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Rauwolfia vomitoria- a promising medical plant for benign prostatic hyperplasia management; yet with challenges

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ABSTRACT

Background: Benign Prostatic Hyperplasia (BPH) is a common condition among aging men. This condition often leads to a reduced quality of life due to its debilitating symptoms. Although conventional allopathic treatments are widely used for managing BPH, they are frequently associated with adverse side effects, prompting a global shift toward natural and alternative therapies. This study aims to investigate the therapeutic effects of *Rauwolfia vomitoria* Aqueous Root Extract (RVARE) as a potential natural oral treatment for BPH.

Methodology: Six groups of male Sprague-Dawley rats were established [$N = 7$/group]. Group 1 comprised of normal rats whilst group 2 to group 6 comprised of BPH induced rats. Group 1: Control group- received normal chow diet. Group 2: Model group- [no treatment]. Group 3: received 10 mg/kg. b. wt. RVARE. Group 4: received 25 mg/kg. b.wt. RVARE. Group 5: received 50 mg/kg. b.wt, RVARE. Group 6: served as a positive control [Finasteride]. The study was carried out for 28 days. Upon termination, blood was sampled for general biochemical, haematological and PSA determination. Systemic organs and the prostate were harvested for histological analyses.

Result: Histopathological analysis of the liver of RVARE treated groups demonstrated alterations. Additionally, a reduction in relative prostate weight compared to the model group was observed, though not statistically significant ($p > 0.05$). However, a significant reduction in prostate specific antigen (PSA) levels was seen in the RVARE-treated groups (Model vs Gp 3, $p = 0.001$; Model vs Gp 4, $p = 0.000$; Model vs Gp 5, $p = 0.001$).

Conclusion: RVARE appears to be effective in reducing prostate size and PSA levels. However, its hepatotoxic effect needs further investigation.

Introduction

BPH is an enlargement of the prostate caused by hyperplasia of prosthetic cells. This is very common in older men (Awedew et al., 2022). In 2019, the global prevalence of BPH stood at 94 million. The disease process has prevalence of approximately 50 to 60% and 80 to 90% among 60-year-old- and 70-year-old males, respectively. A number of medications are on the market for the treatment of BPH. The two broad categories that are used are the 5-alpha reductase inhibitors (i.e. finasteride and dutasteride) and α- blockers (Tamsulosin). Even though these medications are effective in BPH management, side effects reported include, hyperglycaemia, sexual and erectile dysfunction (Kapoor 2012; Traish, 2017). However, aside medication, surgical modalities are also available. Further to these, are radiation and hormonal

Abbreviations: RVARE, *Rauwolfia vomitoria* aqueous root extract; LD, Low dose; MD, Medium dose; HD, High dose; PSA, Prostate specific antigen; SD, Sprague–Dawley; UG, IACUC - University of Ghana -Institutional Animal Care and Use Committee.

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therapies (Wise, 2001). Despite advances in the treatment/management of BPH, most men are reluctant to use these orthodox interventions and will rather opt for phytomedicines. Often, there is the perception of the development of impotence with orthodox medicines (Roehrborn, 2012). The current global shift is towards the use of phytomedicines because they are perceived to be readily available and safer.

Some plant medicines that have been purported to be effective in the management of BPH include *Saw palmetto* (Kwon, 2019), *Pygeum africanum* (Wilt et al., 2002), *Croton membranaceous* (Asare et al., 2015) and *Rauwolfia vomitoria* (Fang et al., 2021). In recent times, *R. vomitoria* has been under a series of investigations for its therapeutic effects. The plant is mainly available in Cameroon, Senegal and Egypt. Other places include, Sudan, and Uganda. This plant grows to about 10 m and carries very small fruits 5 to 8 mm . Among its medicinal uses, the root bark is used as a sedative (Oliver, 1982), and for jaundice treatment (Aquaisua et al., 2017). *R. vomitoria* root bark is also used for treating hypertension (Bouquet and Debray, 1974). Furthermore, the methanolic leaf extract is said to reduce cholesterol levels in animal models. Other benefits of *R. vomitoria* include improving immunity (Isaiah et al., 2012), and having anti-tumour effects in ovarian cancer as demonstrated in animal models (Yu et al., 2013). Recently, *R. vomitoria* was reported to inhibit 5-α reductase in an animal model, thereby shrinking the prostate, increasing the prostate lumen and reducing the epithelium and androgen receptors (Fang et al., 2021). The authors of the afore-mentioned study used a single dose of 20 mg/kg b. wt. The short-fall in that study also includes the fact that the tumour marker prostate specific antigen (PSA), was not determined. Last but not the least, the traditional conversion of the human dose to an animal dose, which is based on body weight proportionality was used. Recent literature suggests that, conversion from human weight to the animal weight should be based on the surface area rather than body weight (Reagan-Shaw et al., 2008). In the Fang et al. (2021) study, *R. vomitoria* was said to be more effective than finasteride based on the body weight proportionality calculation. Furthermore, although controversies surround the hepato-toxicity of *R. vomitoria*, that study made no mention of relative organ weights and no histology apart from the prostate, was examined.

This study therefore sought to fill the gap in literature by

1. employing three doses.
2. recalculating the finasteride concentration for the positive control group.
3. determining the prostate specific antigen (PSA) levels.
4. examining any other organ that may be adversely affected.
5. using the aqueous extraction method as done indigenously.

Methods

Study site

Rats were obtained and housed at the Department of Animal Experimentation [Noguchi Memorial Institute for Medical Research (NMIMR)], University of Ghana. The animals were allowed to acclimatize for 7 days in plastic cages with wire screen top at room temperature. Wood shavings was used as bedding in accordance with ethics guidelines. Rats were housed under 12-hour light and 12-hour darkness. Temperature and humidity were set at 22 ± 3 °C and 40 to 45%, respectively, and the rats were fed with the commercial rat chow diet and drank water throughout ad libitum.

Study design

Experimental procedures were carried out in accordance with the international ethics guidelines on animal care, the National Institutes of Health Guide for the care and use of Laboratory animals, the University of Ghana-Institutional Animal Care and Use Committees (IACUC) guidelines and OECD Test Number 407 (2008). However, male sex was used because of the focus on the prostate, which is a male disorder. The protocol was reviewed and approved by the University of Ghana Institutional Animal Care and Use Committee (UG- IACUC) with ethics approval number UG-IACUC 041/23–24. The study was designed using adult Sprague-Dawley (S-D) male rats that had undergone BPH induction by castration and subsequent injection of 5 mg/kg b.wt testosterone propionate for 28 days (An and Kong, 2022).

