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Research Article

In-vivo and *In-silico* Investigations on Goron Tula (*Azanza garckeana* F. Hoffm), a Booster of Female Sexual Arousal and Vaginal Lubrication

Ben E. Ehigiator[1*], Raphael I. Okoli[2], Nkem G. Ndubueze[1], Omotayo O. Ebong[1]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Madonna University, Elele, Rivers State, Nigeria; [2]Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, Ambrose Alli University, Ekpoma, Nigeria

ABSTRACT

Female sexual arousal and vagina lubrication are core complexes in achieving and enjoying a desirable sexual life in females. It has been noticed that female sexual arousal disorders have been kept away from public discus and statistics because of the lack of boldness on the part of women in speaking up about it, poor collation of medical cases, and the African mentality that tends to forbid women from being outspoken on sexual satisfaction. *Azanza garckeana*, a fruit native to northern Nigeria, is being used in traditional settings in diverse female sexual disorders and conditions.

This study was designed to evaluate *in-vivo*, the female sex-enhancing claim of the plant. The study examined the vaginal width, ear twitching, and vagina lubrication in *A. garckeana* treated *Oryctogalus cuniculus* (American rabbit). Use of *In-silico* studies to dock previously identified secondary metabolites against targets and enzymes associated with female sexual arousal and vagina lubrication.

The results show that the aqueous extract of *A. garckeana* caused a significant increase in the vagina width and lubrication of *Oryctogalus cuniculus* and significantly enhanced vaginal muscle relaxations and vaginal secretions upon sexual stimulation. This suggests the involvement of a mechanism that involves activation of female sexual excitatory systems and inhibition of those that depress female sexual arousal, or a combination of both. These findings corroborate findings from the molecular docking studies, which suggest that gossypol may play an important role in female sexual arousal and vagina lubrication because it looks to have some affinity with the targets of consideration in this study. Therefore, gossypol may well be responsible for the sex-enhancing activity of the plant.

Keywords: *Azanza garckeana*; *Oryctogalus cuniculus*; Female sexual arousal; Molecular docking; Gossypol; Vagina lubrication

INTRODUCTION

Female sexual dysfunction refers to the persistent or recurring decrease in sexual desire or arousal, the difficulty or inability to achieve orgasm, and or the feeling of pain during sexual intercourse (dyspareunia); while Female Sexual Arousal Disorders (FASD) may refer to the recurrent inability to attain or maintain orgasm until completion of sexual activity [1]. More often than not, it is difficult to categorize female sexual dysfunction, due to the perception of many women to sex and sex-related discussions. However, the following disorders are usually considered: Sexual interest/arousal disorder, female orgasmic disorder, and genito-pelvic pain (dyspareunia), penetration disorder (vaginismus) [2].

According to Thomas and Thurston, predictors of female sexual dysfunction include physical health, number of pre-marital partners, religion and sexual orientation, communication with partners, and attitude towards sexuality [3].

There exists also a distinct disorder known as the hypoactive sexual desire disorder, which manifests as a continuous or recurrent absence of sexual fantasies, thoughts, or desire for sexual activity leading to personal distress [4].

The beginning of sexual arousal in a woman's body is usually marked by vaginal lubrication or wetness; swelling and engorgement of the external genitals, and internal lengthening and enlargement of the vagina, although wetness of the vagina can occur without arousal due to infection or cervical mucus production around ovulation [5].

There are studies to show the degree of correlation between these physiological responses and the woman's subjective sensation of being sexually aroused. The findings are that in some cases there is

Correspondence to: Ben E. Ehigiator, Department of Pharmacology and Toxicology, Madonna, University, Elele, Rivers State, Nigeria, Telephone: +234 8039335474; Email: beevee8488@gmail.com

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a high correlation, while in others, it is surprisingly low [6]. A large component of sexual desire in females is usually responsive rather than spontaneous, indicating that women respond to physical sexual stimulation or arousal rather than fantasy [5].

Azanza garckeana (F. Hoffm) commonly known as Goron tula, (kola of Hausa in Hausa, snot-apple, slime-apple, Rhodesian tree- hibiscus belonging to the family *malvaceae*, native to Botswana, Burundi, Nigeria, Zambia [7]. In Nigeria, it is grown only in Tula village of Gombe state [8]. It's a multipurpose edible fruit of tropical Africa, also an important medicinal plant commonly used in Nigeria for food and as herbal medicine [9].

