ORIGINAL ARTICLE

REMEDIATION OF PROSTRATE-RELATED DISORDERS USING POLYPHENOLS: KOLAVIRON AND QUERCETIN IN PERSPECTIVE

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ABSTRACT

The study aimed to examine the effects of kolaviron and quercetin on testosterone-induced benign prostatic hyperplasia (BPH) in Wistar rats. Fifty rats weighing between 250g and 300g were selected, with forty-two rats being divided into six groups of seven each. The first group served as the control and received 0.5ml of Canola oil. The remaining groups were induced with BPH using a 5mg/kg body weight testosterone injection for four weeks. After BPH induction, the second group received 0.5ml of Canola oil, while the third, fourth, fifth, and sixth groups were treated with 150mg/kg body weight Kolaviron, 15mg/kg body weight Quercetin, 150mg/kg body weight Kolaviron combined with 15mg/kg body weight Quercetin, and 5mg/70kg body weight finasteride for twenty-eight days. BPH induction notably increased levels of various biomarkers such as malondialdehyde, total protein, albumin, globulin, total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, LDL-c, and VLDL-c compared to the control group. However, treatment with Kolaviron and Quercetin effectively reversed these elevations. Notably, the Quercetin group did not exhibit significant differences in triglyceride levels compared to the BPH-induced group. BPH induction also led to a significant reduction in HDL-c levels compared to the control group, which was reversed by Kolaviron and Quercetin treatment. In conclusion, the findings suggest the potential of utilizing kolaviron and quercetin for the treatment of prostate-related conditions.

Keywords: Testosterone propionate, Kolaviron, Quercetin, BPH.

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INTRODUCTION

Prostate cancer, benign prostatic hyperplasia (BPH), and prostatitis are prevalent conditions among older men, and they can all have implications for male fertility [1]. In young people, the prostate weighs about 1.5g at birth and grows to 10g then to an average of 20g by early adolescence. Approximately 50% of men aged 50 and above, and around 90% of males over 80 years old, experience an enlargement of the prostate gland compared to its size during adolescence [2]. This increase in size is clinically known as benign prostatic obstruction (BPO) or benign prostatic enlargement (BPE), with the pathological term being BPH [3]. The transitional zone prostate tissue's normal interactions between fibromuscular stromal and epithelial components are thought to be interfered with, leading to a decreased epithelial/stromal ratio and, ultimately, the micronodular remodelling that characterises BPH [4]. BPH, or benign prostatic hyperplasia, is a prevalent condition among older men. It primarily manifests through symptoms affecting the lower urinary tract (LUTS), leading to disruptions in daily life and diminishing quality of life. BPH is characterized by the gradual enlargement of the prostate gland (PV), resulting in a variety of urinary symptoms, such as recurrent infections, acute urinary retention, and other clinical manifestations in men [5-7]. Prostatitis is an inflammatory and irritating illness that affects the prostate organ. The most common symptoms of prostatitis include discomfort, voiding symptoms, and pelvic pain [7]. BPH is known to cause the development of LUTS, which is typically characterized by irritative and obstructive symptoms. For men experiencing symptomatic benign prostatic hyperplasia, medical treatment options include alpha-adrenergic receptor antagonists (alpha-blockers), which reduce smooth muscle tone in the prostate and bladder neck, or 5 alpha-reductase inhibitors, which decrease prostate volume by inducing epithelial atrophy [6]. The necessity to screen for potential sources of more effective treatment with low or no side effects has arisen due to the adverse effects and high cost of present treatment alternatives. Locally, Polyphenols, such as kolaviron and quercetin, have been proposed as alternative treatments for BPH. Kolaviron is a biflavonoid complex from Garcinia kola, while quercetin is a flavonoid found in many fruits and vegetables [9]. Both compounds were found to have anti-inflammatory and anti-proliferative actions on prostate cells, making them potential candidates for the treatment of BPH [10]. Recent studies have shown promising results in haematological and anti-oxidant indices from the use of kolaviron and quercetin in the treatment of BPH [11, 12]. As a result, a scientific evaluation of the attenuating ability of Kolaviron and Quercetin on Testosterone propionate-induced BPH in male Wistar rats was conducted.

