J. Plant Environ. 06 (01) 2024. 41-50 DOI: 10.33687/jpe.006.01.4837

Available Online at EScience Press

Journal of Plant and Environment

ISSN: 2710-1665 (Online), 2710-1657 (Print)

https://esciencepress.net/journals/JPE

Gamma Irradiation Induced Erectile Dysfunction in Cellular System of Rats: Protective and Ameliorative Roles of *Adansonia digitata* and *Corchorous olitorius* Leaves Based Diet

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ARTICLE INFO

Article History
Received: December 03, 2023
Revised: March 07, 2024
Accepted: March 21, 2024

Keywords
Protective
Ameliorative
Gamma irradiation
Phosphodiesterase-5
Nf-kB
A. digitata
C. olitorius
Leaves-based-diet
Free radical
Nutraceuticals
Erectile dysfunction

ABSTRACT

Gamma irradiations exacerbate reactive oxygen (RO) and reactive nitrogen species (RNS) generation in cellular system of rats. ROS/RNS increased nuclear factor kappa-B (Nf-kB) level, such that, it has been implicated in increased phosphodiesterase-5 (PDE-5) activities. An increased PDE-5 activities have been implicated in erectile dysfunction. Several PDE-5 inhibitors have been in use, but have come with deleterious side effects, hence, there is need to have safe and natural PDE-5 inhibitors. Hence, this study investigated the protective and ameliorative effects of *A. digitata* and *C. olitorius* leaves based-diet on gamma irradiation-induced erectile dysfunction. A total of 48 Wistar rats (190±10g) were grouped into 8 groups of 6. Except for group I, all other groups were exposed to 6 grey gamma irradiation; Groups I and II were fed with leaves-free formulated diet and water only, groups III, IV and V were fed with leaves-based-diet of *A.digitata*, *C. olitorius* and combination before they were exposed to irradiation, whereas groups VI, VII and VIII were exposed to irradiation before they were fed with the leaves-based-diet respectively. The rats were sacrificed, tissues and blood were collected for PDE-5 and Nf-kB assays. Radiation significantly ($p<0.05$) increased the activities of PDE-5 and Nf-kB concentration in rats. Administration of the *A. digitata* and *C. olitorius* leaves based-diet significantly ($p<0.05$) reduced PDE-5 activities and Nf-kB concentration when compared with the irradiation control group. It can be concluded that leaves of *A.digitata* and *C.olitorius* may be used against erectile dysfunction.

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INTRODUCTION

Irradiation is capable of generating high concentration of reactive oxygen and nitrogen species (ROS/RNS) in the cellular system of Human (Ismail, *et al*., 2015). An increased ROS/RNS further exacerbates oxidative stress and cellular alterations (Haliwell, *et al*., 1995). A recent work by Airaodion *et al*., (2019) has lent credence to the role of ROS/RNS in possible erectile dysfunction. This work explains how radiation from phone placed together with raw egg rapped in a polytene bag, cooked the egg. He then infers such effect to how radiation from phone (placed in the pocket) could cause changes to the structure-functions of the male scrotums, by extension possibly altering male sexual functions.

An increased ROS/RNS, have been implicated in the activation of nuclear factor kappa-B (Nf-kB) through the activation of membrane kinases that phosphorylate inactive Nf-kB for activation (Derosa, *et al*., 2022). Nf-kB is located in the cytosol in an inactive form and it is

