compared along the columns

For the extract, 333.33 and 1333.33 µg/ml of the extract increased amplitude of uterine contraction from 6.00±0.00 mm in the basal to 10.67±0.67 mm and 22.00±0.58 mm respectively and represented percentage contractile activities of 77.83±0.00% and 266.67±0.00% respectively as shown in (Table 3.4).

Table 3.5: Contractile effect of salbutamol on oxytocin and *P. dactilyfera*

Dose Applied	Response amplitude (mm)	Percentage inhibition (%)
***P. dactilyfera* (666.67 µg/ml) + salbutamol (0.067 µg/ml**	0.00±0.00[a]	100.00±0.00[c]
***P. dactilyfera* (2666.66 µg/ml) + salbutamol (0.067 µg/ml)**	0.00±0.00[a]	100.00±0.00[c]
Oxytocin (0.017 iu) + Salbutamol (0.067 µg/ml)	15.67±0.33[b]	25.62±1.35[a]
Oxytocin (0.034 iu) + Salbutamol (0.067 µg/ml)	15.67±0.33[b]	32.39±1.10[a]

Table 3.6: *In vivo* activity of *P. dactilyfera* on pregnant rats

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Treatment Groups	Pregnancy Test	Type of Administration	No. that Littered	Percentage (%) that Littered
Group 1	Positive	Normal Saline	5	100
Group 2	Positive	Conc. *P. dactyfera* extract, ad libitum for one day (24hrs)	5	100
Group 3	Positive	Conc. *P. dactyfera* extract ad libitum for two days (48hrs)	5	100
Group 4	Positive	Conc. *P. dactyfera* extract ad libitum for 3 days (72hrs)	5	100

In the table above, all the pregnant rats both in control and treatment groups littered. This is similar to the report of [17] who treated rats with Cherry juice for 24hrs, 48hrs and 72hrs respectively.

Table 3.7: Effect of extracts of *P. dactylifera* on some hematological parameters in anaemic Wistar rats

GROUPS	Platelets ($x10^9$/L)	Hemoglobin (g/dL)	White blood cells (mm^3)	Red blood cells $x10^6$/L	Packed cell volume (%)
Normal control	284.00 ± 7.13^a	10.36 ± 0.25^b	5920.00 ± 73.48^b	156.00 ± 2.45^c	43.60 ± 0.67^{bc}
Phenylhydrazine (Pos. ctrl)	410.00 ± 11.83^b	6.44 ± 0.19^a	6800.00 ± 37.84^c	120.00 ± 2.73^a	37.60 ± 1.12^a
Phenylhydrazine + fero-hemoglobin (Neg. ctrl)	336.00 ± 4.00^a	10.28 ± 0.37^b	5280.00 ± 44.30^b	158.00 ± 4.90^c	41.00 ± 3.49^b
Phenylhydrazine + 1000 mg/kg extract	308.00 ± 8.54^a	10.70 ± 0.30^b	4160.00 ± 74.83^a	188.00 ± 3.74^b	38.00 ± 0.55^b
Phenylhydrazine + 2000 mg/kg extract	272.00 ± 8.71^a	10.22 ± 0.42^b	4360.00 ± 12.41^a	186.00 ± 9.79^b	40.20 ± 2.99^b

Phenylhydrazine + 3000 mg/kg extract	290.00 ± 5.52[a]	12.56 ± 0.16[c]	5220.00 ± 56.20[b]	170.00 ± 4.18[c]	44.60 ± 1.89[c]

Results with different superscript show significant difference ($p<0.05$) when compared along the groups.