MATERIALS AND METHODS

Testosterone propionate brand name: Recostrone, manufactured by Greenfield Pharma, Jiangsu Co Limited, China, was procured from ND-Harris & associates Onitsha, Nigeria. Quercetin (≥95% HPLC) was acquired from Sigma-Aldrich Co. (St. Louis, MO, USA) through ND-Harris & associates Onitsha, Nigeria. Whereas Finasteride a product of Aurobindo Pharma-Milpharm Ltd. ATC code: G04CB01 was

purchased from Fidelity Medical Store, Igoli-Ogoja, Cross River State, Nigeria.

Collection of Garcinia kola and Kolaviron extraction

We purchased garcinia kola seeds from a nearby vendor in Boki, Cross River State-Nigeria. Kolaviron was extracted from G. kola seeds that were in good condition and evaluated according to a previously established method. [13].

Experimental animals

The experiment involving animals received ethical approval from the Animal Ethical Committee of the University of Calabar's Faculty of Basic Medical Science (Approval Number: 114BCM262). Fifty Wistar rats weighing between 250 to 300g were sourced from the Animal House at the Faculty of Basic Medical Sciences, University of Cross River State, Okuku campus, Nigeria. Following acclimatization to the handling and experimental environment, they were housed in normal plastic cages (60cm by 40cm in size) with top mesh wire covers, at 45% relative humidity and 26 ^{0}C room temperature, with a 12-hour light-dark cycle. Throughout the trial, the rats were given free access to water and Mazuri pelletized rat chow.

Induction and confirmation of BPH

Thirty-five rats were induced with BPH, and seven were not. Testosterone propionate was used for the induction of BPH. A 5mg/kg body weight intraperitoneal injection of testosterone propionate was administered within the inguinal region of the forty experimental rats daily for four (4) weeks [14]. Once induction was completed, at the end of the fourth week, three (3) rats from the Testosterone propionate-treated and three from the non-treated cluster were arbitrarily chosen and sacrificed and examined for gross prostate enlargement (both gross and microscopic anatomical review of the prostate was doled out alongside the Prostate-specific antigen (PSA) concentration to indicate successful positive BPH induction.

Experimental design

Thirty-five (35) rats induced with BPH were arbitrarily divided into five (5) sample groups (groups 2-6) consisting of seven (7) rats each, whereas seven rats (non-induced) constituted group one (1) as shown in table 1 below. The rats were treated in line with the scheme in Table 1.

Biochemical Analysis

The levels of malondialdehyde (MDA) were analyzed using a double-beam spectrophotometer, following the method previously outlined [12]. Different parameters, such as total cholesterol (TC), triacylglycerol (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein-cholesterol, total protein, albumin, globulin, total bilirubin, and conjugated bilirubin, were determined using kinetic assay kits sourced from Randox (United Kingdom).

Statistical analysis

The examination was subjected to statistical analysis employing one-way ANOVA via GraphPad Prism (version 8). Mean values, along with Standard Error of Mean, were provided, and statistical significance was established at $p < 0.05$ (n=7).

RESULTS

The findings illustrated in Figures 1-6 demonstrate a

noteworthy elevation (p<0.05) in Serum MDA, total protein, albumin, globulin, total bilirubin, and conjugated bilirubin after testosterone propionate administration in comparison to the control cohort. However, this rise was substantially mitigated (p<0.05) with KV, QC, and KV+QC interventions relative to the BPH group. Nevertheless, serum albumin and globulin levels in the KV and QC-treated cohorts did not display significant variances (p<0.05) from the BPH group.

The data from Table 2 indicated that inducing BPH resulted in higher levels of serum TC, TG, LDL-c, and VLDL-c and lower levels of HDL-c compared to the control group. Treatment with KV, QC, and KV + QC significantly (p<0.05) reduced serum TC, TG, LDL-c, and VLDL-c levels while increasing HDL-c compared to the BPH-treated group. However, the QC-treated group showed no significant difference in serum TG concentration, and the KV-treated group showed no significant difference in serum VLDL-c concentration compared to the BPH group.