inhibited (repressed) by IkB (inhibitory kappa-B) such that it prevent it translocation into the nucleus where it bind to the DNA binding region (DBR) of genes expressing for Phosphodiesterase-5 (PDE-5) and other pro-oxidant proteins (prostaglandins, cyclooxygenase-2, inducible nitric oxide synthase, hexokinase-2 BCL-2, IL-2 BAX) that are capable of exacerbating erectile dysfunction (Derosa, *et al*., 2022). Increased Nf-kB activation will increase PDE-5 expression and activities. PDE-5 is a member of the PDE family, (PDE-5) is one of the well-studied phosphodiesterases (PDEs) that specifically targets cyclic guanosine mono phosphate (cGMP) typically generated by nitric oxide (NO)-mediated activation of the soluble guanylyl cyclase (Takimoto, *et al*., 2005). thus,n the crucial role of cGMP in erectile function, specifically PDE-5 targets cGMP (Talalay, *et al*., 2003) by catalyzing the hydrolysis of phosphodiester bond in cGMP through its catalytic domain, thereby converting cGMP to the inactive 5'-GMP form, thus weakening erection and other sexual processes (Rohini, *et al*., 2009P). Pharmacological inhibition of PDE-5 has been demonstrated to attenuate any possibilities of erectile dysfunction (Branda, *et al*., 2004).

PDE-5 has largely been implicated in erectile dysfunction. Several therapeutic agents have been in place to inhibit the activities of PDE-5 and manage erectile dysfunction, some which are sildenafil, tadalafil, verdenafil and vardenafil-based analogues (Adair, *et al*., 2000). But have come with one or more side effects. Commonly reported side effects of sildenafil and other PDE-5 inhibitors include dyspepsia, headache, visual disturbance and flushing (Lewanda, *et al*., 2007). Other side effects include epistaxis, insomnia, nasal congestion, and rhinitis (Adair, *et al*., 2000), hence there is need for a natural product that is part of our daily food to act as PDE-5 inhibitors, because most sexual dysfunction patients lack strict adherences to daily drugs dose aside from other associated effect. Several plant products such as vegetables, fruits and bark of trees have been reported by folklore medicine in the treatment and management of erectile dysfunction, but no scientific report on their plant-based diet. The therapeutic effects of herbal remedies in the area of erectile dysfunction have been validated in numerous scientific studies and journals. Even today, plant materials continue to play major roles in primary health care as well as in many diseases. Several plant materials including fruits (Orange, Pawpaw, Apples), vegetables (*Occimum grattisimum*, *Sida acuta*) have been employed in the treatment or management of PDE-5' induced erectile dysfunction, but there is no scientific report that have validated the use of leave-based diet in the treatment or management of radiation induced erectile dysfunction. Therefore, creating a leave-based diet is opening the way to creating a nutraceutical against erectile dysfunction.

Corchorus olitorius (Linn) is a leafy vegetable that belongs to the family Tiliaceae. It is known as Jute mallow in English and *Ewedu* in Yoruba, *Oyoor* in Edo (Ajayi, *et al*., 2010). The leaves (either fresh or dried) are cooked into a thick viscous soup or added to stew or soup and are rich sources of vitamins and minerals (AOAC, 1990) with various therapeutic uses in herbal medicine. The leaves extracts have been reported to possess anti-hypertensive, anti-diabetic, anti-malarial, hepatoprotective, anti-microbial, anti-inflammatory, analgesics, anti-diarrhea, anti-viral, anti-carcinogenic and anti-mutagenic properties (Ajayi, *et al*., 2010).

A. digitata is a member of the baobabs' family and commonly known as *Kukah* in Hausa, *Luru* in Yoruba and *tree of life* in English (Kamani, *et al*., 2008). The leaf of the baobab tree is food for many populations in Africa, especially the central region of the continent. *Adansonia digitata* is a commonly used traditional plant which are consumed in food or used in the direct treatment of several diseases such as anemia, diabetes, lipid peroxidation disorders, ischemia reperfusion diseases and inflammatory bowel syndrome in South-west Nigeria (Kamani, *et al*., 2008). The powdered leaves are used as a tonic, anti-asthmatic, antihistamine and anti-tension properties. The leaves are also used to treat insect bites, guinea worm, internal pains, dysentery, and diseases of the urinary tract, ophthalmic and otitis. Baobab leaves are used medicinally as a diaphoretic, astringent, expectorant and as a prophylactic against fever (Nwozo and Bello, 2015). The carotenoid content of baobab leaves has also been established to contribute to the prevention of oxidation in the human cell and lots of other diseases. Thus, the present study investigated the protective and ameliorative effects of *A. digitata* and *C.olitorius* leaves-based diet on irradiation-induced erectile dysfunction in Rats.