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Table 3.8: Effect of extracts of *P. dactylifera* on antioxidant status and lipid peroxidation in Wistar rats

GROUPS	SOD	CAT	GPx	MDA
Normal control	11.43 ± 0.03^{a}	28.72 ± 0.71^{b}	173.66 ± 10.63^{a}	0.82 ± 0.03^{a}
Hydroxy phenol (Pos. ctrl)	10.25 ± 0.03^{a}	20.39 ± 1.22^{a}	95.21 ± 3.42^{b}	1.58 ± 008^{b}
Hydroxy phenol + fero-hemoglobin (Neg. ctrl)	11.40 ± 0.02^{a}	23.67 ± 1.91^{a}	130.34 ± 16.85^{c}	0.75 ± 0.06^{a}
Hydroxy phenol + 1000 mg/kg extract	11.47 ± 0.01^{a}	17.59 ± 0.45^{a}	125.02 ± 0.78^{c}	0.95 ± 0.05^{a}
Hydroxy phenol + 2000 mg/kg extract	11.46 ± 0.01^{a}	22.84 ± 2.74^{a}	130.20 ± 6.34^{c}	0.91 ± 0.05^{a}
Hydroxy phenol + 3000 mg/kg extract	11.44 ± 0.01^{a}	27.98 ± 0.62^{b}	151.21 ± 2.62^{a}	0.81 ± 0.07^{a}

Results with different superscript show significant difference ($p<0.05$) when compared along the groups.

Table 3.8 above showed a non-significant ($p>0.05$) increase in SOD activity of the normal control (11.43 ± 0.03), and the extract-treated groups when compared with the positive control group (10.25 ± 0.34).

Result of the effect of *P. dactilyfera* on catalase shows that the positive control (20.39 ± 1.22) was significantly ($p<0.05$) and non-significantly ($p>0.05$) decreased when compared with the normal control (28.72 ± 0.71), and the negative control (23.67 ± 1.91), respectively. Also, the extract treated groups show a dose-dependent increase with the highest dose (27.98 ± 0.62) having a significant ($p<0.05$) increase when compared with the positive control.

Result of the effect of *P. dactilyfera* on glutathione peroxidase showed that there was a significant ($p<0.05$) difference when the positive control (95.21 ± 3.40) was compared with the normal control (173.66 ± 10.63), as well as the negative control (130.34 ± 16.84) and the extract-treated groups.

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Result of the effect of *P. dactilyfera* on malondialdehyde (MDA) showed that the MDA concentration of the positive control group (1.58 ± 0.08) showed a marked significant ($p<0.05$) increase when compared with the normal control (0.82 ± 0.03), and the extract treated groups.

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3.1.8 Results of extracts of *P. dactylifera* fruits on selected biochemical parameters

