Clinical Nutrition Open Science 36 (2021) 151–162

Contents lists available at ScienceDirect

Clinical Nutrition Open Science

journal homepage: www.clinicalnutritionopenscience.com

Original Article

Biochemical and hormonal parameters analysis of metoclopramide-induced hyperprolactinemic female wistar rats administered leaf extract of *Kigelia africana*

E.N. Uhuo*, C.P. Nwuke, C.E. Oriaku, J.O. Chilaka

Department of Biochemistry, College of Natural Science, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria

ARTICLE INFO

Article history:
Received 11 July 2020
Accepted 22 March 2021
Available online 29 March 2021

Key words:
Hyperprolactinemia
Metoclopramide
Bromocriptine
Kigelia africana
Hormonal and biochemical parameters

SUMMARY

Aim and Scope: To investigate the biochemical and hormonal parameters in metoclopramide-induced hyperprolactinemic female wistar rats administered leaf extract of *Kigelia africana*.

Methods: A total of thirty female wistar rats were grouped into: (i) Normal control (n = 5) and (ii) Experimental (n =25) to induce hyperprolactinemia. The experimental group was divided into five groups of five animals each, given a total of six in all. Group 1 received the distilled water alone; Group2 was metoclopramide-induced hyperprolactinemic rats only; Group3 comprised of metoclopramide-induced hyperprolactinemic rats administered bromocriptine (2.5mgKg^{-1}b.wt.) Groups 4–6 were metoclopramide-induced hyperprolactinemic rats administered 100, 200 and 400 mgKg^{-1} b.wt. *K. africana* methanol extract respectively. After treatments, biochemical and hormonal parameters were analyzed.

Results: The study observed significant increase (P<0.05) in estradiol serum level, follicle stimulating hormone, luteinizing hormone and progesterone at 400 mgKg^{-1} b.wt of the extract compared with the normal control. Reduction of prolactin level was recorded in all hyperprolactinemic rats administered 400 mgKg^{-1} b.wt, of the extract against normal control and hyperprolactinemic control. Similarly, bromocriptine at 2.5 mg Kg^{-1} b.wt. produced the same effect. Non significant increase (P>0.05) of cholesterol and protein levels were obtained in experimental rats treated with *K.africana*

* Corresponding author.
E-mail addresses: emmyuhuo@yahoo.com, uhuo.emmanuel@mouau.edu.ng (E.N. Uhuo).

https://doi.org/10.1016/j.nutos.2021.03.004

extract as against the normal control and hyperprolactinemia control.

Conclusion: The extract, especially at the dosage of 400 $mgKg^{-1}$b.wt could ameliorate hyperprolactinemia in rats. Fertility hormones can be improved by *K.africana* extract through its stimulatory effect.

1. Introduction

Infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. The most common overall cause of female infertility is the failure to ovulate, which occurs in 40% of women with infertility issues. Not ovulating can result from several causes, such as Ovarian or gynecological conditions, such as primary ovarian insufficiency (POI) or polycystic ovary syndrome (PCOS). Infertility, as asserted by World Health Organization, affects one out of every four couples in the developing countries [1]. Some factors such as genetic, anatomic, hormonal and immunological problems are implicated. Secondary sources like sexually transmitted infections, surgery and obesity cannot be ruled out [2]. Prolactin is a peptide hormone secreted by the anterior pituitary gland which plays a pivotal role in a variety of reproductive functions. Its primary role is the secretion of milk and lactation, as well as in reproductive mammary development and parental behavior [3].Furthermore, prolactin negatively modulates the secretion of pituitary hormones responsible for gonadal function, including luteinizing hormone and follicle-stimulating hormone. Prevention of gonadotropic hormones secretion occurs due to excess prolactin. When secretion of gonadotropin is impaired, the secretion of Follicle-Stimulating Hormones and Luteinizing Hormones are reduced and this inhibits gamete production [4]. Normal serum prolactin levels vary between 5 and 25 ng/mL in females although physiological and diurnal variations occur [5]. Serum prolactin levels are higher in the afternoon than in the morning, and hence should preferably be measured in the morning. Prolactin levels normalize within approximately 6 months after delivery in nursing mothers and within weeks in non-nursing mothers [6].

Hyperprolactinemia is a condition of elevated serum prolactin as a result of overproduction of prolactin by the pituitary gland. It is one of the hormonal causes of female infertility. Hyperprolactinemia is the most common pituitary hormone hypersecretion syndrome in both men and women; it most commonly affects women aged 25–34 years old and male occurrence is 4 times less frequent. Dopamine agonist agents like bromocriptine, cabergoline, pergolide and quinagolide are usually the first drugs of choice for controlling hyperprolactinemia but their usage is associated with gastrointestinal, cardiovascular and neurological adverse effects [7].

There is a belief that herbs, as natural products, are inherently safe without side effects and that efficacy can be obtained over a wide range of doses. Furthermore, traditional medicine has remained as the most affordable and easily accessible source of important drugs such as atropine, codeine, dioxin, morphine and quinine. The phytochemical composition, antioxidant activities and safety of *K. africana* leaf extracts have been reported by Uhuo *et al.,* [8]. Traditionally, *Kigelia africana* plant is most commonly used in Southeastern Nigeria in treatment of infertility and related conditions. [9].

Due to paucity of scientific information/data, it is therefore, the aim of this research to analyze the biochemical and hormonal parameters in metoclopramide-induced hyperprolactinemic female wistar rats administered methanol leaf extract of *K. africana*.