MATERIAL AND METHODS

Plant materials and authentication

Fresh leaves of *Adansonia digitata* and *Corchorus olitorius* leaves were purchased from 'Ipata' Market, Ilorin, Kwara

State, Nigeria. The plants were authenticated at the Herbarium Unit of the Department of Plant Biology, University of Ilorin, Kwara State. Voucher Specimen Number for *Adansonia digitata* and *Corchorus olitorius* (UICH/001/951 and UITH/002/154) were deposited in the Herbarium respectively.

Experimental animals

A total of 48 rats (190 ± 5.00 g) were obtained from the Animal Holding Unit of the Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. The rats were housed in clean cages and well-ventilated house conditions (Temperature: 28-30°C), (Photoperiod; 12hr light, 12hr dark), (Humidity: 45-55%). They were fed with leaves-free pelletized-formulated feed and clean tap water which were provided before and during administration of leaves-based diet.

Drugs, chemicals and assay kits

The assay kit for Nf-kB and PDE-5 is a product of Cayman Laboratory LTD., USA. All the chemicals were prepared in all-glass distilled water.

Secondary metabolite constituents of *Adansonia digitata* and *Corchorus olitorius*

Qualitative and quantitative secondary metabolites screening of *A. digitata* and *C. olitorius* leaves were determined, by using the methods by Mahajan, (1997). All determinations were made in triplicates.

Feed formulation

The following feed constituents as shown in Table 1 were added together in the quantity arrived at in Table 3 by putting into consideration the proximate analysis result in Table 2.

Table 1. Feed constituents and sources.

Feed Constituents	Sources
Corn starch: was prepared using yellow Corn: source of starch	Obtained from 'Oja-Tuntun' Market, Ilorin, Kwara State, Nigeria
Vitamins-mineral mix: Source of essential vitamins	Product Ahirma, India
D-methionine and L-Lysine: Source of amino acid	Product Ahirma, India
Maize husk: source of cellulose	Was purchased and milled in Olufadi Market, Ilorin
Soybean oil: source fat and oil	Was purchased and milled in Olufadi Market, Ilorin
Pulverized leaves of *Corchorus olitorius*	At 80 % inclusion
Pulverized leaf of Adansonia digitata	At 80% inclusion

Note that 80% leaves inclusion into the diet, were arrived at from a previous study that compared varying percentages such as 20, 40 and 80% inclusion**.** 80% is the most effective of the doses.

Feed composition

As shown in Table 3, the yellow corn was washed with clean water, dried at room temperature for 7 days and grinded with grinding machine (Steelman K207, H.M and co Ltd, China). The Maize husk was also grinded to shaft (50% grinding) with grinding machine (Steelman K207, H.M and co Ltd, China). Soybean was grinded with grinding machine (Steelman K207, H.M and co Ltd, China) to powdered form. Soybean oil of 500ml was added to the mixture. Vitamin and Mineral mix were added adequately with respect to the result of the proximate analysis in Table 2. D-methionine and L-lysin were adequately added. The pulverized leaves of *A. digitata* and *C. olitorius* were adequately added to the mixture in 80% inclusion.

Table 2. Formulation of *Adansonia digitata* and *Corchorus olitorius* leaves-based diets.

Ingredients	Control diet	*A. digitata* based diet (80%)	*C. olitorius* based diet (80%)	ADCO based diet (80%)
Corn Starch	512	102.40	102.40	102.40
Soybeans	250	250	250	250
Soy Oil	40	40	40	40
Maize Husk	40	40	40	40
Vit/Min Mix	50	50	50	50
Sucrose	100	100	100	100

D-Methione	4	4	4	4
L-lysin	4	4	4	4
A. digitata	-	409.60	-	204.80
C. olitorius	-	-	409.60	204.80
Total	1000	1000	1000	1000

ADCO: *A. digitata + C. olitorius*

Compounded diets were administered to experimental animals *ad libitum* for a period of 2 weeks. Forty (48) albino rats were randomly selected into 8 groups of 6 animals each. The groupings were distributed in tables below.

