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ORIGINAL RESEARCH

# A new treatment for mild erectile dysfunction with *Garcinia kola* nuts: a phase II randomised clinical trial

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**Purpose:** Our objective was to assess the efficacy of *Garcinia kola* (*G. kola*) nuts in treating erectile dysfunction in adult men.

**Methodology:** A phase II single-blind clinical trial was conducted at Yaoundé Central Hospital, Cameroon. Men aged above 25 years who had experienced erectile dysfunction for at least three months were recruited. *G. kola* nuts were authenticated, cleaned, and bagged according to each participant's daily dose. We included 40 patients who completed questionnaires, including the International Index of Erectile Function (IIEF-15) and underwent clinical and paraclinical assessments. They were then randomly divided into two comparable groups to receive *G. kola*: group A (2 × 10 ± 1 g daily, $n = 20$) and group B (2 × 20 ± 1 g daily, $n = 20$). Patients were followed up every three weeks for 12 weeks. The primary outcome of the trial was an improvement in erectile function. Secondary outcomes included satisfaction with sexual intercourse, orgasm, sexual desire, overall satisfaction, and overall IIEF-15 score.

**Results:** The mean ages of the participants in groups A and B were 46.95 ± 11.94 and 49.15 ± 14.66 years, respectively. Half of the patients had been complaining of erectile dysfunction for 1–5 years. At baseline, the mean erectile function of groups A and B was 18 ± 3.01 and 19.1 ± 1.60, respectively. From the first appointment, there was a significant difference between the erectile function of group A (18.15 ± 2.94, $p = 0.874$) and group B (21.7 ± 2.34, $p < 0.001$). At the trial's baseline, the overall IIEF-15 scores were 42.7 ± 6.7 and 43.55 ± 4.3 for groups A and B, respectively. After six weeks, this score increased to 45.93 ± 5.96 in group A and reached 51.75 ± 4.34 in group B ($p = 0.004$). This increase continued until the end of the intervention. No major side effects were reported.

**Conclusion:** The *G. kola* nuts may improve erectile dysfunction and may be an alternative option for men suffering from mild erectile dysfunction. Long-term studies with a large cohort and optimal dosage are needed to confirm this trend. Trial registration: Pan African Clinical Trial Registry, identifier PACTR202310817915957.

**Keywords:** *Garcinia kola*, bitter kola, erectile dysfunction, clinical trial

## Introduction

According to the conclusions and recommendations of the National Institutes of Health (NIH) Consensus Conference on impotence in 1993, the term "erectile dysfunction" replaced "impotence" and represents the inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance.[1] Erectile dysfunction, as stated by the NIH, is an important public health problem deserving increased support from basic science investigations and applied research.[1] Over the years, the number of people suffering from erectile dysfunction has grown steadily, leading some authors to project the prevalence of erectile dysfunction to reach 322 million men by 2025, particularly in Africa, Asia, and South America.[2]

Nearly 30 years after their marketing authorisation by the United States Food and Drug Administration, 5-phosphodiesterase (PDE5) inhibitors became the first-line medical treatment for erectile dysfunction; however, the variability of their efficacy and side effects have contributed to the emergence of other drugs.[3] This is the case for several plants from traditional pharmacopoeia with different mechanisms of action on erections. For instance, botanical drugs have been widely investigated as potential erectile dysfunction treatment drugs and have shown promising therapeutic effects.[4] Examples of these include *Kaempferia parviflora*, a plant used to enhance sexual performance, which contains large amounts of low-affinity PDE5 inhibitors, and *Withania somnifera* (ashwagandha) that demonstrated a significant subjective perception of sexual well-being and assisted in increasing serum testosterone levels.[5,6]

While clinical trials on humans have been conclusive for some plants, others are still being tested. *Garcinia kola* (*G. kola)* nuts, known locally as "bitter kola" because of their bitter taste, have been the subject of numerous studies on their effectiveness on sexual function in animals.[7-10] It is a vital edible fruit and medicinal tree species distributed in most tropical forests of West and Central Africa.[11] A pilot study conducted in Nigeria on the various uses and outcomes of *G. kola* among the people of Oshimili found that *G. kola* acts as an antibacteria, anti-virus, and protects against cancer.[12] These nuts contain numerous bioactive compounds, the most abundant of which are biflavonoids. This gives them aphrodisiac, antiatherogenic, anti-inflammatory, and antioxidant properties, among others, which may help treat erectile dysfunction.[13]

In a previous study, Sewani et al.[7] demonstrated that *G. kola* nuts had potent aphrodisiac activity in male albino rats. From this perspective, *G. kola* nuts may represent a more accessible, less

expensive drug with few or no side effects for a disease whose prevalence is increasing with the resurgence of metabolic diseases.

The primary aim of our study was to evaluate the pharmacological efficacy of *G. kola* nuts in treating erectile dysfunction in men. The secondary aims of this study were to identify the qualitative phytochemical composition of our sample of *G. kola* nuts, determine the variation in erectile function during the intake of *G. kola* nuts, and assess patient compliance with the consumption of *G. kola* nuts.

## Materials and methods

### Study design

This was a two-arm, single-blind, randomised, active comparator-controlled clinical trial. The study design and workflow are summarised in the Consolidated Standards of Reporting Trials (CONSORT) flow chart in Figure 1. The study design was an intention-to-treat analysis.