A. garckeana has been reportedly used in traditional medicine for the treatment and management of more than 20 human diseases and ailments such as cough, chest pain, infertility, sexually transmitted diseases, and menstrual abnormalities [10]. Multiple classes of bioactive metabolites that include amino acids, phenols, lipids, ascorbic acid, tannins, and saponins have been isolated from *A. garckeana* [11] (Figure 1).

Phytochemical analyses have revealed that *A. garckeana* contains various phytochemical compounds such as flavonoids, amino acids, glycosides, saponins, sterols, etc.

Compared to previous knowledge in literature, this study was designed to appraise and investigate the aphrodisiac effect of *A garckeana*, and to gain insight into the potential effects by docking some of its identified compounds like Gossypol, 6,6-dimethoxygossypol, stigmasterol, e-docosyl 3-(3,4dihydroxyphenyl), acrylate: Betulinic acid, 0-naphthoquinones, Mansonones D, Mansonones E, Mansonones F, Mansonones G, Mansonones H, Azazone A, and Azazone B [12-14]. Arginine, aspartic acid, and glutamic acid, with active sites of enzymes and receptors involved in sexual function such as; Inhibition of Phosphodiesterase-5 [15,16]. Nitric oxide stimulation [17]. Activation of epithelial beta-adrenergic receptors [18]. Stimulation of Neuropeptide Y, Stimulation of melanocortin receptor 4 "MC4R", Inhibition of neprilysin, inhibition of adenosine deaminase, and stimulation of adenosine [19-22].

This study investigates *in-vivo*, the vaginal width, ear twitching, and vagina lubrication of *A. garckeana*-treated *Oryctogalus cuniculus* (American rabbit) and *in-silico*, docking identified secondary metabolites against targets and enzymes affiliated with female sexual arousal and vagina lubrication.

MATERIALS AND METHODS

Acute toxicity test

The acute toxicity test (LD50) was carried out using the Organization of Economic Co-operation and Development guidelines [23].

- *In-vivo* studies involved the use of the *Azanza garckeana* aqueous extract on female *Oryctolagus cuniculus* (American rabbit).
- *In-silico* studies involved the ligand library generation of identified secondary metabolites of *A. garkceana* and docking with targets related to female sexual libido and lubrication, by comparing compound affinity for targets, with standards.

In-vivo studies:

Collection and identification of A. garckeana: *A. garckeana*, was bought from an online social media vendor and was identified at the Pharmacognosy Department of the Faculty of Pharmacy Madonna University, Elele, Rivers State Nigeria.

Preparation and administration of A. garckeana: About 387 grams of *A. garckeana* was weighed on an electronic weighing balance (Zhengzhou Nanbei Instrument Equipment Co. Ltd.). *A. garckeana* was thereafter immersed in warm water overnight, to tenderize the fruit. The soaked *A. garckeana* fruits were pulverised into smaller particles to enable increased surface absorption. Then the fruits were soaked again in a 500 ml beaker with about 300 ml of water added, to continue the extraction and left overnight.

Upon filteration, a slimy filtrate was obtained, which was placed in a water bath and allowed to evaporate to dryness leaving behind dried gummy aqueous extract of *A. garckeana*. Weighing 31.7 grams.

Experimental animals: Twelve female rabbits (*Oryctogalus cunilicus*), weighing between 1187 and 1190 g were obtained from the Animal Farm of the Department of Pharmacology and Toxicology, Delta State University (DELSU), Abraka. They were kept in two different rabbit hutches (two rabbits per hutch) and fed with standard animal feed and clean water and allowed to acclimatize for 1 week. The female rabbits were shared into three groups. The animals were kept in line with laid down principles for animal care as prescribed in Helsinki's 1964 declaration. Ethical approval was obtained from the Department of Pharmacology and Toxicology of Madonna University, Nigeria-MAD/PHARM/21/212.

- Group A: Four female rabbits given water and feed only.
- Group B: Four female rabbits given 250 mg/Kg of *A. garckeana* extract.
- Group C: Four female rabbits given 500 mg/Kg of *A. garckeana* extract.

Vagina width and lubrication test: Prior to the administration of the extract, the diameters of the vagina for both sets of female rabbits were taken using a measuring thread. Group B animals were given 5 ml of aqueous extract of *A. garckeana* orally while those in group C, were given 10mls of aqueous extract of *A. garckeana* orally, and left for an hour to observe various onsets of action.