Animal exposure to radiation and induction of cellular alterations

Experimental rats were exposed to single dose of 6 grey whole-body gamma radiation by the method described by Oladiji *et al*., (2007) which was briefly modified by Bello *et al*., (2017). The experimental animals were kept in a carton cage with holes made round the carton for ventilation (carton was used to restricts the movement and ensure uniform exposure of rats to radiation) instead of the usual radiation exposure coat that was used by Oladiji *et al*., (2007). Radiotherapy Machine with Cobalt 60 was the source of radiation. The exposure was carried out in the Department of Radiotherapy, Radiation unit, College of Medicine, University of Ibadan, Ibadan, Nigeria. The radiation exposure was done in two phases; the ameliorative groups, the rats were exposed to radiation and then fed with the *Adansonia digitata* and *Corchorus olitorius* leaves-based-diet. While for the protective, the rats were initially fed with *Adansonia digitata* and *Corchorus olitorius* leaves-based diet before they were exposed to radiation.

Animal groupings and administration of leaves-based diets

Animal groupings are presented in Table 3.

Table 3. Animal groupings.

Animal Grouping	Treatment
Positive Control	Non-irradiated and fed with normal rat chow
Negative Control	Irradiated and fed with normal rat chow
80-FBAD-IR	Fed with *A. digitata* based diet before Irradiation
80-FBCO-IR	Fed with *C. olitorius* based diet before Irradiation
80-FBADCO-IR	Fed with combined *A. digitata* + *C. olitorius* based diet before Irradiation
IR-80-FBAD	Irradiated before been fed with *A. digitata* based diet
IR-80-FBCO	Irradiated before been fed with *C. olitorius* based diet
IR-80-FBADCO	Irradiated before been fed with combined *A. digitata* +*C. olitorius* based diet

AD; *A. digitata,* CO*: C. olitorius,* ADCO*: A. digitata + C. olitorius,* 80*: 80% inclusion;* FB; feed based.

Ethical approval

Ethical approval was obtained from the University of Ilorin Ethical Committee, University of Ilorin. The ethical approval number was obtained as follows UERC/ASN/2018/1409 on the 13th of September 2018. The study was conducted following the guidelines on the care and use of laboratory animals.

Assays and parameters determined on irradiated rats fed with *A. digitata* and *C. olitorius* leaves-based diet

Assay parameters and scientific procedure is presented in Table 4.

Table 4. Assay parameters and associated scientific procedure followed.

Assays	Procedure and References
Nf-kB	ELISA: adopting the method by Cayman *et al.* (2003)
Phosphodiesterase-5 (PDE-5)	ELISA: adopting the method by Cayman *et al.* (2003)

Data analysis

Data were expressed as mean ± SEM of 6 determinations, except otherwise stated. All results were statistically analyzed using Duncan Multiple Range Test and complemented with Student's t-test. Statistical Package for Social Sciences, version 21 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Statistical significance was set at 95% confidence interval (Yakubu *et al*., 2017).

RESULTS

This table shows the proximate composition of *A.digitata* and *C. olitorius* Leaves in percentage. This was considered in the feed formulation in Table 5.

Table 5. Proximate composition of *A.digitata* and *C. olitorius* leaves.

Plant Sample(s)	Moisture Content (%)	Crude Protein (%)	Crude Fibre (%)	Total Ash (%)	Crude Fat (%)	NFE (%)	Total (%)
A. digitata	10.75± 0.05	21.87±0.01	8.80±0.09	15.96±0.14	3.84±0.06	38.33±0.61	100
C. olitorius	11.20± 0.11	22.31±0.02	9.40 ±0.10	14.28±0.13	3.72±0.16	39.54±0.05	100
A. digitata + C. olitorius	10.80±0.17	20.46±0.14	10.0±0.21	14.40±0.03	3.31±0.01	41.03±0.02	100

NFE: nitrogen free extract.