DISCUSSION

Herbs and herbal products are widely utilized around the world to cure a variety of diseases and illnesses. Herbal treatments are increasingly popular in underdeveloped nations such as Nigeria. Locals have reported using Kolaviron and Quercetin as a treatment for prostate disorders such as BPH and prostate cancer. [15]. This study aimed to assess the potential mitigating impacts of Quercetin and Kolaviron on testosterone propionate-induced benign prostatic hyperplasia (BPH) in male Wistar rats, aiming to provide empirical evidence for these assertions.

Malondialdehyde (MDA) is one of the most commonly utilized indicators for lipid peroxidation levels. Lipid peroxidation contributes to the pathophysiology of tissue damage caused by many toxic chemicals. [16]. This study measured the concentration of malondialdehyde (MDA) in the blood serum of rats experiencing benign prostatic hyperplasia (BPH). Serum levels of these biomarkers rose upon BPH induction, suggesting that one of the probable progressive and causal routes linked to BPH pathogenesis is oxidative stress. The findings of this investigation support previous studies that elevated plasma peroxidase levels such as MDA and H_2O_2 were identified in BPH patients compared to controls. [17-19].

Elevated levels of total protein, albumin, globulin, total bilirubin, and conjugated bilirubin suggest a disruption in cellular functions and integrity, including hepatocellular injury, necrosis, increased membrane permeability, and cholestasis from the toxicological perspective. [20-22]. A previous study examined the impact of chemical-induced male reproductive impairment on serum electrolytes and liver enzymes [23], and this corroborates our findings. Albumin transports and regulates interstitial fluid balance throughout the body [24, 22]. The investigation revealed that the group induced with BPH exhibited elevated levels of various markers including total protein, albumin, globulin, total bilirubin, and conjugated bilirubin compared to the control group. These changes are likely a result of liver cell damage due to BPH induction. Conversely, the groups treated with Kolaviron, Quercetin, and a combination of Kolaviron and Quercetin showed increased levels of these markers

compared to the BPH-induced group, indicating the potential antioxidant effects of the extracts observed in this study. This finding aligns with prior research [23].

Nearly every human tissue synthesizes cholesterol, which the body uses for several vital functions. For instance, it controls the fluidity and permeability of all cell membranes to minuscule ions and molecules [25]. Moreover, bile acid, steroid hormones, and vitamin D are all formed with the help of cholesterol [25]. As a result, the body's major tissues' cells must have an uninterrupted supply of cholesterol.

In the current investigation, the development of BPH resulted in an increase in total cholesterol in the serum. Similarly, BPH increased triglyceride, LDL-c, and VLDL-c levels. On the other hand, BPH induction resulted in HDL-c depletion, indicating a probable relationship between BPH and cardiovascular problems. It has been shown that elevated cholesterol concentrations hinder the oxidation of fatty acids, leading to an increase in triglyceride levels [25]. Excessive free radicals within cells can lead to unregulated chain reactions and lipid peroxidation, potentially contributing to various health issues such as cancer and atherosclerosis [26]. Malondialdehyde, a lipid peroxidation product that serves as a gauge for oxygen free radical levels, was reported to be elevated in hypercholesterolaemic atherosclerosis in a prior study [27]. As a result, treatment with kolaviron and quercetin might lead to a reduction in lipid peroxidation, consequently lowering levels of triglycerides, LDL cholesterol, VLDL cholesterol, and total cholesterol, while simultaneously increasing concentrations of HDL

cholesterol. These findings align with a previous investigation [28], which demonstrated that kolaviron reduced LDL cholesterol, overall cholesterol levels, and the likelihood of developing coronary heart disease.

CONCLUSION

The remediation of prostrate-related disorders using polyphenols: kolaviron and quercetin shows a positive impact on the parameters assessed. The significant reduction in serum biochemical parameters due to induction of BPH were all reversed following treatment with Kolaviron and Quercetin. According to the findings of this study, Kolaviron and Quercetin at doses of 150mg/kg and 15mg/kg body weight could be potential remedies for prostate disorders. This study gives scientific backing to the claims by locals about the usage of kolaviron and quercetin in the treatment of prostrate-related issues.