### Setting

This phase II clinical trial was conducted at the Urology Department of the Yaoundé Central Hospital, Cameroon. The protocol for this study was reviewed and approved by the Institutional Ethics Committee of the Université des Montagnes (Ref N° 2023/027/UdM/PR/CEAQ), and all methods were carried out following relevant guidelines and regulations for human subject protection. The study lasted five months, from 15 February to 15 July 2023.

### Participants and recruitment

#### Study population

The study population comprised adult male volunteers suffering from erectile dysfunction for at least three months who provided free and informed consent to participate in the study. Patients were enrolled in the Pan African Clinical Trials Registry with the unique identification number PACTR202310817915957. Patients were included in the study based on the inclusion and exclusion listed criteria below.

Inclusion criteria:

- All patients over 25 years of age experiencing erectile dysfunction for at least three months.

Exclusion criteria:

- Patients suffering from hypogonadism, prostate cancer, and chronic renal disease.

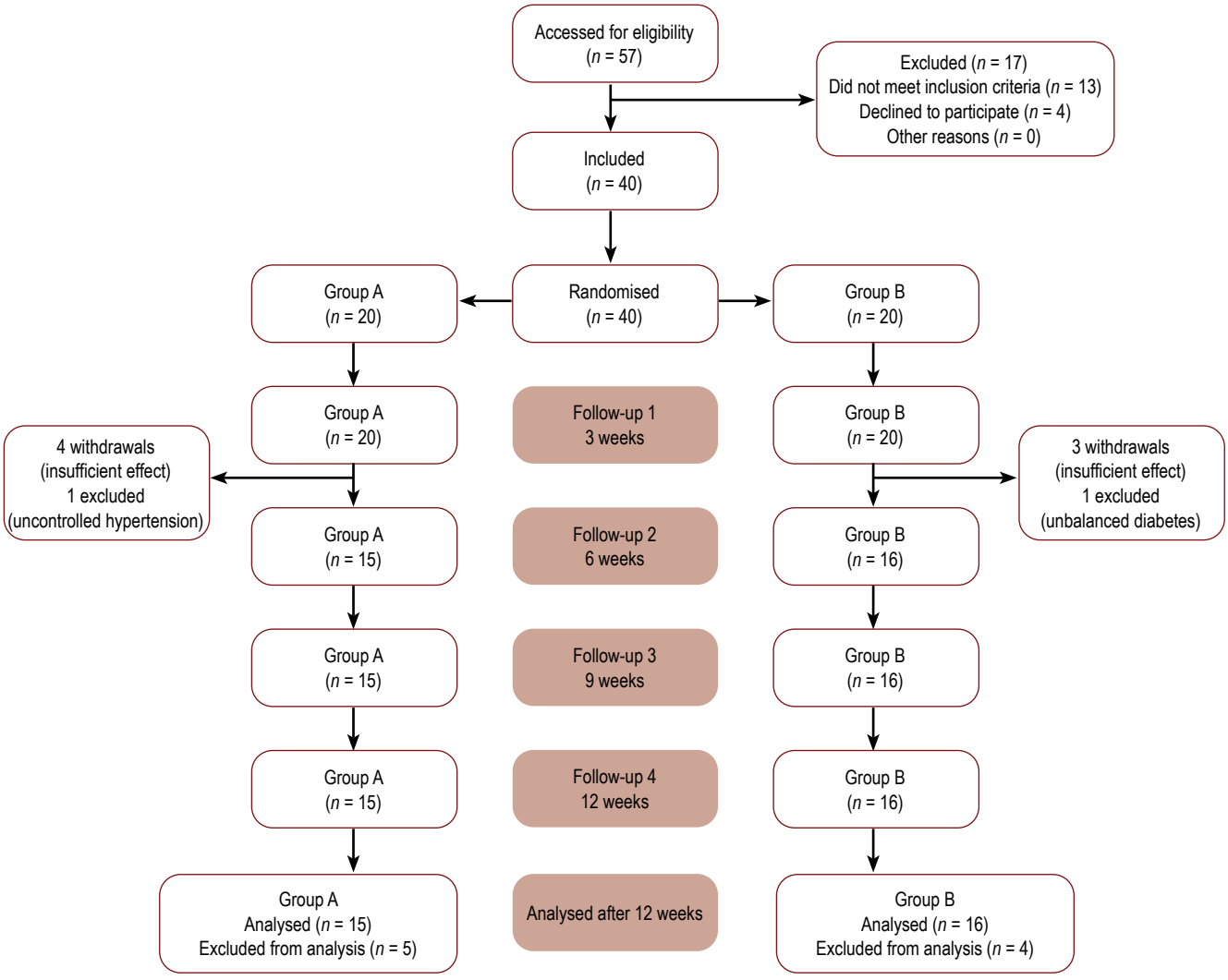


Figure 1: CONSORT flow chart

- Patients who had consumed *G. kola* nuts or traditional pharmacopoeia during the two weeks before the consultation.
- Any patient who presented with an unbalanced chronic condition during the study (i.e. blood glucose levels > 1.8 g/L in diabetic patients and > 1.26 g/L in patients not known to be diabetic, stage 2 hypertension [≥ 160/100 mmHg] taken at least twice).
- Severe intolerance to *G. kola* nuts during the intervention.
- Withdrawal of consent to participate.

Group A – participants taking 10 ± 1 g/day of *G. kola*, group B – participants taking 20 ± 1 g/day of *G. kola*

### *Sample size considerations*

The Whitley and Ball formula was used to calculate the sample size of a study designed to compare means between groups of the same size, where:[14]

$$n = \frac{2}{d^2} \times C_{p \cdot power}$$

- $n$ is the number of subjects required in each group,
- $d$ is the standardised difference, and
- $C_{p.power}$ is a constant defined by the values chosen for the $p$-value and power in the statistical tables.