Forty-two (42) S-D male rats weighing 250–300 g were used based on the 3 R principles of reduction, refinement and replacement. The minimum of 7 rats per group was based on the study of (Miniawy et al., 2017).

Plant extract preparation

The root of *R. vomitoria* (a locally known shrub called *Kakapenpen*) was harvested from Swedru in the Central Region of Ghana. The plant was identified by its vernacular name by the farmers and its botanical name by the plant identification app PlantNet from Google. Further authentication was done by a taxonomist (Mr. Peter Adjei) from the Centre for Scientific Research into Plant Medicine (CSRPM) herbarium. The roots were carefully washed with water, and the back peeled and dried in subdued sun for two weeks. The dried root back was pulverized, into fine powder. The powdered root bark underwent aqueous extraction according to the protocol of Afriyie et al. (2013) and freeze-dried. Freeze-dried samples were packaged in sample bottles, labelled appropriately, and stored at room temperature (25 °C-27 °C) prior to the on-set of the experiment.

Experimental design

The following groups were established: group 1 (Control group), Group 2 – BPH-induced with no treatment- (model group), Group 3 – BPH-induced and treated with 10 mg/kg b. wt. *R. vomitoria* (LD =Low dose group), Group 4 – BPH-induced and treated with 25 mg/kg b.wt. *R. vomitoria* (MD=Medium dose group), Group 5– BPH-induced and treated with 50 mg/k g b.wt. *R. vomitoria* (HD=High dose group), Group 6- BPH-induced and treated with Finasteride (Positive control group). All plant extracts and finasteride were administered via oral route by gavage at varying doses for 28 days.

Finasteride preparation

Finasteride™ tablets (RelonChem, UK) (5 mg per tablet) was crushed in a mortar with pestle, and diluted with distilled water to obtain the animal equivalent dose (31.25 mg/kg b.wt.) using the body surface area formula as suggested in the study of Reagan-Shaw et al. (2008).

On the 29th day, rats were anaesthetized with 0.1 ml/100 g of b.wt. of Anaket (Neon Laboratories, India) and Chanazin (Chanelle Pharma, Ireland) (4:1) and blood samples drawn by cardiac puncture and discharged into EDTA tubes for haematological analysis. Heparinized Eppendorf tubes were used for chemistry analyses such as liver and kidney function tests, using a dry chemistry analyser and gel separator tubes for PSA test. Rats were then euthanized using Isoflurane (Pharmanova, India) in a glass euthanasia chamber and organs (such as prostate, seminal vesicle, liver, kidneys, heart, lungs, spleen and pancreas) harvested. Organs were weighed using Mettler Toledo analytical balance (Greifensee, Switzerland), and subsequently rinsed in normal saline solution before being placed in 10% buffered formalin for histological analysis.

Histology tissues were processed using Leica TP 1020 tissue processor (Wetzlar, Germany) which employed the routine paraffin embedding procedure. The embedded tissues were sectioned to a thickness of 4 μm using a rotary microtome. They were further processed in alcohol-xylene changes and subsequently stained with haematoxylin and eosin (H & E). Slides were prepared and examined using Olympus

CX23 light microscope (Tokyo, Japan).

Laboratory determinations

Relative organ weight

The relative organ weight of each animal was calculated as follows: Relative organ weight (%) = [organ weight (g) / body weight (g)] x 100.

Biochemical analyses

General chemistry

The general chemistry analysis was performed using the Seamaty microfluidic dry chemistry analyser (Sichuan Province, China). The parameters measured included total protein, globulin, albumin, albumin/globulin ratio, total bilirubin, direct bilirubin, GGT (L-γ-glutamyl transferase), AST (aspartate aminotransferase), ALT (alanine aminotransferase), ALP (alkaline phosphatase), CHE (cholinesterase), TBA (total bile acid), amylase, CK (creatine kinase), creatinine, uric acid, BUN, glucose, total cholesterol, TG (triglycerides), HDL (high-density lipoprotein), and LDL (low-density lipoprotein).

PSA analysis

PSA analyses was carried out using MyBiosource Rat PSA ELISA kit (San Diego, USA) according to the manufacturer's instructions. In brief, this was a sandwich-based ELISA technique. The optical density (OD) of the final chromogen was measured at 450 nm using a BioTek microplate reader (Winooski, Vermount, USA). Unknown concentrations were extrapolated from the standard curve.

Haematological analyses

The Mindray haematology analyser (Anhui, China) was used for performing the haematology analyses. The analyser employed the electrical impedance method to determine the count and size distribution of red blood cells (RBC), white blood cell (WBC) and platelet (PLT). In addition, it used the colorimetric method to determine the Haemoglobin (HGB).

Statistical analysis

Data analysis was conducted using XL STAT 2024. To examine the effects of the independent variables on multiple dependent variables, a Multivariate Analysis of Variance (MANOVA) was performed. Wilks' Lambda was used as the test statistic to assess the overall significance of the model, identifying areas where significant differences occurred among the groups. Continuous variables were expressed as mean ± SD. The MANOVA results revealed statistically significant differences ($p < 0.05$) in the dependent variables across the different groups.

Following the MANOVA, a Tukey's post-hoc test was applied to determine area where these significant differences were observed. The Tukey test results indicated specific comparisons between groups where p-values were less than 0.05.

Results

Effect of R. vomitoria on relative organ weight after 28 days oral administration

Relative organ weight of heart, kidneys, lungs, spleen, liver, pancreas, seminal vesicle and prostate showed no statistically significant changes. Even though differences were not statistically significant, the relative weight of the seminal vesicles were slightly increased in the experimental groups compared to the control group, with the highest increase in the medium dose group. The relative prostate weight increased in the experimental groups compared to control group. However, when compared to the model group, the relative prostate weight decreased with the greatest decrease in the Finasteride group followed by RVARE high dose group (Table 1).

Effect of R. vomitoria on liver function after 28 days oral administration

Liver function test (TBA, DBIL, IBIL, AST, GGT, ALT, GlO, ALB/GLO) did not show any significant differences amongst groups except ALB, ALT, and ALP which had statistically significant differences. ALB decreased amongst treatment groups compared to the control and model groups. A statistically significant difference was observed between the model and the medium dose groups ($p = 0.003$) as well as in the model group and the high dose group ($p = 0.034$). TP increased in the low dose group compared to the control but decreased in medium dose group, high dose and finasteride groups compared to the control group. However, changes were not statistically significant (Table 2). Statistically, significant differences were observed between model and medium dose groups ($p = 0.001$) as well as the model group and high dose group ($p = 0.035$). TB increased in the low dose and high dose treatment groups, compared to the control and model group, but was not statistically significant. A statistically significance was observed between the control and finasteride group ($p = 0.040$). ALT decrease in RVARE treatment groups compared to the control as well as the model groups. A statistically significant difference was noted in the low dose group compared to the model group ($p = 0.034$) (Table 2).