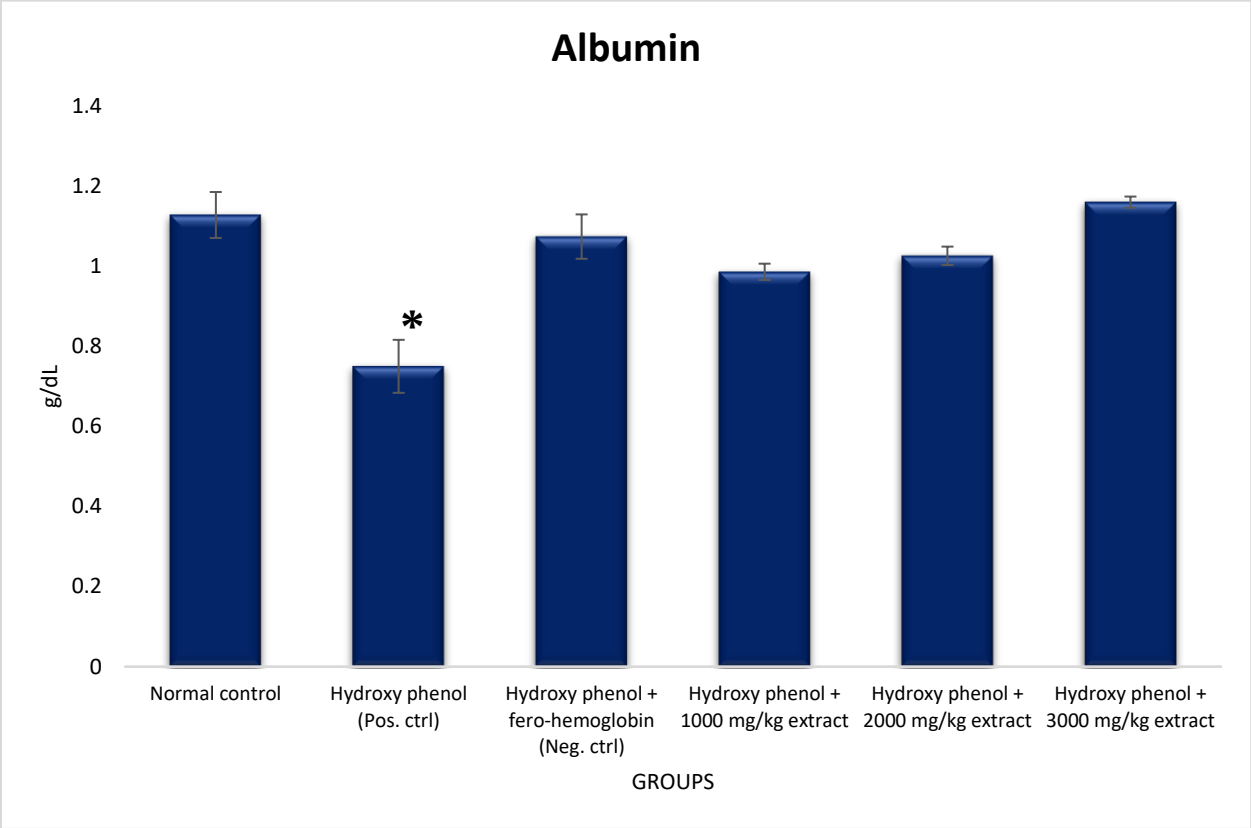

Figure 3.1: Effect of extracts of *P. dactylifera* on serum albumin concentration in anaemic Wistar rats

The chart in figure 3.1 shows that the positive control (0.75 ± 0.07) was significantly ($p<0.05$) decreased when compared with the normal control (1.13 ± 0.06), negative control (1.07 ± 0.06), and the treated groups.

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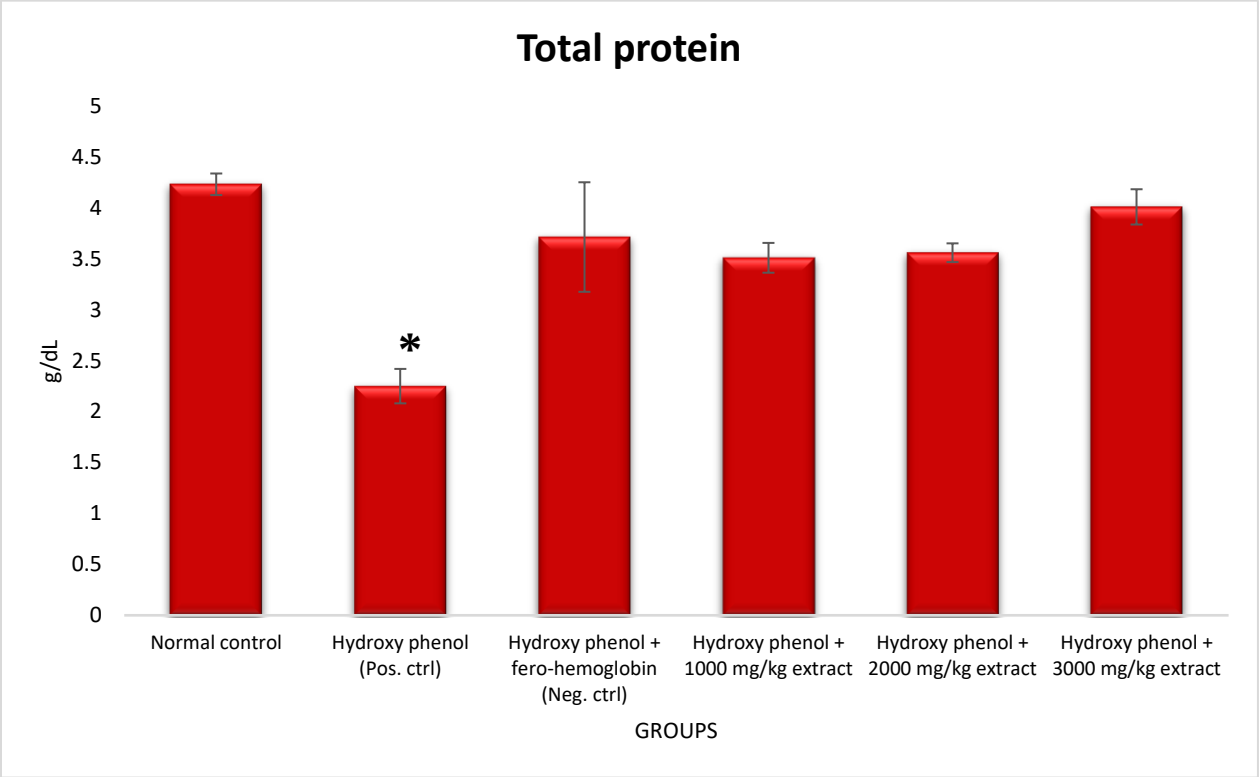