Assuming that the significance threshold is 0.05 for a power of 80%, the $C_{p.power}$ is 7.9:

$$n = \frac{2}{1.05^2} \times 7.9 = 14.3$$

Therefore, the minimum number of patients required is 15 per group. If we estimate the number of patients who refuse and/or withdraw consent to be 20%, the number of patients to be approached is calculated, where:

$$N = \frac{n}{1-q} = \frac{15}{1-0.20} = 18 \text{ patients}$$

- $N$ is the number of patients to be approached,
- $n$ is the initial sample, and
- $q$ is the percentage of people who can refuse/withdraw their consent from the study.

To increase the statistical power of our study, we retained 18 patients per group (i.e. a total of 36 participants).

## *Intervention*

### *Collection of biological material*

*G. kola* nuts were purchased from the popular local market (Mokolo Market) in the Yaoundé II district, the capital city of Cameroon. The strains were authenticated at the National Herbarium of Cameroon and registered at 27839 SRF/Cam. The nuts were cleaned, weighed, and bagged according to the daily dose to be received by each patient.

Each pack contained 25 sachets, and each sachet contained two nuts (Figure 2). We made up two types of sachets, one of 10 ± 1 g and the second of 20 ± 1 g. These doses were derived from those used in rats, for which Sewani et al.[7] reported significant results. We first sorted each nut by weight into batches of 3–4 g, 4–5 g, 5–6 g, 6–7 g, 7–8 g, 8–9 g, 9–10 g, 10–11 g, and 11–12 g using a precision balance. We then matched the nuts to obtain bags of 10 ± 1 g (3–4 g + 6–7 g and 4–5 g + 5–6 g) and bags of 20 ± 1 g (11–12 g + 8–9 g and 10–11 g + 9–10 g). Nuts weighing 7–8 g were used for phytochemical screening, and the rare nuts weighing less than 3 g or more than 12 g were excluded from the study.

## *Preclinical phase*

### *Extraction preparation*

The outer shell of the nuts was removed beforehand. The nuts were cut into small pieces using a knife and then air-dried, away from the sun, for seven days. They were then ground using an electronic mill to obtain a fine powder. The extract was prepared according to the laboratory protocol.[15] The powder was macerated in two solvents (distilled water and 70% ethanol) at a ratio of 250 g of powder to 1 L of solvent for 72 hours. The mixtures were filtered once using cotton wool and Whatman number 1 filter paper. The filtrates obtained were concentrated in a rotary evaporator (BÜCHI) and then dehydrated in an oven at 50 °C for 72 hours to get two dry, brown-black extracts. The net yields were weighed, and the extracts were stored in a refrigerator.

### *Phytochemical screening*

Phytochemical screening of the extract was carried out to qualitatively determine the presence or absence of phytochemicals.


**Figure 2:** Bitter kola nuts
A – nuts in 10 g pack, B – nuts in 20 g pack, C – pack of 25 sachets containing two nuts per sachet

### Clinical phase

We began recruiting patients over two months, from 15 February to 15 April 2023. The diagnosis of erectile dysfunction was made by a urologist during a consultation. The principal investigator then presented the study to the patient and asked for their participation. Each participant signed a free and informed consent form before completing an anonymous, self-administered questionnaire in two parts:

- The first part included sociodemographic information (marital status, employment status, number of current sexual partners), medical and medication history, characteristics of erectile dysfunction, physical parameters on the day, and significant data from the physical examination.
- The second part of the International Index of Erectile Function (IIEF-15) assesses erectile function (six items), satisfaction with sexual intercourse (three items), orgasm (two items), sexual desire (two items), and overall satisfaction (two items).

This was followed by a physical examination in which basic parameters were taken: blood pressure, pulse, weight, fasting capillary glycaemia, and urine dipstick. Participants were encouraged to have at least two sexual intercourse sessions per week. A schedule of visits was drawn up, and appointments were made for the various dates. A total of four appointments were scheduled, and telephone calls were made every five days between visits for reminders and follow-up.

The participants were randomly divided into two groups of equal size, following a draw carried out by a third party who was not part of the study. Groups A and B received a dose of 10 ± 1 g and 20 ± 1 g of *G. kola* nuts, respectively, only known by the principal investigator, to be taken twice daily (at 6 a.m. and 8 p.m.). These times were chosen because of their proximity to the times at which the participants had sexual intercourse and because of the morning peak in testosterone.

The total duration of the intervention was 12 weeks. Each participant was allocated a code. During each visit, the parameters were recorded, and the patient completed an IIEF-15 self-report questionnaire and compliance and tolerance questionnaires. At each visit, each participant in each group received enough treatment for 25 days, covering the three weeks between appointments.

### Assessment of efficacy

The primary objective of the present study was to explore whether *G. kola* nuts 20 ± 1 g was superior to *G. kola* nuts 10 ± 1 g. The primary endpoint was improvement in erectile function. *G. kola* nuts (20 ± 1 g) were considered superior to *G. kola* nuts (10 ± 1 g) if the difference between the mean changes from baseline to the endpoint in the IIEF-15 domain was > 1 point. The secondary endpoints were satisfaction with sexual intercourse, orgasm, sexual desire, overall satisfaction, and overall IIEF-15 score.