Effect of R. vomitoria on renal function after 28 days of oral administration

Renal function parameters (CREA, UA, BUN/CREA) showed no significant statistical differences. BUN differences were seen in the RVARE treatment groups compared to the model group. A statistical difference was observed between the model and low dose group ($p = 0.011$) as well as the control and model group (0.016) (Table 3).

Effect of R. vomitoria on lipid profile after 28 days

Lipid profile (TC, TG, HDL and LDL) showed no statistically significant differences amongst groups ($p > 0.05$). However, a dose dependent decrease was seen in TC, TG, and HDL, compared to model group (Table 4).

Effect of R. vomitoria on miscellaneous biochemistry analyses after 28 days administration

Biochemical parameters (GLU and CK) showed no statistically significant differences amongst groups. A significant decrease in AMY was observed in RVARE treatment groups compared to the model and control groups with a statistical difference of $p = 0.035$. PSA values also decreased in the RVARE treatment groups compared to the control and model groups. Significant differences were observed between the model and low dose groups ($p = 0.001$), model and medium dose ($p = 0.000$) and between model and high dose ($p = 0.001$). Furthermore, a significant difference was observed between the control and low dose ($p = 0.027$), control and medium dose ($p = 0.000$) as well as control and high dose groups ($p = 0.037$) (Table 5).

Effect of R. vomitoria on haematological analyses after 28 days oral administration

Red blood cell and platelet indices in Table 6 (RBC, HGB, HCT, MCV, MCH, MCHC, PLT, MPV) showed no statistically significant differences. From Table 7, WBC Indices (WBC, Lym%, Mon%, Bas %) did not show any significant change with the exception of Neu% and Eos% which showed statistical differences between the control and high dose groups (Table 7).

Table 1
Effect of *R. vomitoria* aqueous root extract on relative organ weight after 28 days oral administration with low dose (LD) 10 mg/kg b. wt. (LD), medium dose (MD) 25 mg/kg b. wt. and high dose(HD) 50 mg/kg b. wt. kg (HD).

Organs	Control	Model	LD	MD	HD	Finasteride	P-value
R. Heart	0.32 ± 0.04	0.32 ± 0.02	0.3 ± 0.02	0.35 ± 0.05	0.3 ± 0.03	0.4 ± 0.1	NS
R. kidneys	0.36 ± 0.03	0.38 ± 0.02	0.37 ± 0.03	0.40 ± 0.20	0.37 ± 0.03	0.3 ± 0.02	NS
R. lungs	0.66 ± 0.09	0.70 ± 0.10	0.67 ± 0.10	0.70 ± 0.10	0.70 ± 0.03	0.6 ± 0.10	NS
R. Spleen	0.21 ± 0.04	0.18 ± 0.02	0.20 ± 0.10	0.30 ± 0.20	0.30 ± 0.05	0.20 ± 0.10	NS
R. Liver	3.4 ± 0.2	3.2 ± 0.3	2.9 ± 0.2	3.4 ± 0.6	3.0 ± 0.4	3.03 ± 0.3	NS
R. Pancreas	0.20 ± 0.02	0.30 ± 0.07	0.30 ± 0.10	0.36 ± 0.20	0.30 ± 0.10	0.30 ± 0.07	NS
R. S. vesicle	0.40 ± 0.10	0.87 ± 0.20	0.87 ± 0.30	0.90 ± 0.50	0.80 ± 0.50	0.70 ± 0.40	NS
R. Prostate	0.20 ± 0.01	0.30 ± 0.03	0.27 ± 0.02	0.28 ± 0.04	0.20 ± 0.03	0.20 ± 0.04	NS

Values are expressed as mean ± standard deviation. $n = 7$ per group. NS= Statistically not significant. R. Heart= Relative weight of heart %, R. Liver= Relative weight of liver %, R. Kidney =Relative weight of kidneys % R. seminal vesicle = Relative seminal vesicle %, R. prostate = Relative prostate weight %, R. Pancreas= Relative weight of pancreas; R. Spleen= Relative weight of Spleen %; R. Lung= Relative weight of lungs %.

Table 2
Effect of *R. vomitoria* on liver function of BPH-induced rats after 28 days of oral administration with low dose (LD)10 mg/kg b.wt. RVARE, medium dose (MD) 25 mg/kg b.wt. RVARE and high dose (HD) 50 mg/kg b.wt. RVARE.

	Control group	Model group	LD	MD	HD	Finasteride	P-value
ALB	37.0 ± 3.2	40.6 ± 2.2 [h;g]	35.4 ± 5.8	29.8 ± 5.6 [g]	32.3 ± 1.8 [h]	34.05 ± 2.4	0.003 g;.0.034[h]
TP	71.0 ± 7.3	79.4 ± 3.7 [h;g]	74.5 ± 7.0	63.7 ± 4.9 g	68.7 ± 3.5[h]	70.9 ± 3.4	0.001 g; 0.035[h]
GLO	33.9 ± 4.2	38.8 ± 2.7	39.1 ± 2.4	33.8 ± 3.3	36.5 ± 2.3	36.8 ± 5.3	NS
A/G	1.1 ± 0.1	1.05 ± 0.1	0.9 ± 0.1	0.9 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	NS
TB	0.8 ± 0.5 [e]	1.35 ± 0.75	1.8 ± 0.2	1.1 ± 0.7	1.7 ± 0.4	2.1 ± 0.5 [e]	0.040[e]
DBIL	0.5 ± 0.3	0.87 ± 0.5	1.03 ± 0.1	0.8 ± 0.7	0.8 ± 0.3	1.2 ± 0.2	NS
GGT	2.7 ± 0.8	3.0 ± 0.7	4.3 ± 1.2	6.08 ± 4.7	3.2 ± 1.3	3.0 ± 1.0	NS
AST	123.2 ± 9.2	161.7 ± 53.3	122.5 ± 34.1	125.4 ± 36.6	159.6 ± 22.9	115.8 ± 30.6	NS
ALT	76.2 ± 13.2	105.2 ± 39.6[f]	57.8 ± 14.6 [f]	61.4 ± 36.8	74.4 ± 26.2	73.6 ± 24.1	0.034[f]
ALP	227.2 ± 2	240 ± 47.4	211.0 ± 70.9	263.8 ± 156.9	215.2 ± 77.3	239.4 ± 83.8	NS
TBA	17.9 ± 3.1	27.7 ± 5.13	17.7 ± 7.0	17.48 ± 9.11	20.3 ± 7.05	24.9 ± 4.4	NS
IBIL	0.4 ± 0.1	0.47 ± 0.41	0.8 ± 0.3	0.3 ± 0.2	0.9 ± 0.5	0.9 ± 0.4	NS

Values are expressed as mean ±standard deviation. NS = Statistically not significant.
Statistically significant at $p < 0.05$. Total protein (TP), globulin (GLO), albumin (ALB), albumin/globulin ratio, total bilirubin (TB), direct bilirubin (DB), GGT (γ-glutamyl transferase), AST (aspartate aminotransferase), ALT (alanine aminotransferase), ALP (alkaline phosphatase), TBA (total bile acid), *e*=control vs finasteride; *f* =model vs low dose; *g*=model vs medium dose; *h*= model vs high dose,.