2. Material and methods

2.1. Plant material

Fresh leaves of *K. africana* were collected from Umuezeoka, Ezza-North LGA, Ebonyi State, Southeast Nigeria. The leaves were carefully rinsed under running water, dried under room temperature (25°C) in the laboratory and later milled and weighed before extraction.

2.2. Assay kits and chemicals

Assay kits for prolactin, progesterone, estradiol, follicle stimulating hormone and luteinizing hormone were supplied by Sigma-Aldrich Chemicals., Pomona/Kempton Park 1619, Johannesburg, South Africa. Assay kits for protein, cholesterol and were procured from Randox Laboratories Ltd, Co-Atrim, United Kingdom. metoclopramide and bromocriptine were bought commercially in Healthy living Pharmacy, Enugu State, Nigeria. All other reagents used were of analytical grade and were prepared using glass-distilled water.

2.3. Experimental animals

Female (wistar rats) wistar rats weighing 80–120 g were obtained from the animal house of Department of Zoology and Environmental Science, University of Nigeria, Nsukka. They were housed in clean iron cages under standard environmental conditions of temperature (24±1°C) and relative humidity (45–50%) under a 12 h dark-light cycle. They were acclimatized for 7 days before dosing and allowed free access to drinking water and standard pellets feed. All experimental protocols were approved by the Animal Ethics Committee, College of Natural Science, Michael Okpara University of Agriculture, Abia State according to the Guide for the Care and Use of Laboratory Animals.

2.4. Preparation of extract

Five hundred grams (500 g) of milled plant material was extracted in 2.0 L methanol for 72 h at 30°C on an orbital shaker (Stuart Scientific Orbital Shaker, UK) at room temperature. This was centrifuged at 1500 rpm for 5 min and the filtrate further filtered with watman No 4 filter paper. It was then concentrated using rotary evaporator at 40^0C and the yield was 20.52 g. This was reconstituted in distilled water to give the required concentrations of, 100, 200 and 400 mg Kg^{-1} b.wt used in this study.

2.5. Experimental design

A total of thirty female wistar rats were grouped into two major parts (i) Normal control, which daily received 0.5 mL of distilled water (n = 5) and (ii) Experimental, which daily received 0.5 mL of 5 mgKg^{-1} b.wt. metoclopramide dissolved in distilled water (n =25) to induce hyperprolactinemia. The experimental group was subdivided into five of five rats each, given a total of six in all. Group 1 received the distilled water alone; Group 2 were metoclopramide-induced hyperprolactinemic rats only; Group 3 consisted of metoclopramide-induced hyperprolactinemic rats administered bromocriptine (2.5 mg Kg^{-1}b.wt.),Groups 4–6 comprised metoclopramide-induced hyperprolactinemic rats administered 100, 200 and 400 mgKg^{-1} *K. africana* methanol extract respectively. The extracts and drugs were suspended in distilled water and were orally administered for 21 days using gavage and experiment was terminated on the 22nd day by humanely sacrificing the animals.

2.6. Preparation of serum and tissues

The rats were starved of food overnight, and sacrificed by decapitation. The blood sample was aseptically collected via cardiac puncture and transferred into sample labeled bottles, while the heart was still beating. The collected blood was allowed to stand for 2 hours to perfect clotting and

centrifuged (model SM800B, Surgifriend Medicals, Essex, England) at 1000 rpm. Sera were removed with Pasteur pipette for hormonal assay.

The rats were thereafter quickly dissected and their uteri were excised and transferred into ice-cold 0.25 M sucrose solution. This was then homogenized in ice-cold 0.25 M sucrose solution (1:5 w/v).The homogenates were further centrifuged at 105.5 rpm for 15 min to obtain the supernatants which were kept frozen overnight at -20°C before being used for the various biochemical assays.

3. Results

Fig. 1 Shows the effects of methanol extracts of *K.africana* on cholesterol level of metoclopramide-induced hyperprolactinemic female wistar rats. Significant increase ($P< 0.05$) of cholesterol level was recorded in the experimental group administered 400 mg kg^{-1} b.wt, *K. africana* extract against the control groups (NM-CON and HPT-CON).Similar trend was observed in HPT-BCR compared with the control groups. Estradiol concentration increased significantly ($P<0.05$) in group administered 400 mg kg^{-1} *K. africana* extract (HPT-400) of the extract as against negative control (HPT-CON) and group received 100 mg/kg b.wt. *K. africana* extract (HPT-100) of *K.africana* (Fig. 2).Follicle-stimulating hormone concentration was higher ($P<0.05$) in the treatment groups than hyperprolactinemia control (HPT-CON) as shown in Fig. 3. Luteinizing hormone concentration increased significantly ($P<0.05$) in the treatment groups, HPT-400, HPT 200 and HPT-100 respectively compared with control groups (NM-CON and HPT-CON). After the administration of 400 mg/kg b.wt., and 200 mg/kg b.wt of the extracts, luteinizing hormone increased accordingly compared with group treated with 2.5 mg/kg b.wt bromocriptine (HPT-BCR), normal control (NM-CON) and hyperprolactinemia control (HPT-CON) respectively (Fig. 4). Progesterone concentration in the experimental group administered 400 mg/kg b.wt, of the plant extract was significantly elevated ($P<0.05$) compared with the normal control; MN-CON, as well as group received standard drugs (Bromocriptine) shown in Fig. 5. At the end of the administration of metoclopramide to the experimental groups, the prolactin level in the experimental groups increased significantly ($p<0.05$) than the normal control; MN-CON. However, administration of *K.africana* extract to all tested concentrations (100–400 mg/kg b.wt) as well as the standard drug (bromocriptine) significantly reduced ($p<0.05$) the concentration of the hormone to status similar to the normal control group (Fig. 6). One of the uterine biochemical indices, protein was observed to be non-significantly increased ($P>0.05$) in the experimental groups (200–400 mg/kg b.wt) as against the normal control and hyperprolactinemia control (Fig. 7).