*G. kola* nuts (20 ± 1 g) were superior to *G. kola* nuts (10 ± 1 g) if the difference between the mean changes from baseline to the endpoint in each domain was > 1 point. The endpoint visit (follow-up) was defined as the last post-baseline assessment during single-blind treatment for which efficacy evaluations were available.

### Assessment of compliance/safety

Compliance with treatment was assessed using the Girerd test.[16] This test classifies participants according to the total number of "yes" answers as follows:

- Good compliance: score = 0
- Minimal compliance problem: score = 1 or 2
- Poor compliance: score ≥ 3

The safety of the clinical trial was monitored by the occurrence of adverse effects, control of clinical abnormalities, and tolerance of treatment. Tolerance was obtained on a declarative basis by each participant and handed in at each appointment.

### Data management and monitoring

During the study, we considered the following terms:

- The IIEF-15 has five items:[17]
  - For the IIEF-15 erectile function domain (six items), erectile function was classified as mild (22–25), mild to moderate (17–21), moderate (11–16), severe (6–10), or non-interpretable (0–5). In addition, this score can be used to assess other parameters, such as:
    - Satisfaction with sexual intercourse (three items): low (0–5), medium (6–10), and high (11–15).
    - Orgasm (two items): rare (0–3), infrequent (4–6), and frequent (7–10).
    - Sexual desire (two items): low (0–3), moderate (4–6), and high (7–10).
    - Overall satisfaction (two items): low (0–3), moderate (4–6), and high (7–10).
  - Erectile dysfunction: recurrent or persistent inability to obtain and/or maintain an erection sufficient for satisfactory sexual activity. A period of three months is commonly accepted before starting treatment.

### Statistical analysis

The collected data were revised, coded, and entered into Census and Survey Processing (CSPro) version 7.5 software. The samples were then analysed using the IBM Statistical Package for the Social Sciences (SPSS) version 27.0 (SPSS Inc., IBM Corp., Armonk, United States of America).

Qualitative data are presented as numbers and percentages, while quantitative data are expressed as the means, standard deviation (SD), and ranges or medians with interquartile ranges. The nonparametric Wilcoxon test was used to compare means between two related groups, and the Mann–Whitney U test was used to compare means between two independent groups. The confidence interval was 95%, and the accepted margin of error was 5%. A *p*-value less than 0.05 was considered statistically significant.

## Results

At the start of the study, we included 40 patients. They were randomly divided into two groups, A and B, of equal size, and the intervention began. Three weeks after the first follow-up appointment, seven patients (four in group A and three in group B) were dissatisfied with the results and decided to withdraw from the study. Two patients were excluded from the study due to unstable clinical conditions. The hypertensive patient in group A was excluded because his systolic blood pressure was above 170 mmHg at several measurements with a headache. The type 2 diabetic patient in group B was excluded because his blood glucose level was above 1.8 g/L. Consequently, 31 participants returned at the second follow-up visit and agreed to participate.

### *Demographics and other baseline characteristics*

#### *Patient demographics*

The average age of the population in group A was 46.95 ± 11.94 years, and 49.15 ± 14.66 years in group B, with extremes of 28–68 and 26–73 years, respectively. The predominant age ranges were 45–55 years for group A and 55–65 years for group B. There were 22 (65%) married patients. Most participants (55%) had completed university education. The demographic details of the patients are shown in Table I.

#### *Clinical features*

In our study population, 85% (*n* = 34) of patients had erectile dysfunction for more than six months. It was generally progressive in onset (70% of participants, *n* = 28), permanent in 22 (55%) men, associated with persistent nocturnal erections in 62.5% (*n* = 25) of cases, provoked erections in all patients, and preserved libido in 67.5% (*n* = 27) of cases. We observed that 25 (62.5%) patients had a single sexual partner during the previous six months. A total of 37.5% (*n* = 15) had had two sexual encounters per week in the year preceding the study, and 82.5% (*n* = 33) had had more than two sexual encounters per week in the last three months.

Comorbidities were found in 77.5% (*n* = 31) of the population. The main comorbidities encountered in the population were benign prostatic hyperplasia in 25% (*n* = 10) of patients, arterial hypertension in 22.5% (*n* = 9) of patients, and type 2 diabetes in seven (17.5%) participants. Of the 40 patients, 24 (60%) had already used traditional pharmacopoeia to treat their problems, and five (12.5%) were taking sildenafil. Only five hypertensive patients were taking medication. Table II highlights the sexual history of the patients.

Most participants (70%, *n* = 28) had normal blood pressure, of whom 13 were in group A and 15 were in group B. Of the patients, 12 had above-normal systolic blood pressure at the start of the study (seven in group A, five in group B), of whom 11 had stage 1 hypertension, and one had stage 2 hypertension, which differs from the nine known hypertensive patients. Diastolic blood pressure was high in 27.5% (*n* = 11) of patients. All participants had a body mass index above normal. Of these, 60% (*n* = 24) were class 1 obese, with 11 and 13 in groups A and B, respectively. In addition, 25% (*n* = 10) of patients had an abnormality on physical examination due to prostatic hypertrophy, with five patients in each group.

At baseline, erectile dysfunction was mild to moderate in both groups. Satisfaction with sexual intercourse was moderate in both groups. Orgasm was frequent in group A and infrequent in group B. Sexual desire was moderate in both groups. Overall satisfaction with their sexual life was moderate in both groups, as shown in Table III.