Table 3
Effect of *R. vomitoria* on renal function of BPH-induced rats after 28 days of oral administration with low dose (LD)10 mg/kg b.wt. RVARE, medium dose (MD) 25 mg/kg b.wt. RVARE and high dose (HD) 50 mg/kg b.wt. RVARE.

	Control group	Model group	LD	MD	HD	Finasteride	P-value
CREA	28.5 ± 7.4	39.8 ± 6.3	29.4 ± 10.7	34.8 ± 7.2	36.8 ± 11.8	24.9 ± 11.02	NS
UA	243.4 ± 80.5	291.9 ± 140.8	315.8 ± 272.8	225.9 ± 45.9	165.9 ± 114	170.3 ± 49.0	NS
BUN	5.08 ± 0.60[a]	6.74 ± 1.06[a;f]	5.09 ± 0.57[f]	5.60 ± 0.70	5.53 ± 0.49	5.90 ± 0.70	0.016[a],0.011[f]
BUN/ CREA	192.1 ± 62.0	177.3 ± 52.5	217.8 ± 155.4	166.8 ± 40.4	168.87 ± 73.4	208.7 ± 27.6	NS

Values are expressed as mean ± standard deviation. NS = Statistically not significant. Statistically significant at $p < 0.05$. a=Control vs model; *f* =model vs low dose. UA=uric acid; BUN=blood urea nitrogen; CREA=Creatinine.

Table 4
Effect of *Rauwolfia vomitoria* aqueous root extract on lipid profile after 28 days of oral administration with low dose (LD) 10 mg/kg b.wt., medium dose (MD) 25 mg/kg b.wt. and high dose (HD) 50 b.wt. mg/kg *R. vomitoria*.

	Control group	Model group	LD	MD	HD	Finasteride	P-value
TC	1.5 ± 0.2	1.7 ± 0.2	1.7 ± 0.4	1.4 ± 0.1	1.4 ± 0.3	1.4 ± 0.2	NS
TG	0.9 ± 0.5	1.4 ± 0.4	1.1 ± 0.5	1.1 ± 0.2	1.03 ± 0.3	0.9 ± 0.2	NS
HDL	0.9 ± 0.1	1.04 ± 0.3	1.03 ± 0.2	0.9 ± 0.1	0.9 ± 0.3	0.8 ± 0.2	NS
LDL	0.2 ± 0.1	0.06 ± 0.1	0.2 ± 0.2	0.1 ± 0.09	0.09 ± 0.1	0.2 ± 0.1	NS

Values are expressed as mean ±standard deviation. NS = Statistically not significant; TC=total cholesterol; TG=Triglycerides; HDL=High density lipoprotein; LDL=Low density lipoprotein.

Histological analyses of prostate, seminal vesicle and liver after 28 days of oral administration of R. vomitoria are presented in Figs. 1 to 3

The efficacy of R. vomitoria is seen in, demonstrates seminal vesicles normal secretory activities. However, Fig. 3 demonstrates hepatotoxicity.

Discussion

R. vomitoria is a promising new medicinal plant that is being investigated for its therapeutic benefits. Several benefits of *R. vomitoria* include sedation (Oliver-Bever, 1982), anti-hypertensive properties (Bouquet and Debray, 1974), hypoglycaemic effect (N'douaa et al., 2016), anti-hypercholesterolemia (Owoade et al., 2021), aphrodisiac and fertility effects (Otis et al., 2021).

Pharmacological models for the management of BPH that have been well researched abound. There are various allopathic treatment models for BPH. In order to enhance urine-flow, some drugs such as Tamsulosin

Table 5
Effect of *R. vomitoria* on Miscellaneous Biochemistry analyses (Glucose, amylase, creatine kinase, Prostate specific antigen) after 28 days of oral administration with low dose (LD) 10 mg/kg bwt., medium dose (MD) 25 mg/kg bwt. and high dose (HD) 50 mg/kg b.wt.

	Control group	Model group	LD	MD	HD	Finasteride	P- value
GLU	12.8 ± 3.6	15.0 ± 6.0	12.7 ± 7.7	8.8 ± 2.1	7.7 ± 1.9	9.1 ± 2.7	NS
AMY	1902 ± 133	1937 ± 181 g	1662 ± 342	1386 ± 413 g	1545 ± 74	1855 ± 222	0.035 g
CK	241.8 ± 87.5	343 ± 163.9	368.7 ± 270.4	208.6 ± 93.5	583.8 ± 198.2	294.8 ± 139.6	NS
PSA	0.85 ± 0.1[b;c;d]	0.96 ± 0.1[f,g,h]	0.58 ± 0.1[b;f]	0.53 ± 0.1[c,g]	0.57 ± 0.1[d;h]	0.74 ± 0.1	0.027[b],0.010[c], 0.037[d], 0.001[f,h], 0.000 g

Values are expressed as mean ± standard deviation. NS = Statistically not significant; Statistically significant at $p < 0.05$.GLU=glucose; AMY=amylase; CK=creatine kinase; PSA =prostate specific antigen. *g*= model vs medium dose; *b*=control vs low dose; *c*=control vs medium dose; *d*=control vs high dose *f*=model vs low dose; *h*=model vs high dose.

Table 6
Effect of *RVARE* on red blood cell and platelet indices after 28 days of oral administration with low dose 10 mg/kg b.wt, medium dose (MD) 25 mg/kg b.wt and High dose (HD) 50 mg/kg b.wt RVARE.