Statistical analysis: Data were analyzed, using Graph Pad Prism (5.01), one-way Analysis of Variance (ANOVA) followed by Dunnett's multiple tests, to compare replicate means of treated groups with control and p values<0.05, 0.001 and 0.0001 were considered significant.

In-silico studies:

Ligand library generation: Identified secondary metabolites of *A. garkceana* employed for this study were determined from published literature and were used in the creation of the ligand library. Twenty-five (25) secondary metabolites were retrieved from NCBI Pub Chem library, in Standard Database Format (2D). The ligand library generated was imported to a docking software (Maestro) and prepared using the (Schrodinger suite version 2018-1b), as described by Brooks et al [24-26].

Protein preparation: Human PDE-5 complexed with an inhibitory coligand (2.3 Å), human endothelial nitric oxide synthase laced with activator coligand (1.76 Å), Human Adenosine deaminase in complex with an inhibitory coligand, (2.00 Å), human neuropeptide Y_1 complexed with an against (2.75 Å), human neprilysin in complex with the inhibitor (2.54 Å) and human B2-adrenergic G protein-coupled receptor complexed with a stimulatory coligand (2.40 Å).

Module in Maestro 11.5 was used to prepare each protein complex. Missing hydrogen atoms, missing loop, and missing side-chains of protein structure were fixed while the added hydrogen atoms were optimized at pH 7.0. Optimized structures were then minimized using the OPLS3 force field by converging heavy atoms to Root Mean Square Deviation (RMSD) of 0.3Å [27].

2H42, 3DWB, 1NDZ, 5ZBQ, 6THP, 2RH1 respectively. Modeled Melanocortin 4 receptor, retrieved from GPCRdb. It was prepared, using the Protein Preparation Wizard as described by [27].

Pharmacokinetic parameters (ADME/TOX Prediction): The pharmacokinetic properties of the hit compounds were estimated using the Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) of the hit ligands, and predicted using the Qikprop module in Maestro 11.5 [24].

RESULTS

Acute toxicity test

Table 1 shows the acute toxicity test (LD50) results, using the method Organization of Economic Co-operation and Development guidelines [23].

Clinical toxicity symptoms such as respiratory distress, salivation, weight loss, and change in the physical appearance of hair as well as maternal mortality were not observed at any period of the experiment. The LD50 is expected to exceed 5000 mg/Kg. Doses were chosen in agreement with the work done by Yusuf, et al. using the said plant on wound healing [8].

Observable arousal sign in female rabbits

As shown in Table 2, the observable arousal signs of vaginal lubrication, ear twitching, and agility of the female rats in experimental groups were significantly higher compared to the control.

Table 1: Results of acute toxicity tests in female rabbits.

Dose	No of Deaths
10 mg/Kg	0/4
1000 mg/Kg	0/4
2000 mg/Kg	0/4
5000 mg/Kg	0/4

Table 3 shows the width change, measured with a thread. It was observed that the vaginal width increased significantly on the administration of the extract.

Scores of identified phytochemical compounds docked into the substrate-binding sites of Phosphodiesterase 5

Among the compounds docked into the substrate-binding sites of PDE-5 in comparison with an inhibitory coligand. Results showed that (-)-6-methoxygossypol and Gossypol, 6,6'- dimethoxygossypol presented with a high affinity for this target (Figure 2).

The free energy of binding of phytochemicals of *A. garckeana* docked into the substrate-binding sites of PDE-5 represented in the form of a heat map. (The scale is a spectrum from purple (-2 kcal/mol) to red (-12 kcal/mol).

Scores of identified phytochemical compounds docked into the substrate-binding sites of Endothelial nitric oxide synthase

Among the compounds docked into the substrate-binding sites of endothelial nitric oxide synthase, (an enzyme responsible for the production of endothelial nitric oxide) which was in comparison

Table 2: Effect of *A. garkeana* on observable arousal sign in female rabbits. Animals per group (n)=4.

Observable arousal signs	Untreated n	Treated 250 mg/ Kg	Treated 500 mg/ Kg
Vagina Lubrication	-	+	+
Ear Twitching	-	-	+
Agility	-	+	+

+: Presence, -: Absence

Table 3: Effect of *A. garkeana* on observable distention of vaginal diameter 1 hour post-treatment compared to pre-treatment.