#### *Biological features*

Of the 40 initial urine dipsticks performed, five revealed abnormalities, notably proteinuria (one), glucosuria (four), and leukocyturia (one). Most patients (82.5%) had normal fasting blood

**Table I:** Demographic characteristics of the study population at baseline

| Characteristics | Study population | | | | | |
|---|---|---|---|---|---|---|
| | Group A | | Group B | | Total | |
| | *n* = 20 | % | *n* = 20 | % | *n* = 40 | % |
| **Mean age ± SD (years)** | 46.95 ± 11.94 | 50 | 49.15 ± 14.66 | 50 | | 100 |
| **Age minimum; age maximum (years)** | 28.68 | 50 | 26.73 | 50 | 26.73 | 100 |
| **Age ranges (years)** | | | | | | |
| 25–35 | 4 | 10 | 3 | 7.5 | 7 | 17.5 |
| 35–45 | 4 | 10 | 4 | 10 | 8 | 20 |
| 45–55 | 5 | 12.5 | 5 | 12.5 | 10 | 25 |
| 55–65 | 6 | 15 | 4 | 10 | 10 | 25 |
| 65–75 | 1 | 2.5 | 4 | 10 | 5 | 12.5 |
| **Marital status** | | | | | | |
| Single | 8 | 20 | 6 | 15 | 14 | 35 |
| Married | 9 | 22.5 | 13 | 32.5 | 22 | 65 |
| Divorced | 2 | 5 | 1 | 2.5 | 3 | 7.5 |
| Widowed | 1 | 2.5 | 0 | 0 | 1 | 2.5 |

SD – standard deviation

Table II: Participants' sexual history at baseline

| Characteristics | Study population | | | | | |
|---|---|---|---|---|---|---|
| | Group A | | Group B | | Total | |
| | *n* = 20 | % | *n* = 20 | % | *n* = 40 | % |
| **Duration of erectile dysfunction (months)** | | | | | | |
| 3–6 | 3 | 7.5 | 3 | 7.5 | 6 | 15 |
| 6–12 | 5 | 12.5 | 3 | 7.5 | 8 | 20 |
| 12–24 | 4 | 10 | 6 | 15 | 10 | 25 |
| 24–60 | 6 | 15 | 4 | 10 | 10 | 25 |
| 60–120 | 2 | 5 | 2 | 5 | 4 | 10 |
| > 120 | 0 | 0 | 2 | 5 | 2 | 5 |
| **Mode of onset** | | | | | | |
| Sudden | 6 | 15 | 6 | 15 | 12 | 30 |
| Progressive | 14 | 35 | 14 | 35 | 28 | 70 |
| **Frequency** | | | | | | |
| Permanent | 12 | 30 | 10 | 25 | 22 | 55 |
| Intermittent | 8 | 20 | 10 | 25 | 18 | 45 |
| **Persistence of spontaneous nocturnal/morning erections** | | | | | | |
| Yes | 13 | 32.5 | 12 | 30 | 25 | 62.5 |
| No | 7 | 17.5 | 8 | 20 | 15 | 37.5 |
| **Libido** | | | | | | |
| Preserved | 15 | 37.5 | 12 | 30 | 27 | 67.5 |
| Decreased | 5 | 12.5 | 8 | 20 | 13 | 32.5 |
| **Sexual partners during the last six months** | | | | | | |
| Unique | 10 | 25 | 15 | 37.5 | 25 | 62.5 |
| Multiple | 10 | 25 | 5 | 12.5 | 15 | 37.5 |

Table III: IIEF-15 score of the study population at baseline

| Items | Mean ± SD | | Minimum; maximum | |
|---|---|---|---|---|
| | Group A *n* = 20 | Group B *n* = 20 | Group A *n* = 20 | Group B *n* = 20 |
| Erection (out of 30) | 18.0 ± 3.01 | 19.1 ± 1.60 | 12; 23 | 17; 22 |
| Sexual satisfaction (out of 15) | 7.00 ± 1.89 | 7.45 ± 1.28 | 4; 10 | 5; 10 |
| Orgasm (out of 10) | 7.1 ± 1.02 | 6.95 ± 0.76 | 5; 9 | 6; 8 |
| Sexual desire (out of 10) | 6 ± 1.03 | 5.65 ± 1.35 | 4; 8 | 4; 8 |
| Overall satisfaction (out of 10) | 4.6 ± 1.05 | 4.4 ± 0.82 | 3; 6 | 3; 6 |
| Total IIEF-15 | 42.7±6.76 | 43.55 ± 4.3 | 31; 53 | 37; 51 |

SD – standard deviation

glucose levels. Among the seven known diabetic patients, two in group B had fasting blood glucose levels above 1.26 g/L.

### *Preclinical phase results*

Chemical screening revealed the presence of several secondary metabolites. Table IV summarises the qualitative determination of the various secondary metabolites and their solubilities in aqueous and hydro-ethanol solvents. Phytochemical compounds such as catechic tannins, flavonoids, flavonols, saponosides, polyphenols, alkaloids, coumarins, and betacyanins were present.

The results of the qualitative analysis indicated that the two solvents used for extraction were effective, with the hydro-ethanol solvent being more efficient at extracting more of the active compound. Alkaloids, catechic tannins, and saponosides were more abundant in the hydro-ethanolic extract than in the aqueous extract. Anthraquinone, chalcone, mucilage, steroids, cardiac glycosides, quinone, anthocyanin, resin anthocyanins, oxalate, gall tannins, and phobotannins were absent from both extracts. In addition, we found vitamins such as vitamin C and primary metabolites such as carbohydrates and proteins. Lipids and carotenoids were absent.