	Control	Model Group	LD	MD	HD	Finasteride	P-value
RBC	8.7 ± 0.8	9.3 ± 0.5	9.13 ± 0.7	8.67 ± 0.6	8.9 ± 1.2	8.6 ± 1.0	NS
HGB	14.6 ± 0.8	15.6 ± 0.7	14.7 ± 1.1	14.3 ± 1.1	14.0 ± 1.9	13.92 ± 2.0	NS
HCT	43.1 ± 2.8	46.5 ± 2.4	44.6 ± 3.2	43.5 ± 3.1	41.7 ± 5.9	43.7 ± 7.7	NS
MCV	49.4 ± 3.0	50.1 ± 1.4	48.9 ± 1.62	50.3 ± 3.2	47.0 ± 2.1	50.8 ± 4.9	NS
MCH	16.7 ± 0.9	16.8 ± 0.6	16.1 ± 0.5	16.5 ± 0.9	15.8 ± 0.6	16.2 ± 0.6	NS
MCHC	33.8 ± 0.6	33.5 ± 0.5	32.9 ± 0.6	32.8 ± 0.9	33.66 ± 0.4	32.1 ± 2.7	NS
PLT	886±246.8	909 ± 70.2	1224.8 ± 225.3	884.8 ± 305.8	814.2 ± 439.9	805.2 ± 526.3	NS
MPV	7.4 ± 0.4	7.7 ± 0.7	7.5 ± 0.3	7.4 ± 0.7	7.58 ± 1.1	7.7 ± 0.95	NS

Values are expressed as mean ± Standard deviation. $n = 7$; NS = Statistically not significant; RBC: red blood cell count ($x10^6$); HGB: haemoglobin concentration (g/dL); HCT: hematocrits (%); MCV: mean corpuscular volume (fL); MCH: mean corpuscular haemoglobin (pg); MCHC: mean corpuscular haemoglobin concentration (g/dL) MPV: mean platelet volume (fL); PLT: platelet count (%).

Table 7
Effect of *R. vomitoria* on white blood cell indices after 28 days oral administration with low dose (LD) 10 mg/kg bwt., medium dose (MD) 25 mg/kg b.wt. and high dose (HD) 50 mg/kg b.wt.

	Control	Model Group	LD	MD	HD	Finasteride	P-value
WBC	7.13 ± 2.2	5.7 ± 1.6	8.7 ± 5.0	7.87 ± 3.4	8.8 ± 4.6	6.1 ± 2.6	NS
Neu %	27.6 ± 6.9[d]	36.3 ± 9.7	34.9 ± 8.1	43.4 ± 12.7	49.3 ± 19.3[d]	33.2 ± 7.6	0.043[d]
Lym %	57.0 ± 10.6	52.0 ± 9.9	51.9 ± 9.0	44.6 ± 13.2	41.4 ± 17.7	50.9 ± 16.0	NS
Mon %	8.17 ± 1.03	7.7 ± 1.3	9.5 ± 3.3	8.13 ± 0.7	6.9 ± 1.9	10.6 ± 8.3	NS
Eos %	6.7 ± 3.4[d]	3.5 ± 1.5	3.43 ±2.3	3.6 ± 3.1	2.18 ± 0.8[d]	4.7 ± 1.9	0.025[d]
Bas %	0.5 ± 0.6	0.4 ± 0.3	0.32 ± 0.2	0.27 ± 0.1	0.22 ± 0.1	0.62 ± 0.7	NS

Values are expressed as mean ± standard deviation. NS = statistically not significant; Statistically significant at $p < 0.05$.WBC: white blood cell count ($x10^3$); Eos: Eosinophils (%) count; Mon: Monocyte (%); Bas: Basophils count (%); Neu: Neutrophils count (%); Lym: lymphocytes (%), *d*= control vs high dose.

target the bladder neck smooth muscles by relaxing them; thereby enhancing urine flow. These are referred to as Alpha blockers (alpha-1 adrenergic receptor antagonists) (Lepor, 2007). The reverse side is having an over-reactive bladder the promotes frequent urination. The application of some drugs reduce the involuntary bladder contractions. These drugs are referred to as anticholinergics (i.e. Tolterodine) (Kaplan et al., 2005).

Similarly, beta-3 adrenergic agonists such as Mirabegron also relax bladder muscles to enhance urine flow. However, Phosphodiesterase-5 (PDE-5) inhibitors play multiple roles by relaxing bladder smooth muscles and reducing erectile dysfunction, which accompanies many allopathic drugs for BPH (Su et al., 2020).

Lastly, some operate by blocking the conversion of testosterone to dihydrtestosterone (the hormone that enduces prostate enlargement). These are termed 5-alpha-reducase inhibitors (i.e. Dutasteride and Finasteride) (Tacklind et al., 2010). Allopathic medicines have tremendously improved health and have been well researched. However, other undesirable side effects are sometimes recorded. To this end, some Phytomedicines that have gained prominence are *Serenoa repens, Pygeum africanum and Croton membranaceus.*

Serenoa repens (Saw palmetto) extract is reported to be a natural BPH phytomedicne that operates as a 5-ARI (Kwon, 2019) binding both 5-ARI I and II, thus preventing them from producing DHT and subsequently, the inability to bind cytosolic angrogen receptors. Overall, *Serenoa repens* exhibits anti-proliferative and anti-inflammatory effects (Suzuki et al., 2009).

Pygeum africanum extract has been used for over half a century now and appears to have pharmacological properties beneficial to BPH by modulating bladder contractions (Wilt et al., 2002). Its mechanisms are not clear but are said to inhibit fibroblast production of the stromal compartment of the prostate (Yablonsky et al., 1997).

Croton membranaceus aqueous root extract has been reported to be a phytomedicine for the management of BPH, by shrinking the prostate considerably over a short period (Asare et al., 2015). Its mechanism of action is equated to that of a 5-ARI (Afriyie, 2020). The search for natural alternatives to allopathic drugs continues and *R. vomitoria* has recently been reported to manage prostate enlargement through a 5-alpha reductase inhibition mechanism.

In this 28-day study, BPH-induced rats were treated with different *R. vomitoria* doses of 10 (Low), 25 (Medium), and 50 (High) mg/kg b. wt. alongside a model group (BPH-induced but untreated), a positive control (Finasteride), and a negative control (normal rat). Relative organ weights were not significantly different for almost all organs. Of note, is the fact that more of the treated groups had relative liver weight below the control. The prostate weight increased in the model, low dose and medium dose groups. However, relative prostate weight was the same in the high dose and finasteride group, which were comparable to the control group. On the other hand, significant decreases in lung weights were observed. This may be indicative of a compromised lung function.