4. Discussion

Prolactin is required for breast development and lactogenesis, its over-secretion constitutes reproductive disorder. According to Rossi *et al.*, [10], hyperprolactinemia was the most common endocrine disorder productive of hypersecretion on the hypothalamic-pituitary axis, which occurs predominantly in young women (20–30%) and can lead to several abnormalities, including infertility. Folicle- Stimulating hormone (FSH) and gonadotropic-releasing hormones, which are necessary for ovulation tend to be suppressed by hyperprolactinemia [11].Dopamine is a known prolactin inhibitory factor, which decreases secretion of prolactin from the anterior pituitary gland. The observed reduction in the serum prolactin levels in metoclopramide-induced hyperprolactinemic rats following administration of methanol extract of *K.africana*, suggests that the extract acts as dopamine agonist, which has high binding affinity for the dopamine receptors. This result agreed with the report of Olubunmi and Anthony [12] of reduction in prolactin level of hyperprolactinemic female wistar rats. The result also concord with reports of Chen *et al.*, [13] and Ding *et al.*, [7] in which the administration of plant extracts produced significant reduction ($p<0.05$) in prolactin serum levels in hyperprolactinemic women.

Follicle stimulating hormone (FSH) is essential for gonadal development and maturation at puberty, as well as gamete production. It stimulates the growth and maturation of ovarian follicles by acting directly on the receptors located on the granulosa cells [2].The significant reduction of FSH level of metoclopramide-induced hyperprolactinemia control (HPT-CON) probably, may be due to gonadal dysfunction which delays maturation of ovarian follicles in the pre-ovulatory phase. Assessments of

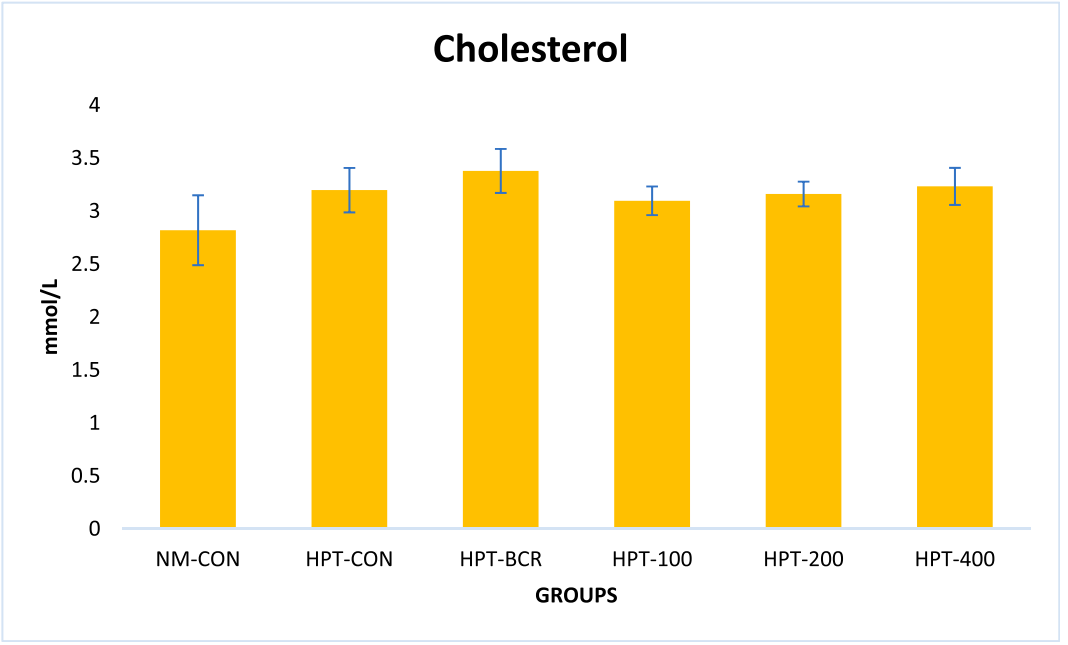

Fig. 1. Uterus cholesterol level of hyperprolactinemic female wistar rats administered with methanol leaf extract of *K. africana.* NM-CON: Normal control, HPT-CON: Hyperprolactinemia control, HPT-BCR: Hyperprolactinemic rats treated with 2.5 mg Kg^{-1} bromocriptine, HPT-100: Hyperprolactinemic rats treated with 100 mg Kg^{-1} *K. africana* extract, HPT-200: Hyperprolactinemic rats treated with 200 mg Kg^{-1} *K. africana* extract, HPT-400: Hyperprolactinemic rats treated with 400 mg Kg^{-1} *K. africana* extract.