Parameter	Untreated	Treated 250 mg/ Kg	Treated 500 mg/Kg
vaginal diameter (cm) pre/post difference	0.00 ± 0.00	0.36 ± 0.033***	0.50 ± 0.037***

Effect of *A. garkeana* on relative vaginal diameter. Animals per group (n)=4. The values are mean ± SEM.; ***p<0.05; when compared with the control group. (One-way ANOVA followed by Dunnett's multiple comparison test).

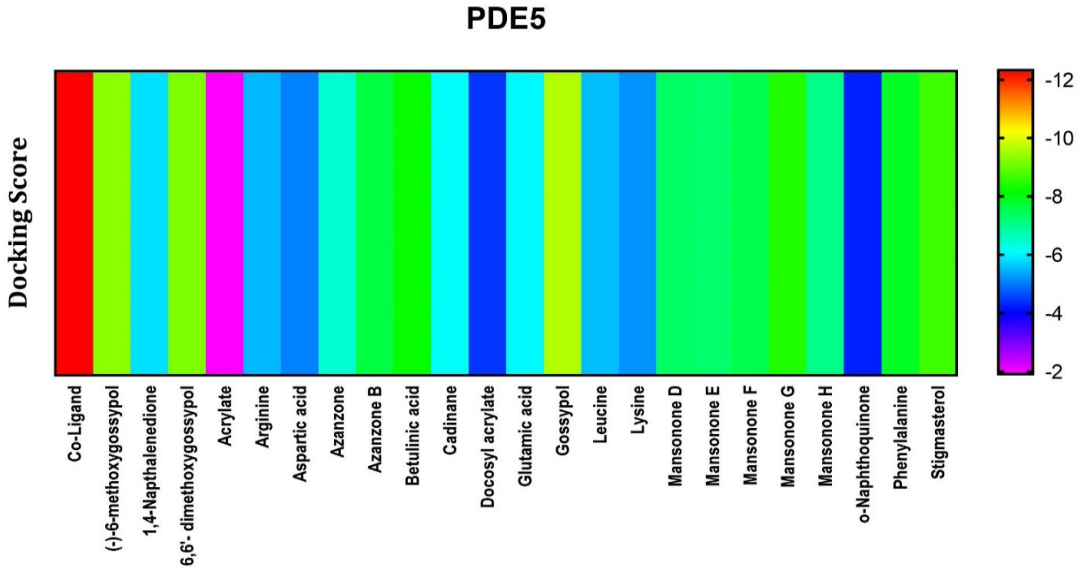

Figure 2: Heat map representation of docking results for compound interaction with PDE-5.

with a stimulatory coligand. Results showed that gossypol looked to have the highest affinity for the enzyme indicating that it may well have some viable activity on stimulation of endothelial nitric oxide synthase (Figure 3).

The free energy of binding of phytochemicals of *A. garckeana* docked into the substrate-binding sites of Human Endothelial Nitric Oxide is represented in the form of a heat map. The scale is a spectrum from purple (-2 kcal/mol) to red (-8 kcal/mol).

Scores of identified phytochemical compounds docked into the substrate-binding sites of *β*2 adrenergic receptor

Among the compounds docked into the substrate-binding sites of β2 adrenergic in comparison with a stimulatory coligand. Results showed that the azazone and mansonone compounds presented with high affinity for this target. Hence are likely to contribute to the female arousal effect by this mechanism of action (Figure 4).

The free energy of binding of phytochemicals of *A. garckeana* docked into the substrate-binding sites of β2 adrenergic represented as a heat map. (The scale is a spectrum from blue (-2 kcal/mol) to red (-10 kcal/mol).

Scores of identified phytochemical compounds docked into the substrate-binding sites of neuropeptide Y

Among the compounds docked into the substrate-binding sites of neuropeptide y, one of the most prevalent peptides in the body [28]. It plays a role in increasing dopamine levels. Dopamine is an important neurotransmitter that plays a vital role in sexual arousal; has a wide-reaching effect on the central nervous system and periphery. It also has the potency of inhibiting cortisol and ACTH release with a stress-protective effect, in comparison with a stimulatory coligand. The Result showed that Gossypol looked to have the highest affinity for the receptor (Figure 5).