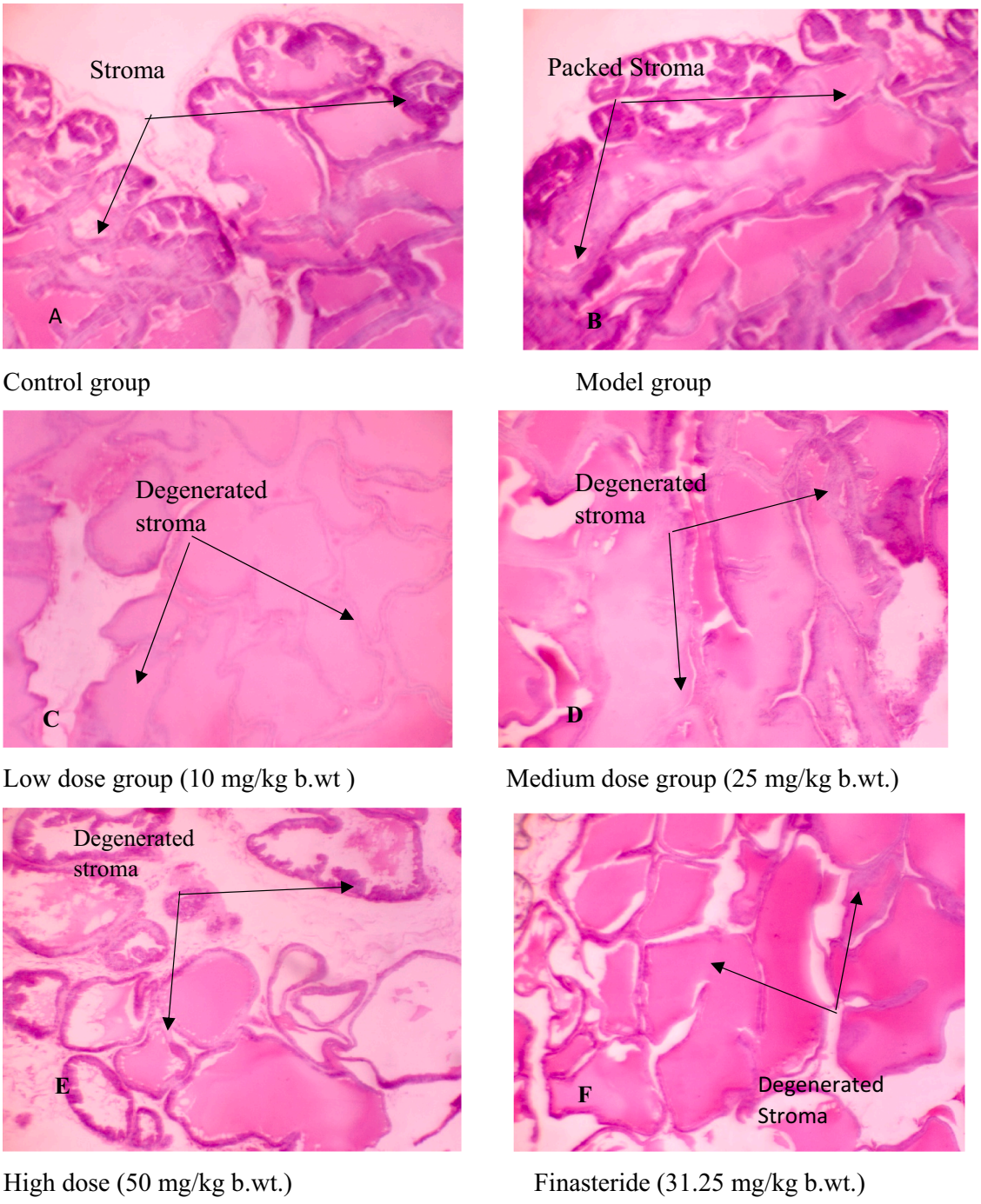


Fig. 1. Photomicrographs of cross section of the prostate tissue of S-D rats (100x). This figure shows the cross section of the prostate tissue in S-D rats following treatment with low dose (10 mg/kg b.wt), medium dose (25 mg/kg b.wt) and high dose (50 mg/kg b.wt) of RVARE for 28 days. Normal histology was observed in control (A). Characteristic is fibromuscular stroma in which there are clusters of smooth muscles mixed with elastic fibers. (Hematoxylin and Eosin stain, 100x). Model group (B) shows protrusions in the periurethral and transition zones of the gland. Treatment groups (C-F) showed degenerated or reduced stroma.

Furthermore, this occurrence at higher doses may signify fibrosis, atrophy and more seriously cell death. Possible toxic effects of plants such as *Digitalis purpurea* (Plantaginaceae), *Ricinus communis* (Euphorbiaceae), and *Allium ascalonicum* (Liliaceae), on lungs have been documented (Seukep et al., 2014).

Haematologically, red blood cell indices were not affected. On the other hand, white blood cell indices were affected with significant increases. Similar WBC increases were obtained by Youmbie et al. (2020) with the stem back extract of *R. vomitoria*. On the other hand, eosinophiles demonstrated a significant decline, and neutrophils a significant increase. Similarly, granulocyte increase was also observed by Youmbie et al. (2020).

Liver function tests demonstrated an increase in bilirubin with all treatment groups. The highest increase was with Finasteride which was significant compared to the control group. It is a common phenomenon to have bilirubin increase from medicinal plants as a result of phenolic compounds. For example, Silymarin flavonoids increased bilirubin concentration in mice (Suk et al., 2019). A similar significant rise in bilirubin was observed with another medicinal plant for BPH, *Croton membranaceus* (Asare et al., 2015). Similarly, a case report has been