Figure 3.2: Effect of extracts of *P. dactylifera* on serum total protein concentration in anemic Wistar rats

From the results in figure 3.2, the positive control (2.25 ± 0.17) showed a significant ($p<0.05$) decrease in total protein concentration when compared with the normal control (4.23 ± 0.11) and other treated groups.

4. Discussion

Date fruit (*P. dactylifera L.*) is a specie of palm mainly cultivated for its edible fruit [4]. The fruits are sweet berries with sugar content of above 50%. Date pulps contain easily digestible sugars (70%), mostly glucose, sucrose, and fructose; dietary fibers and less proteins and fats [18]. Research have shown that date fruit pulp is wealthy in phytochemicals such as sterols, phenolics, carotenoids, procyanidins, anthocyanins and flavonoids [19]. The concentrations and ratio of these phytochemical constituents depend on the stage of fruit picking, type of the fruit, location, and soil conditions. From this research, it was observed that tannins had the highest concentrations when compared with other phytochemicals, while steroids were not detected or detected in a very low concentration. Other phytochemicals although present in minute concentrations include alkaloids, flavonoids and saponins. Flavonoids have been shown to have antibacterial, anti-inflammatory, anti-allergic, anti-viral and antineoplastic properties. The high alkaloid content of Niger date fruit

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could be contributory to the longevity and pharmacological properties of the fruit. Tannin found in date palm fruit might be of pharmacologically useful as astringents. The astringent property of tannin had been reported to have protective role on underlying tissues thereby improving wounds healing [20]. Tannins may as well help against microbial degradation of dietary proteins in the rumen. Saponins have been shown to have tumor inhibitory property on experimental animals.

Table 3.2 shows the results of the effects of the extract on hematological properties, of phenyl-hydrazine (PHZ)-induced anemic wistar rats. The significant reduction in the values of the assessed erythrocyte indices in the present study: red blood cell count, hemoglobin concentration and hematocrit scores, as well as increase in platelets and white blood cells count following the administration of PHZ to the experimental animals, supports the previously described and reported toxic effects of PHZ on the red blood cell [21]. These findings are in consistence with previous reports of reductions in hemoglobin levels, red blood cell counts, packed cell volume and an impairment in erythrocyte deformability following PHZ administration in experimental animals [22]. These effects of PHZ predictably results in an anemia (usually of a hemolytic nature) consequent on red cell damage with secondary involvement of the spleen and liver [22]. It was observed that the ameliorative effects of the extract of *P. dactylifera* as seen in this study on blood parameters were dose dependent and fairly comparable with the effects of fero-hemoglobin; a hematinic preparation containing iron, folate and vitamin B_{12} as an active ingredient and useful for the prophylaxis of iron, zinc, vitamin and folic acid deficiencies and curative treatment for anaemia. The observed decrease in HB, HCT, and RBC count in the anemic groups could be because of phenylhydrazine (PHZ) which was used to induce anemia. The observed leukocytosis in the extract-treated groups is an indicator that the extract may have stimulatory effect on the immune system that resulted in the production of more leukocytes. However, this was significant on the animals administered the highest dose of the extract. The extract may have stimulated the kidney to synthesize erythropoietin for hematopoiesis to occur [23-24]. These effects were not completely dose dependent, since it was noticed at both lower and higher doses.