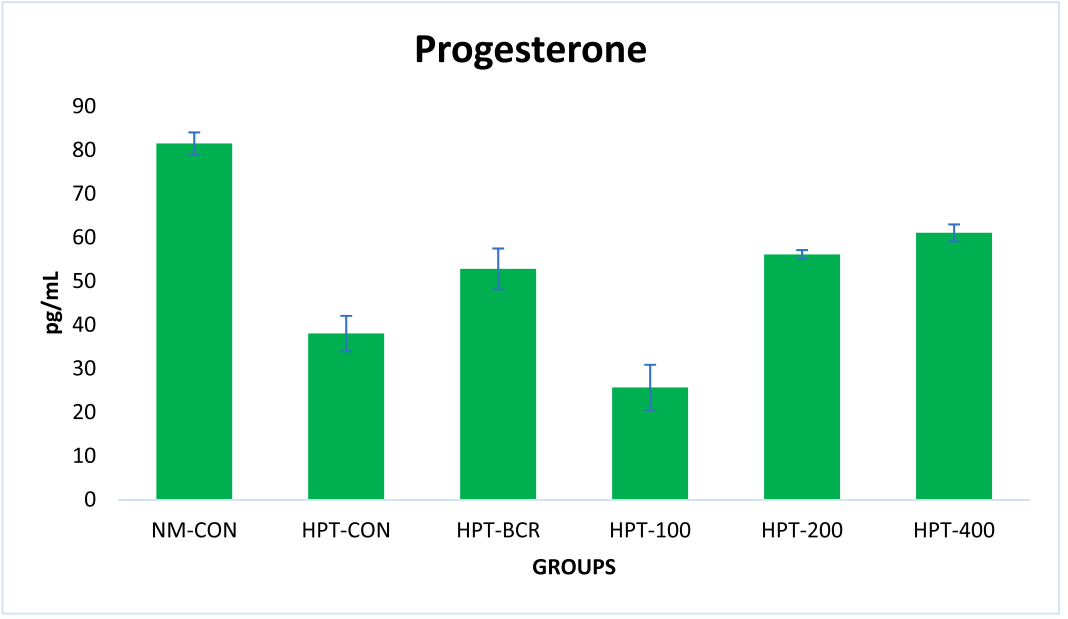

Fig. 2. Progesterone level of hyperprolactinemic female wistar rats administered with methanol leaf extract of *K. africana.* NM-CON: Normal control, HPT-CON: Hyperprolactinemia control,HPT-BCR: Hyperprolactinemic rats treated with 2.5 mg Kg^{-1} bromocriptine, HPT-100: Hyperprolactinemic rats treated with 100 mg Kg^{-1} *K. africana* extract, HPT-200: Hyperprolactinemic rats treated with 200 mg Kg^{-1} *K. africana* extract, HPT-400: Hyperprolactinemic rats treated with 400 mg Kg^{-1} *K. africana* extract.

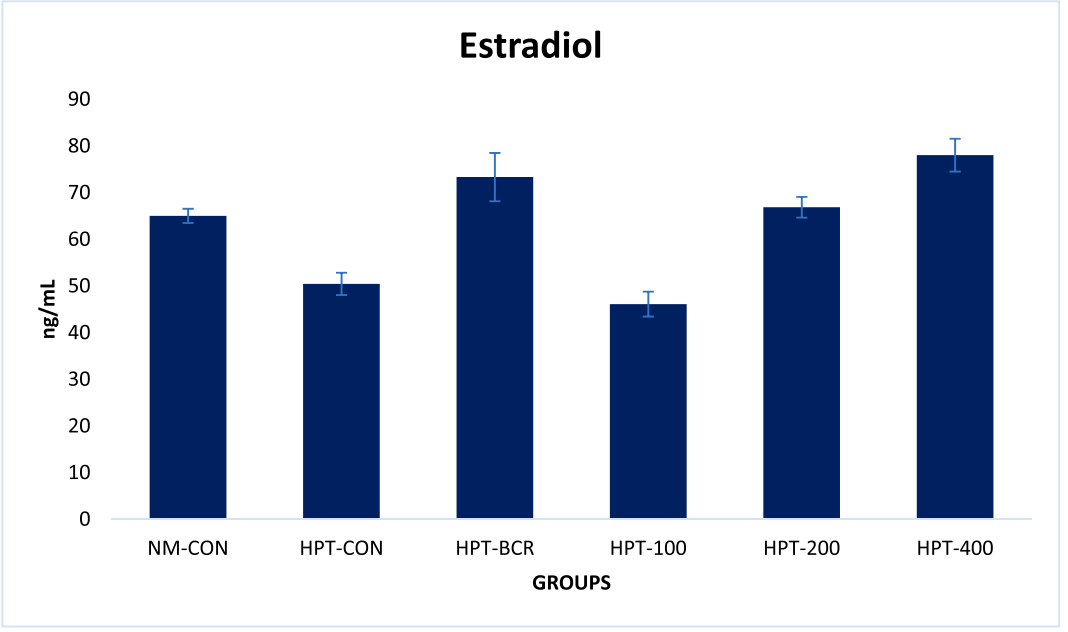

Fig. 3. Estrdiol level of hyperprolactinemic female wistar rats administered with methanol leaf extract of *K. africana*. NM-CON: Normal control, HPT-CON: Hyperprolactinemia control, HPT-BCR: Hyperprolactinemic rats treated with 2.5 mg Kg^{-1} bromocriptine, HPT-100: Hyperprolactinemic rats treated with 100 mg Kg^{-1} *K africana* extract, HPT-200: Hyperprolactinemic rats treated with 200 mg Kg^{-1} *K. africana* extract, HPT-400: Hyperprolactinemic rats treated with 400 mg Kg^{-1} *K. africana* extract.