Secondary metabolite constituents of *Adansonia digitata* and *Corchorus olitorius* leaves

The secondary metabolites constituents of *Adansonia digitata* and *Corchorus olitorius* leaves as shown in table 6 revealed the presence of saponins, alkaloids, polyphenols, tannins, steroids and terpenoids. anthraquinone, cardiac glycosides and phlobatannins were absent. The screening revealed that tannins were the most abundant (198.98 mg/L) in *Adansonia digitata* and polyphenols (203.14 mg/L) the most in *Corchorus olitorius* respectively as shown in Table 6.

Table 6. Secondary metabolite constituents of *A. digitata* and *C. olitorius* leaves.

Metabolites	*Adansonia digitata*	*Corchorus olitorius*
Alkaloids	78.76±0.43	72.36 ± 2.05
Anthraquinone	ND	ND
Cardiac glycosides	ND	ND
Flavonoids	13.42±1.03	104.81 ±0.18
Polyphenols	147.90±0.68	203.14±0.32
Phlobatannins	ND	ND
Saponin	16.59±1.85	22.17± 0.24
Taninn	198.98±0.14	127.40±0.16
Steriods	30.45±0.51	12.59 ±1.85

ND: not detected.

Effects of *A. digitata* and *C. olitorius* leaves-based-diet on PDE-5 activities of rats irradiated rats

As shown in Figure 1a and b, the 6 grey whole-body gamma radiation significantly ($p<0.05$) increased the activities of PDE-5 in both protective and ameliorative when compared to the non-irradiated control rats. Administration of *Adansonia digitata* and *Corchorus olitorius* leaves-based diet to irradiated rats significantly ($p<0.05$) decreased the activities of PDE-5 of the rats, when compared with the control group. The decreased level of PDE-5 activities after the administration of the leaves-based diets was mostly effective in the groups given the combination of the two leaves-based diet at 80% inclusion as shown in Figures 1a and b.