A detoxifying system consists of glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT). In addition, there is also a system consisting of NADPH-dependent methemoglobin reductase, ascorbic acid, glutathione reductase (GR), whose main role is the repairing of damage that follows oxidative stress [25]. In normal physiological state, oxidants generated during metabolism play a significant role in maintaining oxidant-antioxidant ratio. In pathological state, an increase in the reactive free radicals creates an imbalance in this ratio thereby making macromolecules vulnerable to oxidative damage. As a result, proteins undergo rapid oxidation leading to the alterations in their structural integrity and in assessing oxidative damage lipid peroxidation and protein oxidation are generally used as biomarkers [26].

Lipid peroxidation has been identified as a basic deteriorative reaction in the cellular mechanism of anemia and is initiated by the free radicals which oxidize polyunsaturated fatty acids (PUFAs) leading to the formation of conjugate dienes ultimately resulting in the production of hydroperoxides, cyclic peroxides and malondialdehyde. Acting as the first line of defence against the production of such hydroperoxides is a naturally occurring antioxidant glutathione (GSH), a major source of free thiol in most living cells. GSH in addition also participates in diverse biological processes such as the detoxification of xenobiotics and modulation of enzyme activity

by disulfide interchange [27]. However, red cells have a potent antioxidant protection that modifies GSH, and GPx. Synergistic and co-operative interactions of these antioxidants rely on the sequential degradation of peroxides and free radicals as well as on mutual protections of enzymes. Oxidative stress arises when there is an imbalance between radical generating and radical scavenging activity; it may therefore increase formation of oxidation products. Oxidation of erythrocytes induces membrane injury, methemoglobin formation and eventually destruction of the cell. Lipids especially PUFAs are sensitive to oxidation, leading to the term lipid peroxidation, of which, MDA is the most abundant. The accumulation of MDA in tissues or biological fluids is indicative of the extent of free radical generation, oxidative stress and tissue damage [28].

In the present study, the increased content of MDA in the blood serum confirms the ability of phenylhydrazine to induce oxidative damage. The increase in lipid peroxidation products is a result of free radicals' activity altering the lipid composition of the red blood cell membranes [29]. Increased lipid peroxidation induced by phenylhydrazine in the erythrocytes was accompanied by a concomitant decrease in superoxide dismutase activity and catalasewhich was also reported by a recent study [30]. The reduction in the superoxide dismutase activity might be due to the oxidation of cysteine in the enzyme by superoxide anion during its transformation to hydrogen peroxide [31]. Phenylhydrazine also generates superoxide anion and hydrogen peroxide in addition to other free radicals [30]. Superoxide dismutase converts superoxide anion to oxygen and hydrogen peroxide, which is later detoxified by catalase and glutathione peroxidase [31]. Furthermore, the activity of serum glutathione peroxidase in the red blood cells was also affected by the phenylhydrazine administration in this study.

Accordingly, it was observed that the extract had significantly reduced the increase in phenylhydrazine-induced lipid peroxidation content in the erythrocytes. This could be as a result of the presence of phytochemicals such as flavonoids which possess antioxidant properties, thereby scavenging some of the free radicals and giving protection against oxidative damage in the cells. This brings to a reverse the detrimental effect of phenylhydrazine on the serum antioxidants and as a result, protects the cells, especially the red blood cells and its components.

From the study, it was observed in vitro that date fruit extract elicited a dependent contraction of the rat's uterus. The force of contraction for the extract was significantly different ($p < 0.05$) from the basal concentration 6.00 ± 0.00 mm. The contractile effect of date fruit extract 333.33 when compared with that of a standard utero-tonic agent oxytocin 0.017 showed that oxytocin gave greater effect at all doses than that of the extract. This is similar to the report of [32].