### *Efficacy results*

#### *Clinical changes during intervention – the IIEF-15 score erectile function domain*

The primary endpoint, erectile function, increased throughout the study. At baseline, the mean erectile function of groups A and B were 18 ± 3.01 and 19.1 ± 1.60, respectively. At the first appointment, there was a significant difference between the erectile

Table IV: Phytochemical screening of *G. kola* nut extracts

| Chemical compound | Results | |
|---|---|---|
| | Aqueous extract | Hydro-ethanol extract |
| Alkaloids | + | ++ |
| Polyphenols | + | + |
| Coumarins | + | + |
| Flavonoids | + | + |
| Flavonols/flavones | + | + |
| Gallic tannins | - | - |
| Catechic tannins | + | ++ |
| Phobotannins | - | - |
| Oxalates | - | - |
| Anthocyanins | - | - |
| Anthraquinones | - | - |
| Quinones | - | - |
| Betacyans | + | + |
| Saponosides | + | ++ |
| Vitamin C | + | + |
| Proteins | + | + |
| Carbohydrates | + | + |
| Fats | - | - |
| Chalcones | - | - |

+ – significantly present, ++ – abundantly present, - – absent

function of group A (18.15 ± 2.94, $p$ = 0.874) and group B (21.7 ± 2.34, $p$ < 0.001). This difference remained perceptible until the end of the experiment, with scores of 20.87 ± 2.88 and 23.88 ± 2.36 in groups A and B, respectively ($p$ = 0.003) (Figure 3). Nine patients had taken sildenafil in the past. The mean erection score at the start of the trial was 16.88 ± 2.75. At the end of the intervention, it rose to 19.88 ± 8.11, with a difference of 3 units. In the other naive patients, the mean erection score was 19.03 ± 4.23 at the beginning, which increased to 22.12 ± 9.04 at the end, with a difference of 3 units.

Furthermore, none of the patients had severe erectile dysfunction. However, five men (12.5%) had moderate erectile dysfunction, and the rest (87.5%, $n$ = 35) had mild erectile dysfunction. In the group with moderate erectile dysfunction, four patients progressed to mild erectile dysfunction, and one patient regained normal erectile function. After excluding nine patients from the study, 26 men remained with mild erectile dysfunction. From these, 22 (84.6%) recovered a normal erection, while the erectile function of the others ($n$ = 4) stayed at the mild stage despite an increase in score.

### *Overall IIEF-15 score*

At baseline, the overall IIEF-15 scores were 42.7 ± 6.7 and 43.55 ± 4.3 in groups A and B, respectively. There was a significant increase ($p$ = 0.008 and $p$ = 0.027, respectively) in the total scores for patients in group B during the first two appointments (47.9 ± 5.41 and 51.75 ± 4.34, respectively). During the same period, there was a significant difference between the averages of the two groups (Figure 4). This difference was maintained until the end of the intervention despite slight variations in both groups during the last six weeks.

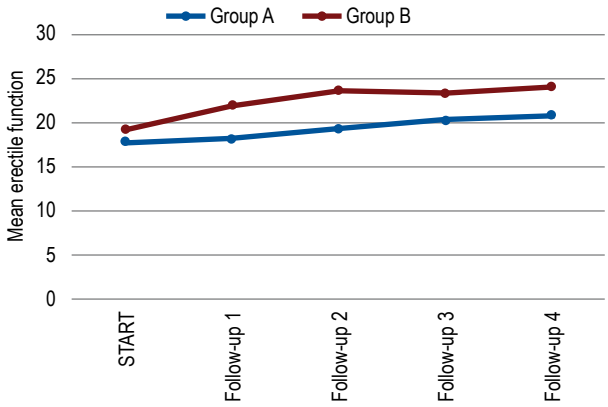


Figure 3: Changes in erectile function during the intervention

### *Other IIEF-15 score domains*

The scores of the remaining components of the IIEF-15 also varied throughout the intervention. At baseline, the orgasm scores were 7.1 ± 1.02 and 6.95 ± 0.76 in groups A and group B, respectively. We detected a significant difference ($p$ = 0.002) in the orgasm scores (7.81 ± 0.75) of patients in group B at the end of the experiment. The peak was reached at the third appointment when group A experienced a slight drop while group B continued to progress. This indicates an increase in orgasm in both groups, more marked in group B. We found no significant difference in orgasm scores either between the two groups or between two consecutive visits.

Moreover, unlike in group A, there was a significant improvement in sexual desire in group B at baseline (5.65 ± 1.35) and the end (6.44 ± 0.63, $p$ = 0.028) of the intervention. This reflects a greater score increase for patients in group B in these two areas.

Overall, there was an increase in sexual satisfaction scores in the different groups. We start with comparable intercourse satisfaction scores in the two groups A and B (7 and 7.45), only to find a difference between them at the first (7.1 ± 1.89, 8.1 ± 1.07, $p$ = 0.048), second (7.67 ± 1.54, 8.88 ± 0.72, $p$ = 0.012), and fourth (8.33 ± 1.68, 9.5 ± 1.32, $p$ = 0.039) appointments. The increase was more noticeable in group B, where there was a significant difference between the first and second appointments.