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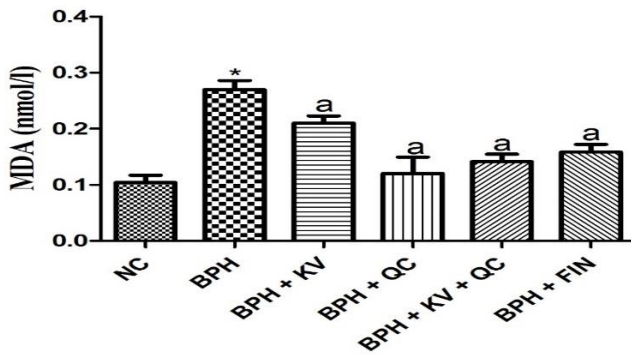
TABLES AND FIGURES

Figure 1: Effect of Kolaviron and quercetin on
Serum MDA concentration
Values are expressed as mean $\pm$ SEM; n=7.
Significant differences from the control group
are denoted by * ($p<0.05$)
Significant differences from the BPH group are
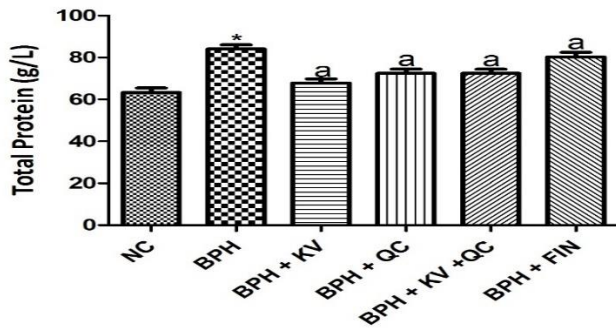denoted by ^{a} ($p<0.05$)

Figure 2: Effect of Kolaviron and quercetin on
Serum Total Protein concentration
Values are expressed as mean $\pm$ SEM; n=7.
Significant differences from the control group
are denoted by * ($p<0.05$)
Significant differences from the BPH group are
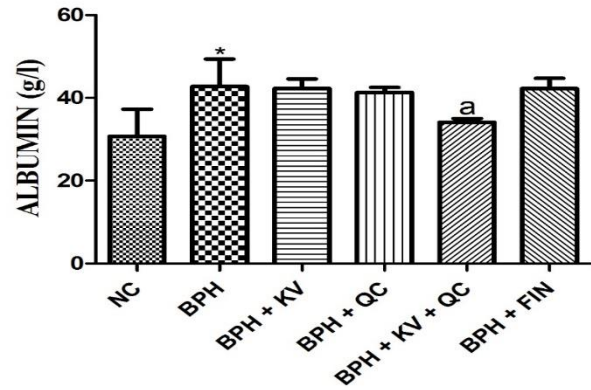denoted by ^{a} ($p<0.05$)

Figure 3: Effect of Kolaviron and quercetin on
Serum Albumin concentration
Values are expressed as mean $\pm$ SEM; n=7.
Significant differences from the control group are
denoted by * ($p<0.05$)
Significant differences from the BPH group are
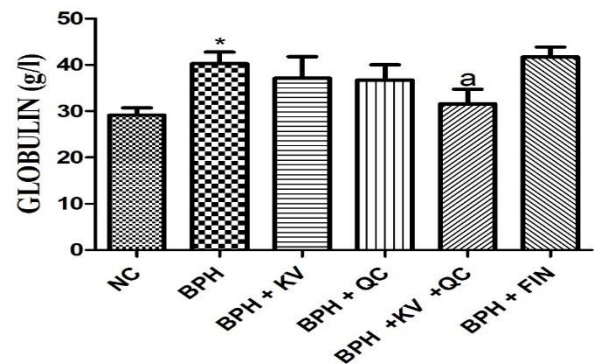denoted by ^{a} ($p<0.05$)