Researches have shown that administration of compounds with estrogenic activity species during early stages of pregnancy resulted in quick movement of the ova through oviducts and subsequent expulsion of the ova and fetus from the uterus [33]. This is possibly due to the presence of some bioactive agents/properties present in the extract which can induce uterine contractions; thus, could serve in facilitation of labour or as an abortifacient. These contractions could be as a result of the binding of some phytochemicals on the histaminergic (H_2) receptor found in the uterus [34]; and in turn promotes the influx of calcium ions (Ca^{2+}) in the smooth muscles [35].

In the *in vivo* study, all the pregnant rats that received date fruits extract littered full term and no abortion was induced. This suggests that the active ingredients of the extracts that have the

contractile effect might have been hampered or transformed by digestive enzymes, thereby causing the juice extract to lose its utero-tonic property when taken orally.
The effect of salbutamol on the extract and oxytocin shows significant inhibitory effect on their contractile activities. Medicinal plants are used to facilitate labor, and their effects are likely to be mediated through the stimulation of muscarinic receptors in uterine tissue. It is also possible that their effects could be *via* the synthesis and release of prostaglandins, which have been established to be myometrial stimulants in mediating the activity of most drugs that stimulate contraction of the uterus [36]. Also, smooth muscle inhibition or relaxation by an agent synthetic or non-synthetic are frequently mediated by different mechanisms such as potassium channel opening or channel blockade, by receptor antagonism such as antimuscarinic, antihistaminic or blockade of adrenoreceptors [37].
Salbutamol significantly inhibited the effect of both *P. dactylifera* and oxytocin. It is a known stimulant of the beta-adrenergic receptors [38], and causes the smooth muscle cell to relaxby activating the Gs proteins, as well as their Gαs subunit stimulates adenyl cyclase. This activation subsequently leads to an increase in concentration of cyclic adenosine monophosphate (cAMP), which activates protein kinase A, and in turn both inactivate the myosin light-chain kinase and activate myosin light-chain phosphatase that cause inhibition. The results suggest that the extract of *P. dactylifera* has a potential oxytocic effect that can be explored for its therapeutic benefits as an alternative treatment for retained placenta and for the induction of labour. With respect to its acclaimed folkloric use in the treatment of threatened abortion and dysmenorrhoea, a relaxant or tocolytic like effect on the uterus was expected. However, the results points to a contractile rather than a relaxant effect [39].

5. Conclusion

P. dactylifera (Date palm) has been a source of carbohydrate and some necessary biological elements such as potassium, calcium and phosphorus. Health promoting compounds like flavonoids and alkaloids are also abundant in the fruit, while others include saponins, tannins and steroids. With respect to this study, data obtained did not indicate much difference when compared with other research on Date palm fruit. Phenylhydrazine induction leads to destruction of red blood cells by generation of free radical generation, which consequently leads to oxidative stress and other biological changes at cellular level resulting in anemia. The study suggests that damage caused by induction of phenylhydrazine affects the red blood cells and as well as biological antioxidants. *P. dactylifera* extract was observed to possess phytochemical properties which confer it some antioxidant defense mechanisms, making it capable of ameliorating the anemic and oxidative stress effects of phenylhydrazine. Furthermore, extracts of *P. dactylifera* possesses some uterine contractile effect but not an abortificent hence it is relatively safe during pregnancy and child birth.

6. Recommendations

The findings of this study have revealed the health benefits of extract of *P. dactylifera* on anemia and reactive oxygen species, as well as some of the phytochemicals present. Therefore, it should be recommended that further studies should be carried out so as to identify the nutrient

compositions *in vitro* and *in vivo*, anti-diabetic effects, anti-lipidemic effects and others such as the effects on liver and kidney functions. Further studies on this drug are also recommended to access for the implications in other organs such as the brain, heart, male and female fertility, etc., and its possible mechanism of action in achieving its uterine contractile effect.

Ethical Approval
All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropiate ethics committe.

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Competing Interests
Authors have declared that no competing interests exist.

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