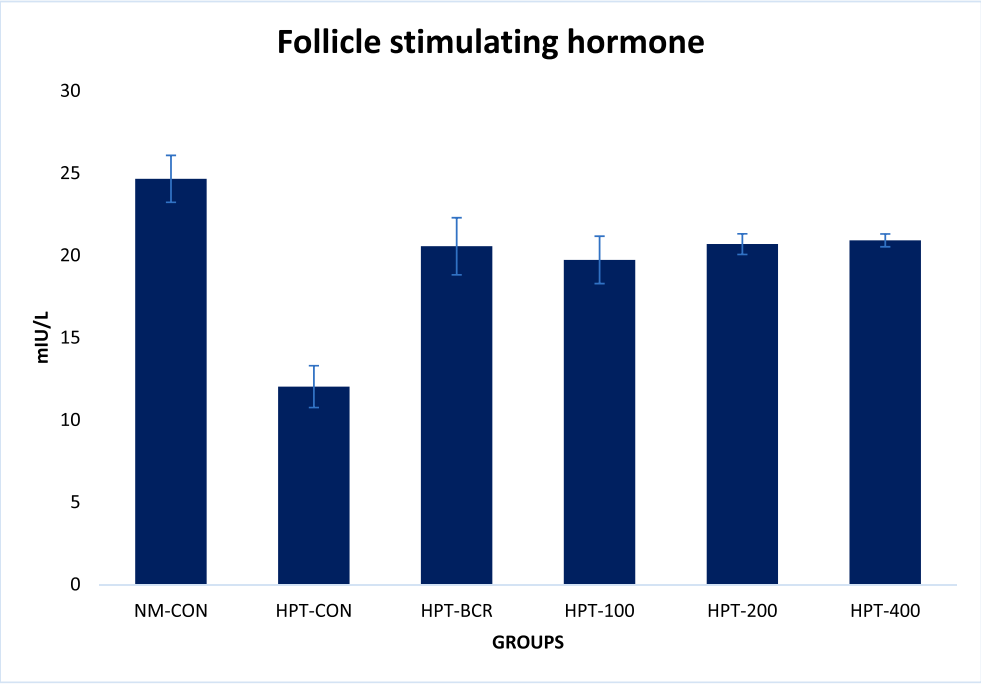

Fig. 4. FSH level of hyperprolactinemic female wistar rats administered with methanol leaf extract of *K. africana*. NM-CON: Normal control, HPT-CON: Hyperprolactinemia control, HPT-BCR: Hyperprolactinemic rats treated with 2.5 mg Kg^{-1} bromocriptine, HPT-100: Hyperprolactinemic rats treated with 100 mg Kg^{-1} *K. africana* extract, HPT-200: Hyperprolactinemic rats treated with 200 mg Kg^{-1} *K. africana* extract, HPT-400: Hyperprolactinemic rats treated with 400 mg Kg^{-1} *K. africana* extract.

the FSH level following administration of *K.africana* (100–400 mg Kg^{-1} b.wt.) extract signifies the extract exerted its stimulatory effect on the anterior pituitary or hypothalamus because, according to El.kashoury *et al.*, [14], the secretion of the hormone is regulated by the gonadotropic releasing hormone of the hypothalamus. Olubunmi and Anthony [12] reported increase in FSH level by administration of Nymphaea lotus (200mgKg^{-1}b.wt) extract on hyperprolactinemic female wistar rats. Also reported increase of FSH serum level by administration of aqueous extract of *Newbouldia laevis* by Egba *et al.*, [15] but the report of Modupe [16] recorded a significant reduction in serum follicle stimulating hormone concentrations following the administration of a herbal decoction to female laboratory rats.

Luteinizing hormone is a hormone produced by gonadotropic cells in the anterior pituitary gland. In females, an acute rise of LH triggers ovulation and development of the corpus luteum. Administration of metoclopramide may inhibit this release, thereby disrupting ovulation by reducing number of mature follicles or impaired oestrous cycle [17]. The upsurge of luteinizing hormone level following administration of 400 mg Kg^{-1} b.wt, of the extract may be attributed to the repair mechanism by the extract of the oestrous cycle and restoration of the normal ovulation in the experimental rats.

Though there is slight contradiction as Mboso *et al.*, [18] reported no significant difference ($p>0.05$) in serum luteinizing hormone concentrations of the experimental groups treated with the extract of *Ereromastax speciosa* when compared with the control.

Progesterone is an endogenous steroid and progestogene sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species. Decrease in serum progesterone level by the metoclopramide administration in this study suggests impaired endometrial function, which disrupts normal secretion of special protein required to nourish an implanted fertilized egg and prenatal development [19]. The observed increase in serum levels of progesterone of hyperprolactinemic rats administered *K. africana extract* was an indication that the extract ameliorated the