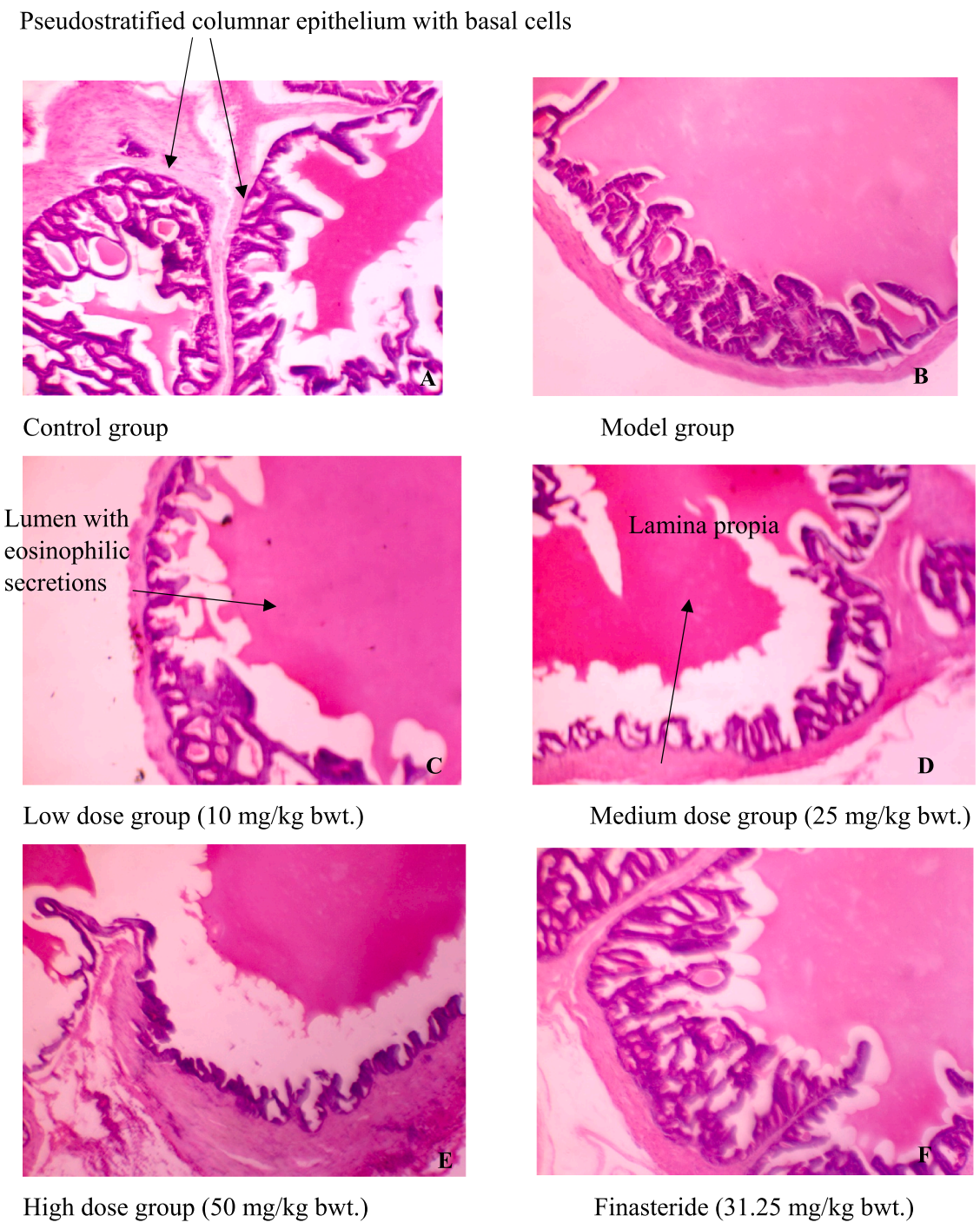
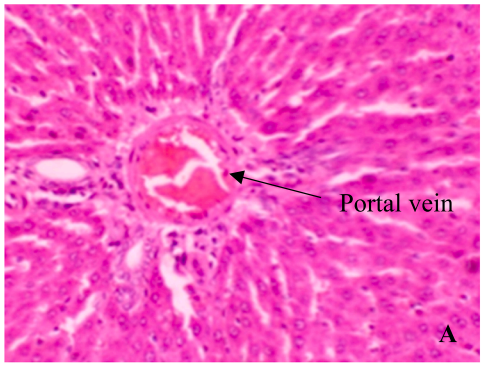


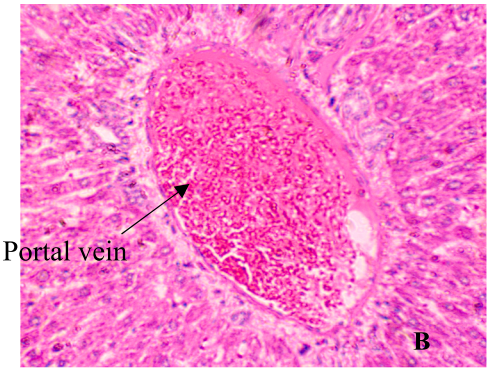
Fig. 2. Photomicrographs of the seminal vesicles (100x). This figure shows the effect of RVARE on the histology of the seminal vesicles (Hematoxylin and Eosin). Control group showed normal tissue histology. All groups showed mucosal folds that extended into the lumen. The lining epithelium of seminal vesicle was pseudostratified columnar epithelium, composed mainly of a single layer of tall columnar principal cells and triangular shaped basal cells. The lumen of seminal vesicle was filled with eosinophilic secretion. The epithelium lies on a thin layer of connective tissue lamina propria. The lamina propria was lined by inner circular and outer longitudinal smooth muscle fiber.

documented of *Serenoa repens* causing acute liver toxicity (Lapi et al., 2010). Further to this *S. repens* had previously been associated with cholestatic hepatitis (Hamid et al., 1997). AST showed a dose dependent increase in all the *R. vomitoria* treated groups, though not statistically significant. However, AST levels were lower than that of the control and model groups. ALT which is more liver specific showed a dose-dependent decrease seemingly suggesting hepatoprotection. On the contrary Youmbie et al. (2020) had significant transaminases increases at 900 mg/kg b.wt. This could be due to the high dose used. Additionally, Eluwa et al. (2010) reported the possibility of hepatotoxicity with the ethanolic extract of *R. vomitoria* root back at doses of 150 and 300 mg/kg b. wt.

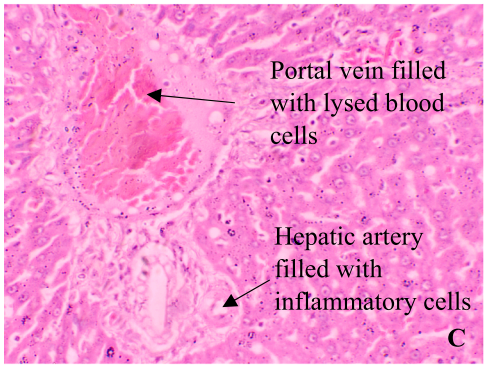
The *R. vomitoria* and finasteride treated groups demonstrated increases in blood urea nitrogen. However, significant differences were observed between the model group and the low dose group. Creatinine and uric acid did not show any significant differences, likewise the BUN/CR ratio. Overall, nephron-toxicity can be ruled out both from the blood and histological examinations. A similar conclusion was drawn by