There was an increase in overall satisfaction at the end of the experience in both groups between the start and the end of the study. At baseline, the overall satisfaction score was 4.6 ± 1.05 in group A and 4.4 ± 0.82 in group B. The score remained comparable despite a slight increase (5 ± 1.03, $p$ = 0.04) in group B at the first appointment. There was a variation in overall sexual satisfaction scores between the two groups. At the end of the experience, there was a significant difference in overall satisfaction between the beginning and fourth follow-ups in group A (5.47 ± 0.92, $p$ = 0.022) and group B (6 ± 0.63, $p$ < 0.001).

### *Vital signs and anthropometric parameters*

There was no significant variation in blood pressure and body mass index; the averages remained equivalent between the groups and between two consecutive appointments. On the other hand, there was a one-way difference in the respiratory rate between groups A

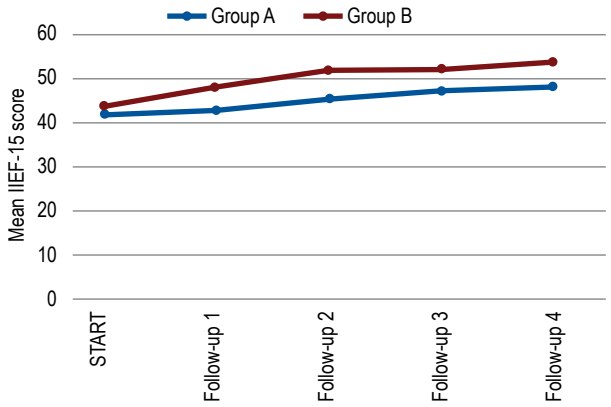


Figure 4: Changes in IIEF-15 score during intervention

and B at the first appointment. Apart from this discrepancy, the mean respiratory rates of each group remained equivalent throughout the procedure.

### *Paraclinical changes during intervention*

There was no significant variation in fasting blood glucose levels during the intervention. However, the number of abnormalities (glucose and protein) detected by urine dipstick in both groups reduced over the course of the experiment from the ninth week.

## *Tolerability and safety results*

### *Compliance of participants consuming G. kola nuts*

Throughout the experiment, we collected 133 Girerd compliance tests. Most (60.9%, *n* = 81) showed good compliance, and 39.1% (*n* = 52) showed minimal compliance. In addition, overall, better compliance was observed in group B than in group A, with 45 group B records compared with 36 group A records showing good compliance, and 23 group B records compared with 29 group A records showing minimal compliance. Figure 5 highlights the variations in compliance for each group.

### *Participants' adverse events related to G. kola nuts*

We noted four patients who experienced adverse effects during the intervention. These side effects were experienced during the first three weeks only. The most frequent side effects were nausea (75%) and asthenia, although none of the symptoms reported led to the discontinuation of treatment.

## Discussion

This two-arm clinical trial investigating the efficacy of *G. kola* nuts on erectile dysfunction involved a population of men with a mean age of 46.9 ± 11.9 years and 49.2 ± 14.7 years who received a dose of 10 ± 1 g in group A and 20 ± 1 g in group B, respectively. Several advanced studies have demonstrated the efficacy of *G. kola* nuts on erectile function in animals, and our current research on adult men confirms this trend, showing changes not only in erectile function but also in other parameters of male sexual function.[7,8,10]

Men often take an indirect approach to expressing their sexual frustration in various ways. The IIEF-15, a 15-item, 5-domain, psychometrically validated questionnaire, is a central, valid, and reliable patient-reported outcome measurement tool to harmonise and standardise patients' complaints and responses about their sexual lives.[18] Our study revealed a 4-point increase in erectile function over six weeks compared to baseline with a daily dose of 20 g. Clinically, it is known that a minimum increase of four points in the erectile function domain score is necessary for patients to feel a benefit.[17]

Exploring the potential of some compounds from *G. kola* seeds, Ojo et al.[19] reported that some bioactive compounds, such as garcinoic acid, showed the highest binding affinity to PDE5 inhibitors, thus showing greater potential in erectile dysfunction management. *G. kola* has also been reported to increase blood testosterone levels.[7] These compounds, similar to those found in our study during extraction, showed active principles with therapeutic attributes present in *G. kola* extracts for managing erectile dysfunction, leading to increased cyclic guanosine monophosphate (cGMP) levels.[19]

It is not irrelevant to remember the biochemistry and physiology of an erection. The result of sexual stimulation is a release of the smooth muscle relaxant, nitric oxide (NO), from endothelial cells. NO diffuses into the smooth muscle cells of the corpora cavernosa, where the main determinant of smooth muscle contraction, known as cGMP, is synthesised. cGMP is hydrolysed and inactivated by the intracellular enzyme PDE5. The PDE5 inhibitors currently used to treat erectile dysfunction inhibit cGMP breakdown by increasing the availability of cGMP and promoting the erect state.[20,21]

Furthermore, studies have reported that the inhibitory activities of *G. kola* extracts may be attributed to their phenolic and flavonoid