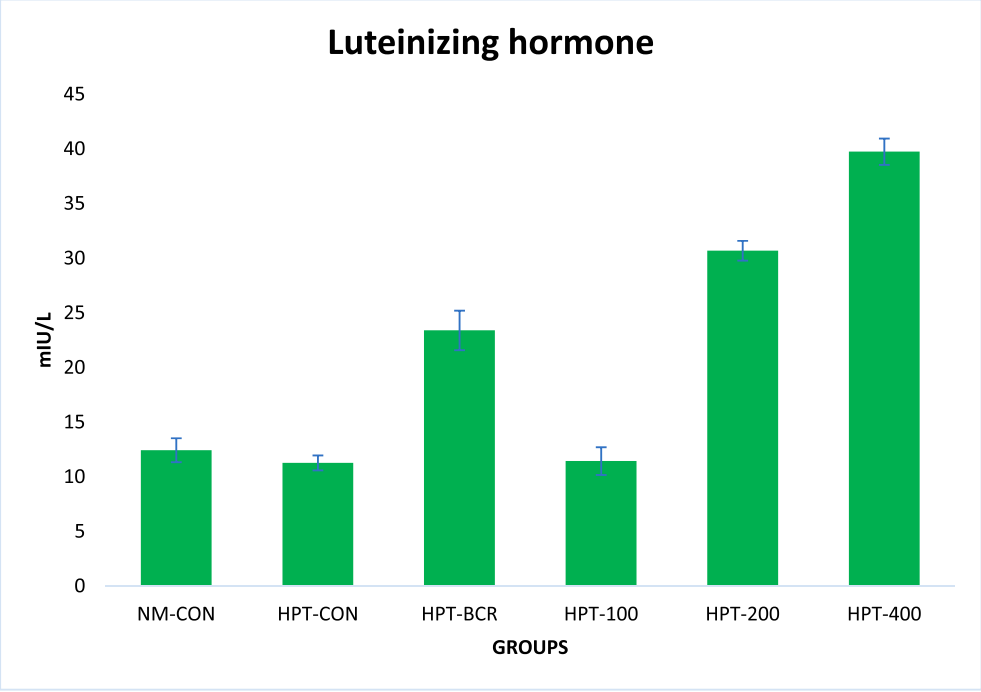

Fig. 5. Luteinizing hormone level of hyperprolactinemic female wistar rats administered with methanol leaf extract of *K. africana*. NM-CON: Normal control, HPT-CON: Hyperprolactinemia control, HPT-BCR: Hyperprolactinemic rats treated with 2.5 mg Kg^{-1} bromocriptine, HTP-100: Hyperprolactinemic rats treated with 100 mg Kg^{-1} *K. africana* extract, HPT-200: Hyperprolactinemic rats treated with 200 mg Kg^{-1} *K.africana* extract, HPT-400: Hyperprolactinemic rats treated with 400 mg Kg^{-1} *K.africana* extract.

damage caused to endometrium function, thus promoting reproduction in this study. This may be due to the presence of steroids in the extract which were easily converted to progesterone [1,20]. This report was in agreement with the reports of Olubunmi and Anthony [12] in which administration of *Nymphaea lotus* increased the concentration of serum progesterone levels in the experimental rats. Similar reports were given by Heidarifar *et al.*, [21]and Moshfegh *et al.*, [22] in which the administration of the extracts of *Anethum graveolens and Phoenix dactylifera* significantly increased progesterone serum concentrations in treated rats.

Estradiol is an estrogen steroid hormone and the major female sex hormone. It is involved in the regulation of the estrous and menstrual female reproductive cycles.

This will alleviates menstrual irregularities experienced in hyperprolactinemic women and promotes conception, thereby preventing infertility. According to Hisa *et al.*, [19], estradiol, in synergy with follicle stimulating hormone (FSH), estradiol stimulates granulose cell proliferation during follicular development, hence helps in ovulation and promotes fertility. Significant increase in serum concentration of estradiol at 400 mg Kg^{-1} *K. africana* extract seems to ameliorate imbalance in the hormone and may promotes ovulation, zygote implantation and subsequent maintenance of pregnancy. Bromocriptine (reference drug) increased the serum level of estradiol and decreased the concentration of prolactin as observed in the study. Bromocriptine and *K. africana* extract could have similar mode of action on pituitary gland for the secretion of the investigated fertility hormones.

Uterine biochemical parameters investigated in this research such as protein and cholesterol concentrations can be used as markers to determine functional capacity of the female reproductive system. The increase in uterine cholesterol level of the experimental rats following administration of *K.africana* extracts could imply stimulation of steroidogenesis, thereby leading to increased steroid