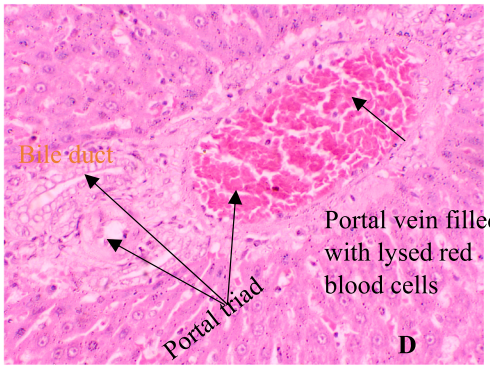
Control Group



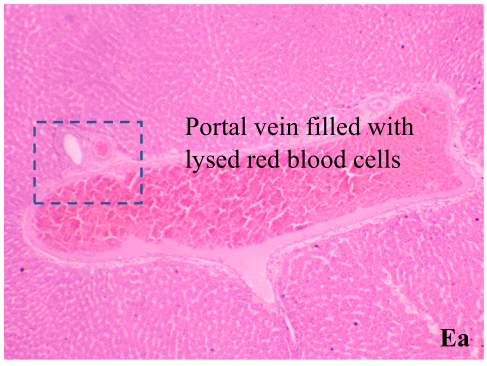
Model Group



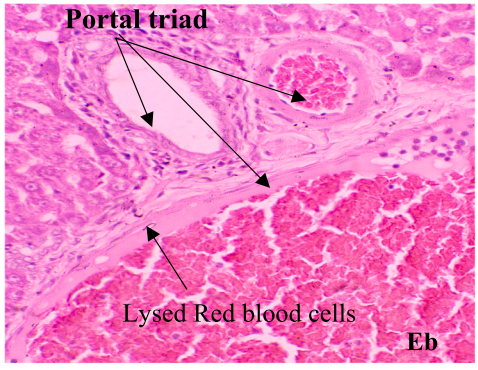
Low dose group 10 mg/kg bwt



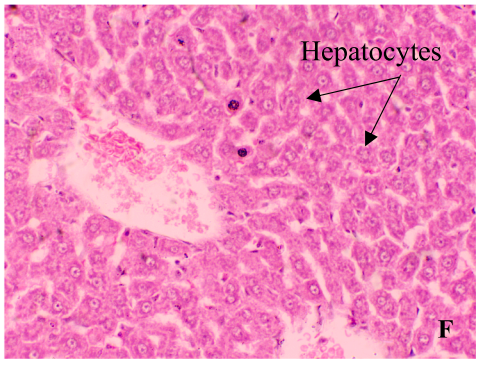
Medium dose 25 mg/kg bwt.



High dose 50 mg/kg bwt.



High dose 50 mg/kg bwt



Finasteride (31.25 mg/kg bwt.)

Fig. 3. Photomicrographs of the Liver (100x) This figure shows the effect of RVARE on the histology of the liver (Hematoxylin and Eosin). Control group (A) showed normal tissue histology however, RVARE treated groups (C-F) showed some distortions in liver tissues with red blood cells and inflammatory cells in the portal vein and hepatic artery. Photomicrograph Eb depicts the boxed area in Ea.

Ibrahim et al. (2015) who did not find renal function test changes, as well as the kidney histological abnormalities, with the use of *R. vomitoria*. Additionally, Asoro et al. (2018) even at high doses of 1600 – 5000 mg/kg b.wt. did not observe any nephrotoxicity.

R. vomitoria did not affect the lipid profile. Faponle et al. (2015) demonstrated that the plant extract potentiated by vitamin C could lower cholesterol. This could be due to β-sitosterol inhibiting cholesterol absorption, and thereby lowering cholesterol levels (Vahouny et al., 1983; Ikeda et al., 1988; Owoade et al., 2021). Indeed *R. vomitoria* contains β-sitosterol (Erumiseli et al., 2021). The plant extract caused a reduction in amylase level and this was only significant between the medium dose and the model groups. If this is anything to go by, as anti-pancreatic inflammation, it was also observed at the same level (medium dose) that glucose was significantly lower compared to all the other groups. Notably, the medium dose also had the lowest pancreatic organ and relative organ weight. The hypoglycaemic properties of *R. vomitora* was reported by N'doua et al. (2016). Other plants for BPH management such as *C. membranaceus* (Asare et al., 2015), *Annona muricata* (Issusilaningtyas et al., 2024), and *Serenoa repens* (Barakat et al., 2020) have also been reported to lower glucose.

The anti-tumour effect of this plant was investigated in ovarian cancer cell lines (Yu et al., 2013). Similarly, *R. vomitoria* is able to inhibit prostate cancer cell line growth (LNCaP) (Bemis et al., 2006).

In this study PSA levels were reduced throughout, either comparing it to the control group or the model groups. A reduction in PSA by *R. vomitoria* is being reported for the first time although its anti-BPH effects have been suggested with LNCaP cell lines (Bemis et al., 2006), BPH-1 cell lines (Huang et al., 2022) and prostate weight (in *in vivo studies*) (Fang et al., 2021). In this study, the histology showed effective erosion of the stromal and epithelial cells at all doses. The prostate cells showed stromal protrusion in the model group with a reduced lumen. However, low dose, medium dose and the high dose *R. vomitoria*, as well as Finasteride did not lead to such protrusions and also demonstrated diminished epithelial cells. The seminal vesicles showed normal architecture for all groups. Thus, from the histology results, as well as the reduction in PSA and relative prostate weights observed in this study, it can be concluded that *R. vomitoria* has therapeutic effects on the prostate. Similar findings with increase in lumen size was observed by Fang et al. (2021). Further to this, the afore-mentioned study demonstrated that *R. vomitoria* is capable of shrinking the prostate, and out-performing Finasteride (Fang et al., 2021). However, this observation concerning *R. vomitoria's* efficiency against Finasteride, was not observed in this study. Differences are attributable to the Finasteride dose used in both studies. As mentioned previously, the current recommendation is to use the body surface area calculation in converting human dose to animal dose (Reagan-Shaw et al., 2008) and not the body weight proportionality used by Fang et al. (2021). Furthermore, a single dose of 20 mg/kg. b.wt. used in that study, gave limited information.

Last but not the least, the study of Fang et al. (2021) examined the prostate histologically. Indeed *R. vomitoria* suppresses BPH by the induction of apoptosis through endoplasmic reticulum stress (Huang et al., 2022). However, other organs were not examined amidst controversies of possible hepatotoxicity. In this study, the liver was extensively examined. We observed its hepatotoxicity at the tissue level even at a low dose of 10 mg/kg b.wt.

Conclusion

In conclusion, although *R. vomitoria* seem to be a promising anti-BPH medicinal plant, the apparent hepato-toxicity calls for further phyto-surveillance of this and future plants that may be purported as being anti-prostamegaly in nature.

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CRediT authorship contribution statement

George Awuku Asare: Writing – original draft, Conceptualization. **Perpetua Dagadu:** Investigation, Data curation. **Samuel Adjei:** Writing – review & editing, Project administration. **Bernice Asiedu:** Writing – review & editing, Conceptualization. **Samkeliso Takaidza:** Conceptualization. **Vivash Naidoo:** Resources. **Brodrick Amoah:** Writing – review & editing. **Ifeoma Celestina Orabueze:** Writing – review & editing, Formal analysis. **Kwasi Bugyei:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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