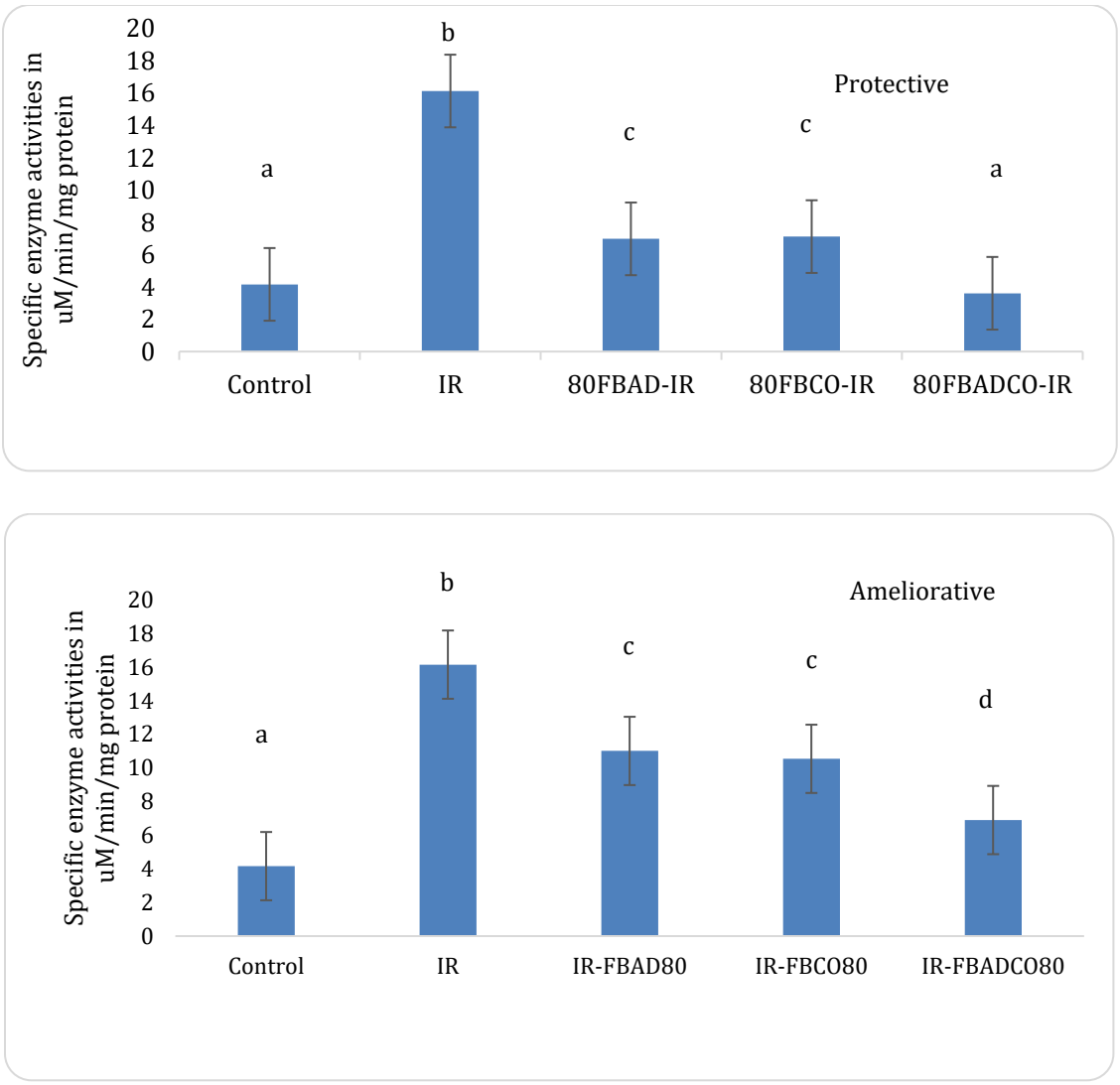

Figure 1a and b. Effects of *A. digitata* and *C. olitorius* leaves-based diet on PDE-5 activities of irradiated Rats. Means ± SEM; n=6, (P < 0.05) Values are expressed as Means ± SEM; n=6, (P < 0.05)
80-FBAD-IR= fed on 80% inclusion feed-based *Adansonia* before exposure to irradiation-
80-FBCO-IR = fed on 80% inclusion feed-based *Corchorus* before exposure to irradiation
80-FBADCO-IR= fed on 80% inclusion feed-based *Adansonia + Corchorus* before exposure to irradiation.

Effects of *A. digitata* and *C. olitorius* leaves-based diet on Nf-kB status of Rats irradiated rats

As shown in Figure 2a and b, that Exposure of rats to 6 grey whole-body gamma radiation have significantly ($p<0.05$) increased the radicalized Nf-kB in both protective and ameliorative when compared to the non-irradiated control rats. Administration of *Adansonia digitata* and *Corchorus olitorius* leaves-based-diet to irradiated rats significantly ($p<0.05$) reduced Nf-kB level of the rats when compared with the irradiated non-administered control rats (IR-Control rats). The decreased level of Nf-kB after the administration of the leaves-based diets is mostly effective in the groups given the addition of the two leaves-based-diet at 80 % inclusion.