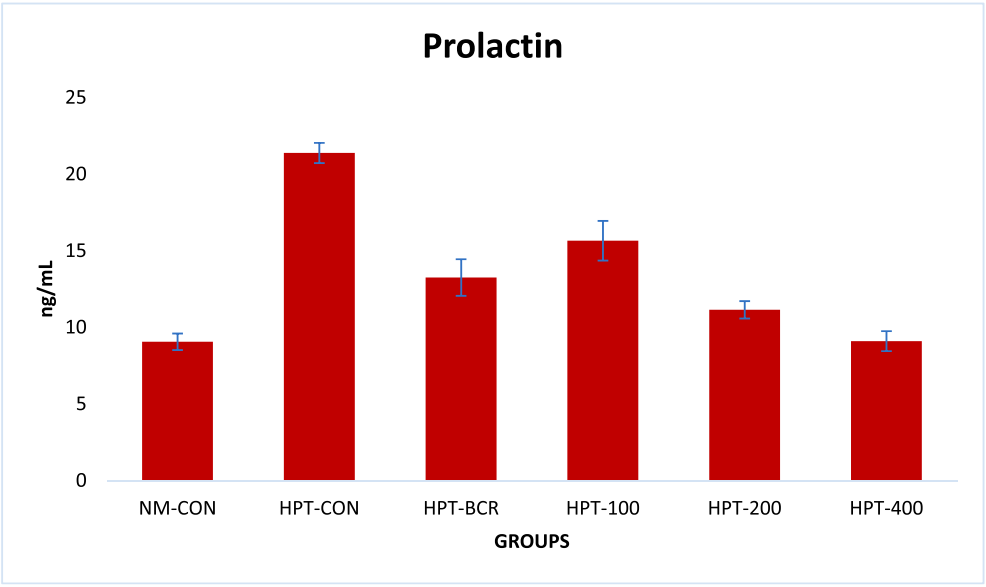

Fig. 6. Prolactin level of hyperprolactinemic female wistar rats administered with methanol leaf extract of *K. africana.* NM-CON: Normal control, HPT-CON: Hyperprolactinemia control, HPT-BCR: Hyperprolactinemic rats treated with 2.5 mg Kg^{-1} bromocriptine, HTP-100: Hyperprolactinemic rats treated with 100 mg Kg^{-1} *K. africana* extract, HPT-200: Hyperprolactinemic rats treated with 200 mg Kg^{-1} *K. africana* extract, HPT-400: Hyperprolactinemic rats treated with 400 mg Kg^{-1} *K. africana* extract.

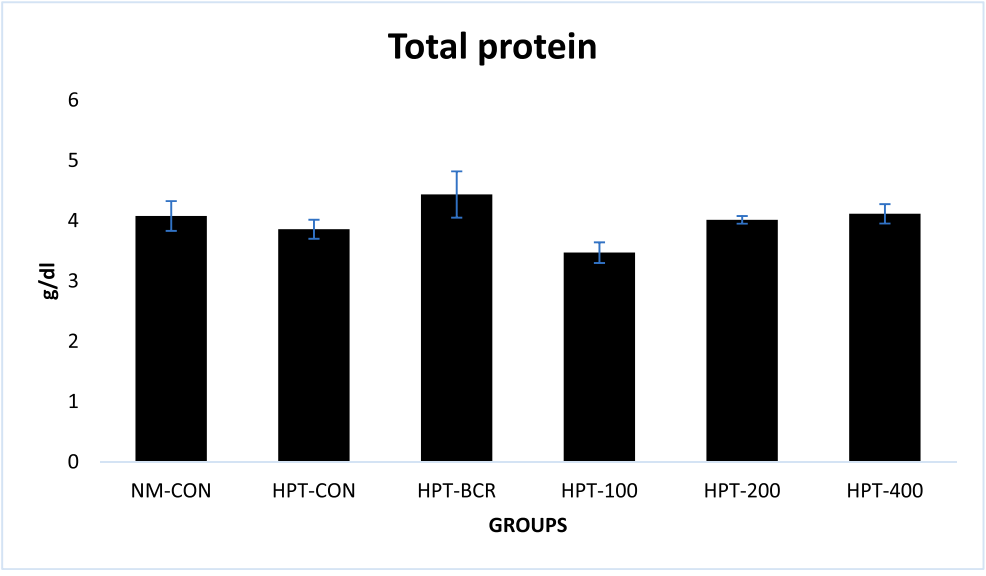

Fig. 7. Total uterus protein conc., of hyperprolactinemic female wistar rats administered with methanol leaf extract of *K. africana.* NM-CON: Normal control, HPT-CON: Hyperprolactinemia control, HPT-BCR: Hyperprolactinemic rats treated with 2.5 mg Kg^{-1} bromocriptine, HTT-100: Hyperprolactinemic rats treated with 100 mg Kg^{-1} *K. africana* extract, HPT-200: Hyperprolactinemic rats treated with 200 mg Kg^{-1} *K.africana* extract, HPT-400: Hyperprolactinemic rats treated with 400 mg Kg^{-1} *K.africana* extract.

hormones' concentration. The rise in protein level could enhance the normal functioning of the reproductive system, which in turn improves conception and reproduction.

5. Conclusion

The study revealed that the administration of methanol extract of *K.africana* can ameliorates hyperprolactinemia. The activities of other reproductive hormones, as well as some (biochemical parameters)">biochemical parameters investigated could enhance conception and reproduction. The potential of *K.africana* in the management of hormonal imbalance, the principal cause of infertility, is the novelty of this work. Results of this study support the use of plant in folk medicine in the treatment of hyperprolactinemia and other related fertility disorders. The applications of the extract in the development of novel drugs for the treatment of hyperprolactinemia are hereby recommended. However, further investigation of the effects of methanol extract of *K.africana on* female reproductive hormones using human subjects is also recommended.

Conflict of interest

Authors declare no conflicts of interest in this study.

Acknowledgments

The author sincerely appreciate his students for their contributions towards the success of this work.

Appendix 1

Table 1
Total uterus protein and cholesterol conc., of hyperprolactinemic female wistar rats administered with methanol leaf extract of *K. africana.*

Groups	Total protein	Cholesterol
NM-CON	4.08 ± 0.25^{ab}	2.12 ± 0.33^{ac}
HPT-CON	3.86 ± 0.16^{ab}	2.10 ± 0.21^{c}
HPT-BCR	4.84 ± 0.38^{b}	2.53 ± 0.10^{abc}
HPT-100 mg/kg	3.47 ± 0.17^{a}	2.29 ± 0.21^{ab}
HPT-200 mg/kg	4.02 ± 0.06^{ab}	2.56 ± 0.16^{b}
HPT-400 mg/kg	4.12 ± 0.16^{ab}	2.78 ± 0.32^{ac}

^{abc}Results with different superscripts are significantly different ($p<0.05$).