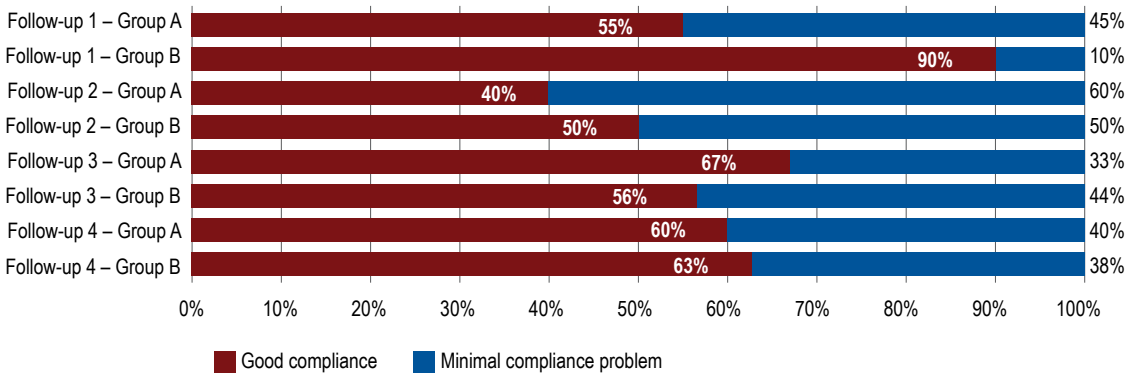


Figure 5: Patient compliance during treatment

components, such as garlic, garcinoic acid, catechin, and delta-tocotrienol, which improve erectile function.[19,22] NO interacts with superoxide to form highly toxic radicals, such as peroxynitrite, leading to decreased removal of superoxide radicals. This reduces the available NO concentration, leading to erectile dysfunction.[23] On the other hand, excessive production of NO has also been implicated as a possible cause of direct cavernosal damage. Excessive NO can be generated in the corpora cavernosa. This increases the formation of peroxynitrite, leading to cytotoxic effects on the cavernosal muscle, especially under inflammatory conditions, such as Peyronie's disease, penile trauma, and priapism.[23,24] This demonstrates the relationship between erectile dysfunction and oxidative stress due to the excessive generation of free radicals in cavernosal tissues, as described in previous reports.[25,26]

Polyphenol compounds, abundant in plant-based human diets like *G. kola,* are antioxidative agents that inhibit free radicals/reactive oxygen species.[24] Many flavones, isoflavones, biflavones, flavonols, flavonoid, glycosides, phenylethanoid glycosides, phenolic acids, prenylated flavonols, and xanthones have been identified as potential PDE5 inhibitors from herbal sources.[27] This finding supports previous studies suggesting that *G. kola* extracts inhibit the activity of enzymes involved in erectile dysfunction and are potential candidates for managing this condition.[19,28] Some of these compounds exhibited a good binding affinity for PDE5.[19] They also comply with Lipinski's rule of five; it is a rule of thumb to evaluate drug-likeness or determine if a chemical compound with a certain pharmacological or biological activity has chemical properties and physical properties that would likely make it an orally active drug in humans.[19,29,30]

*G. kola* belongs to the Guttiferae/Clusiaceae family and has been referred to as a "wonder plant" because almost every part of the tree has medicinal value.[11] It is also called "male kola" owing to its aphrodisiacal effect on men.[31] Iwuji et al.[32] reported that *G. kola* seed meal improved sexual desire and semen characteristics in mature rabbit bucks. *G. kola* (20 ± 1 g) significantly improved sexual behaviour in our trial. A literature review on the efficacy of *G. kola* treatment on sexual behaviour in male Wistar rats revealed an increase in the arousal component (i.e. mount and intromission latencies), libido, erectile response, ejaculation, and copulatory efficiency until 50 days after the beginning of treatment. This aspect of sexual behaviour is highly dependent on androgens, and this observation may be attributed to the increase in testosterone levels described by these investigators.[33] However, on several occasions, studies have reported that sexual desire is multifaceted, depending on contextual, biological, psychological, relational, and sociological factors.[34,35]

Regarding vital parameters in both groups, arterial blood pressure, heart rate, and respiratory rate remained stable throughout the study. Notably, one hypertensive patient was withdrawn from the study because of unstable blood pressure. This was, as we understand it, an isolated case. Moreover, earlier reports revealed that flavonoids, compounds of *G. kola,* have antihypertensive and cardiovascular effects and reduce cardiovascular disease progression.[36-39] Recently, in addition to the various medicinal properties of *G. kola* seeds, their hypoglycaemic effects have been established.[40,41] However, this biological parameter did not vary significantly during the trial.

A recent and long-standing review of the literature on the therapeutic properties of bitter kola is of interest to several regions and systems of the body. In addition to its medicinal effects, *G. kola* has already been described as a "wonder plant", according to Dalziel, in the first half of the 20th century.[42] Other researchers have gone even further, describing the plant as an anti-poison that detoxifies the body.[31,43] However, consuming *G. kola* as a pharmacological product has potential side effects. Although these effects are rare, if documented at all, the present study recorded two signs (vomiting and asthenia) whose intensity was not severe enough to require treatment discontinuation in the two groups evaluated.

### *Study limitations*

This study had limitations that could influence our findings. Our main limitation for this trial is its single-blind design because double-blinding was not achieved as patients instantly recognised the taste of *G. kola*. The use of a control dose instead of a placebo arm or PDE5 inhibitors may explain why around a fifth of participants dropped out. We also have a bias on the satisfaction of men whose erectile function was improved by bitter kola. Additionally, we could not control or standardise the participants' living environments while receiving treatment.

## Conclusion

*G. kola* nuts may improve erectile dysfunction and may be an alternative option for men suffering from mild erectile dysfunction. Long-term studies with a large cohort and optimal dosage are needed to confirm this trend.

### *Conflict of interest*

The authors declare no conflict of interest.


### *Funding source*

None.


### *Ethical approval*

The Institutional Ethics Committee of the Université des Montagnes (Ref N° 2023/027/UdM/PR/CEAQ). Trial registration: Pan African Clinical Trial Registry, identifier PACTR202310817915957.


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