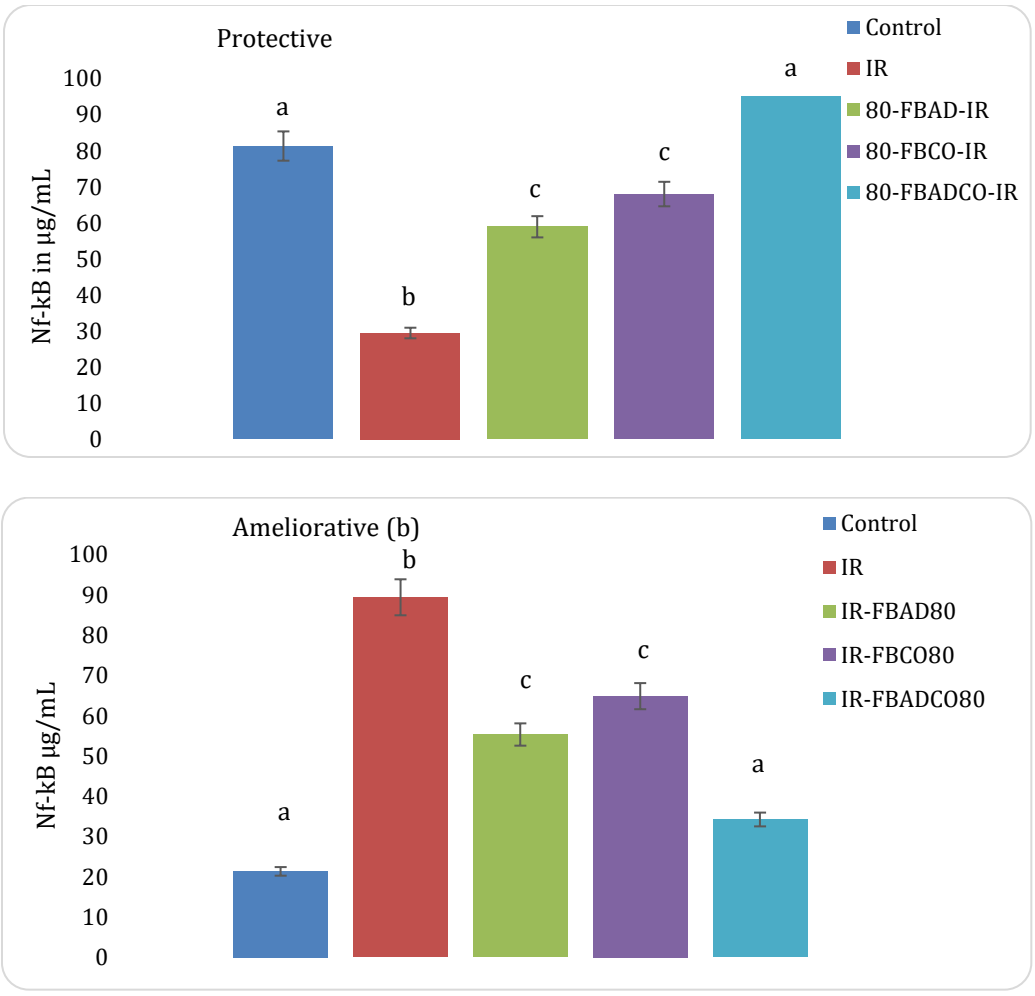

Figure 2a and b. Nf-kB status of gamma-irradiated Rats fed with *A. digitata* and *C. olitorius* Leaves-based diet.
Means ± SEM; n=6, (P < 0.05) Values are expressed as Means ± SEM; n=6, (P < 0.05)
80-FBAD-IR= fed on 80% inclusion feed-based *Adansonia* before exposure to irradiation-
80-FBCO-IR = fed on 80% inclusion feed-based *Corchorus* before exposure to irradiation
80-FBADCO-IR= fed on 80% inclusion feed-based *Adansonia + Corchorus* before exposure to irradiation.

DISCUSSION

The quality of the fiber contents of diet speaks volume of the digestibility of such diet (Bello, *et al*., 2017) have associated the high fiber content of *Ocimum gratissimum* based diet to the increase in peristaltic movement of the gastrointestinal tracts (GIT) of rats fed on the diet. An increase peristaltic movement of the GIT has been associated with increased food digestibility and increase in ghrelin hormone (Burnett, 2005). In the present study, the whole leaves were mixed with the formulated feed, suggesting an increase fiber content in the feed and may also suggest the increase food digestibility as observed in the weight of the rats.