References

[1] Afolayan AJ, Sharaibi OJ, Kazeem MI. Phytochemical analysis and in vitro antioxidant activity of Nymphaea lotus L. Int J Pharmacol. 2013;9:297–304.
[2] Almeida BE, Oliveira JE, Damiani R, Dalmora SL, Bartolini P, Ribela MTCP. A pilot study on potency determination of human follicle-stimulating hormone: A comparison between reversed-phase high-performance liquid chromatography method and the *in vivo* bioassay. J Pharm Biomed Anal 2011;54:681–6.
[3] Aydin M, Cevik A, Kandemir FM, Yuksel M, Apaydin AM. Evaluation of hormonal change, biochemical parameters and histopathological status of uterus in rats exposed to 50-Hz electromagnetic field. Toxicol Ind Health 2009;25:153–8.
[4] Colao A, Di Sarno A, Guerra E, de Leo M, Mentone A, Lombardi G. Drug insight: Cabergoline and bromocriptine in the treatment of hyperprolactinemia in men and women. Nat Clin Pract Endocrinol Metab 2006;2:200–10.
[5] Melmed S, Jameson JL. Disorders of the Anterior Pituitary and Hypothalamus. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's principles of internal medicine. 16th ed. New York: McGraw Hill; 2008. p. 2076–97.
[6] Akter N, Qureshi N, Akter T. Hyperprolactinemia: A Systematic Review of Diagnosis and Management. Delta Med Coll J 2018;6(2):90–101. https://doi.org/10.3329/dmcj.v6i2.38219.
[7] Ding Y, Qian HZ, Wang YQ. Effect of tongdatang serial recipe on antipsychotic drug-induced galactorrhea-amenorrhea syndrome. Zhongguo Zhong Xi Yi Jie He Za Zhi 2008;28:263–5 (In Chinese).

[8] Uhuo EN, Ezeanyika LUS, Ogugua VN. Oxidative and biochemical parameter analysis of alloxan-induced diabetic rats administered methanol leaf and fruit extracts of *Kigelia africana*, Volume 19. London Journals Press; 2019. Issue 3 | Compilation10.
[9] Rossi AGZ, Gomes RCT, de Jesus Simoes M, dos Santos Simoes R, Oliveira PB, Soares JM, et al. Effects of metoclopramide-induced hyperprolactinemia on the prolactin receptor of murine endometrium. Fertil Sterility 2010;93:1643–9.
[10] Ogbeche KA, Ogunbiyi YO, Duru FIO. Effect of Methanol extract of K*igelia africana on* Sperm Motility and Fertility in Rats. Nig Jnl Health Biomed Sci 2002;1(2):113–6.
[11] Fitzgerald P, Dinan TG. Prolactin and dopamine: What is the connection? A review. J Psychopharmacol 2008;22:12–9.
[12] Sharaibi Olubunmi Josephine, Afolayan Anthony Jide. Biochemical and hormonal effects of Nymphaea lotus aqueous extract on hyperprolactinemic female wistar rats. Asian J Biochem 2017;12:91–8.
[13] Chen Z, Wang G, Wang X, Li L, Xiao D. Effects of Zhuangyang capsules on the serum prolactin of schizophrenic patients treated with risperidone. Med J Wuhan Univ 2008;29:798–800.
[14] El-Kashoury AA, Salama AF, Selim AI, Mohamed RA. Chronic exposure of dicofol promotes reproductive toxicity in male rats. Life Sci J 2010;7:5–19.
[15] Egba SI, Sunday GI, Anaduaka EG. The effect of oral administration of aqueous extract of newbouldia laevis leaves on fertility hormones of male albino rats. J Pharm BiolSci 2014;9:61–4.
[16] Modupe AE. Effects of oral administration of a decoction on serum levels of luteinizing hormone, follicle stimulating hormone, progesterone and estradiol in female Dutch-white 1171 rabbits. Res J Med Plants 2015;9:141–5.
[17] Rahman SA, Ahmad NA, Samat NHA, Zahri S, Abdullah AR, Chan KL. The potential of standardized quassinoid-rich extract of *Eurycoma longifolia* in the regulation of the oestrous cycle of rats. Asian Pac J Trop Biomed 2017;7:27–31.
[18] Mboso OE, Eyong EU, Ebong PE, Iwara A, Odey M. The effects of the ethanolic extract of *Ereromastax speciosa* leaf on the serum levels of luteinizing hormone, follicle stimulating hormone, progesterone and estradiol in female pubertal rats. Ann Biol Res 2013;4:136–40.
[19] Hsia SM, Yeh CL, Kuo YH, Wang PS, Chiang W. Effects of adlay (*Coix lachryma-jobi* L. var. *ma-yuen* Stapf.) hull extracts on the secretion of progesterone and estradiol *in vivo* and *in vitro*. Exp Biol Med 2007;232:1181–94.
[20] Noguchi E, Fujiwara Y, Matsushita S, Ikeda T, Ono M, Nohara T. Metabolism of tomato steroidal glycosides in humans. Chem Pharm Bull 2006;54:1312–4.
[21] Hasani-Ranjbar S, Vahidi H, Taslimi S, Karimi N, Larijani B, Abdollahi M. A systematic review on the efficacy of herbal medicines in the management of human drug-induced hyperprolactinemia; Potential sources for the development of novel drugs. Int J Pharmacol 2010;6:691–5.
[22] Moshfegh F, Baharara J, Namvar F, Zafar-Balanezhad S, Amini E, Jafarzadeh L. Effects of date palm pollen on fertility and development of reproductive system in female Balb/C mice. J HerbMed Pharmacol 2016;5:23–8.