Figure 4: Effect of Kolaviron and quercetin on
Serum Globulin concentration
Values are expressed as mean $\pm$ SEM; n=7.
Significant differences from the control group are
denoted by * ($p<0.05$)
Significant differences from the BPH group are
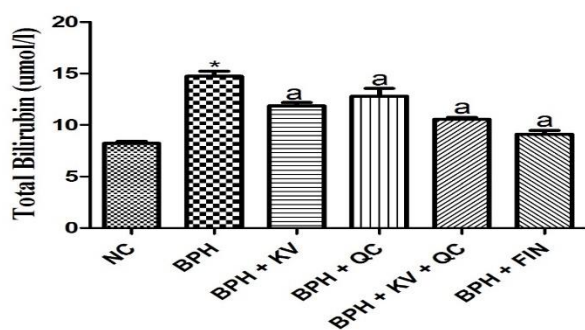denoted by ^{a} ($p<0.05$)

Figure 5: Effect of Kolaviron and quercetin on
serum Total Bilirubin concentration
Values are expressed as mean ± SEM; n=7.
Significant differences from the control group
are denoted by [*] ($p<0.05$)
Significant differences from the BPH group are
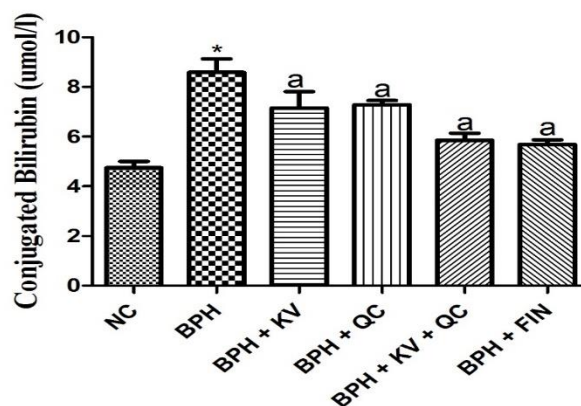denoted by [a] ($p<0.05$)

Figure 6: Effect of Kolaviron and quercetin on
serum Conjugated Bilirubin concentration
Values are expressed as mean ± SEM; n=7.
Significant differences from the control group are
denoted by [*] ($p<0.05$)
Significant differences from the BPH group are
denoted by [a] ($p<0.05$)

Table 1: Experimental design, animal grouping and treatment

Group	Number of animals	Treatment
1	7	0.5ml Canola Oil
2	7	BPH + 0.5ml Canola oil
3	7	BPH + 150mg/kg body weight kolaviron.
4	7	BPH + 15mg/kg body weight quercetin.
5	7	BPH + 150mg/kg body weight kolaviron + 15mg/kg body weight quercetin.
6	7	BPH +5mg/70kg body weight Finasteride.

Table 2: Effect of Kolaviron and Quercetin treatment on serum lipid profile.

Group	Serum TC conc. (mmol/l)	Serum TG conc. (mmol/l)	Serum HDL-c conc. (mmol/l)	Serum LDL-c conc. (mmol/l)	Serum VLDL-c conc. (mmol/l)
Normal control	0.907 ± 0.015	0.673 ± 0.009	0.371 ± 0.008	0.349 ± 0.011	0.273 ± 0.011
BPH control	$1.486 \pm 0.034^*$	$1.123 \pm 0.009^*$	$0.230 \pm 0.003^*$	$0.627 \pm 0.026^*$	$0.513 \pm 0.004^*$
BPH + Kolaviron	1.006 ± 0.010^a	0.977 ± 0.008^a	0.250 ± 0.003^a	0.433 ± 0.005^a	0.333 ± 0.008^a
BPH + Quercetin	1.386 ± 0.034^a	1.063 ± 0.031	0.299 ± 0.005^a	0.573 ± 0.012^a	0.490 ± 0.013
BPH + KV + QC	1.151 ± 0.019^a	0.733 ± 0.019^a	0.341 ± 0.003^a	0.454 ± 0.007^a	0.437 ± 0.003^a
BPH + Finasteride	1.291 ± 0.014^a	0.960 ± 0.009^a	0.324 ± 0.004^a	0.474 ± 0.008^a	0.437 ± 0.005^a

Values are expressed as mean $\pm$ SEM; n=7.

Significant differences from the control group are denoted by * ($p<0.05$)

Significant differences from the BPH group are denoted by [a] ($p<0.05$).