Many of the pharmacological effects associated with most medicine plants have been linked to the presence of the bioactive constituents and the proximate composition in those plants (Cui, *et al*., 2015). Bioactive constituents such as polyphenols, have been implicated in the anti-anemia properties of sorghum bicolor by Quadri and Yakubu, (2015), flavonoids have also been implicated in the protection against possible atherosclerosis by Quadri and Yakubu, (2016), saponins is a major constituent of broom weeds and have been implicated as a major blood purifier by Adebo *et al*., (2018), alkaloids have been implicated as a major anticancer by Bellary *et al*., (2021), Burnett, (2005) have adduced the presence of polyphenol and flavonoids in the *Chasmanthera dependens* in it fertility enhancing potentials of the root (Cui, *et al*., 2015) have implicated the presence of flavonoids in *Chasmanthera dependens* root in the management of sexual dysfunction

in rats by lowering phosphodiesterases activities (Ganapathy *et al*., 2021) increased fiber content have also implicated in the treatment of sexual dysfunction by *Telfaria occidentalis*. As shown in this study, there were appreciable amounts of flavonoids, polyphenols, saponins, alkaloids, steroids and tannins in the leaves of *Adansonia digitata* and *Corchorus olitorius*, so also are the fibre content, protein composition and fatty acid composition, suggesting that the two plant can be used in the treatment and management of sexual dysfunction and lowering of the phosphodiesterases activities and related diseases.

Radiations have been implicated in the exacerbation of reactive oxygen and nitrogen species (ROS/RNS) (Dell'Agli, *et al*., 2006). An exacerbated ROS/RNS has been implicated in the dysregulation of PDE-5 activities by increasing its activities (Ganapathy *et al*., 2021). An increased free radical level will lead to an increased Nf-kB level in rat system (Giro and Ferrante, 2026). Increase Nf-kB concentration will increase PDE-5 activities, thus increasing the hydrolysis of cGMP to soluble 5' GMP, thus increasing possibilities of erectile dysfunction (Huang and Lie, 2013). Polyphenol has been implicated in the stabilization of reactive intermediate (ROS/RNS) and in the scavenging of free radicals, hence preventing the formation of ROS/RNS that might exacerbate PDE-5 activities (Kamatou *et al*., 2011). When this happens, the conversion of cGMP by PDE-5 will have been impaired, thus preventing sexual dysfunction. The leaves of *Adansonia digitata* and *Corchorus olitorius* contained significant ($p<0.05$) amount of polyphenols, which might be responsible for the protection and amelioration against increased PDE-5 activities and Nf-kB concentration in irradiated rats.

Flavonoids have been scientifically validated to scavenge free radicals and stabilize reactive intermediates. Flavonoids reduces the production and activation of Nf-kB by preventing free radical chain reaction in rat fed with castor oil (Kim and Kass, 2017). When Nf-kB production is prevented, the activation of PDE-5 might be significantly reduced (Kim *et al*., 2021). Established that Nf-kB is an activator of PDE-5. So, when the production of the activator is halted, it will affect the activities of PDE-5, thereby preventing the hydrolysis of cGMP to simple GMP, hence preventing sexual dysfunction. The significant ($P<0.05$) amount flavonoids in *Adansonia digitata* and *Corchorus olitorius* can be adduced to the protection and amelioration against increased PDE-5 activities and Nf-kB concentration. Where the most effective of the dose given is that with the combination of the two leaves. From the result obtained above and coupled with several scientific validation, we can therefore conclude that *Adansonia digitata* and *Corchorus olitorous* can be used as oral remedy(nutraceuticals) in the treatment and management of sexual related diseases such as sexual and erectile dysfunction.

ETHICAL APPROVAL

Ethical approval was obtained from the University of Ilorin Ethical Committee, University of Ilorin. The ethical approval number was obtained as follows UERC/ASN/2018/1409 on the 13th of September 2022. The study was conducted following the guidelines on the care and use of laboratory animals.

COMPETING INTEREST

There are no conflict and competing interest among the authors and none with any organization. The research is self-funded.

AVAILABILITY OF DATA AND MATERIALS

The Data and Materials used are available and will be presented when requested.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by BELLO, Olamilekan Kabir, *SHIPEBI, Omotayo Henrietta, LUKMAN, Samiatu and SAMUEL, Joseph Asuku*. The first draft of the manuscript was written by BELLO, Olamilekan Kabir and proof-read by Salawu Musa Oyewole.

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