The free energy of binding of phytochemicals of *A. garckeana* docked into the substrate-binding sites of Neuropeptide Y is represented in the form of a heat map. (The scale is a spectrum from purple (-2 kcal/mol) to red (-14 kcal/mol).

Scores of identified phytochemical compounds docked into the substrate-binding sites of the Melarnocortin 4 receptor

Among the compounds docked into the substrate-binding sites of MC4R in comparison with a stimulatory coligand. Results showed that (-)-6-methoxygossypol, Gossypol, and stigmasterol, presented with high affinity for this target. Hence, they are likely to contribute to the female arousal effect via this mechanism of action (Figure 6).

The free energy of binding of phytochemicals of *A. garckeana* docked into the substrate-binding sites of Melarnocortin 4 receptor is represented in the form of a heat map. (The scale is a spectrum from blue (-2 kcal/mol) to red (-6 kcal/mol).

Scores of identified phytochemical compounds docked into the substrate-binding sites of Neprilysin

Among the compounds docked into the substrate-binding sites of neprilysin in comparison with an inhibitory coligand, results showed that none of the compounds presented with high affinity for this target (Figure 7).

The free energy of binding of phytochemicals of *A. garckeana* docked into the substrate-binding sites of Neprilysin represented

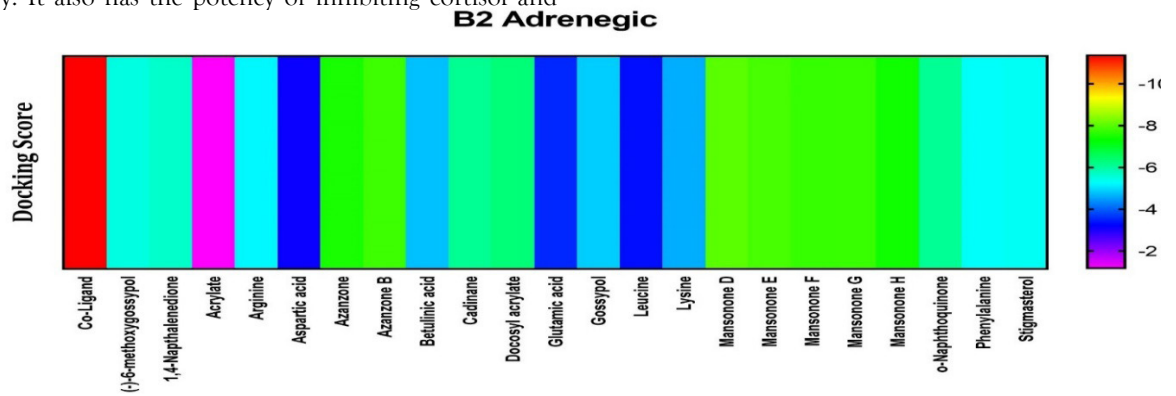

Figure 3: Heat map representation of docking results for compound interaction with Human Endothelial nitric oxide.

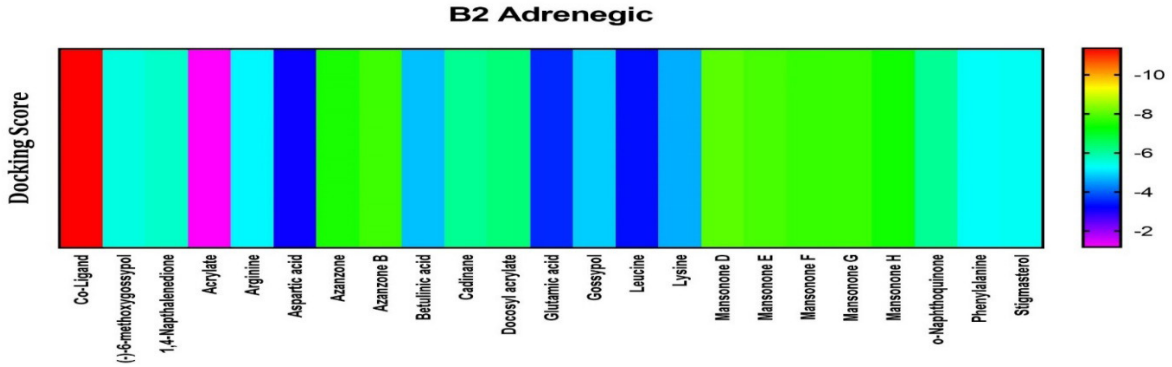

Figure 4: Heat map representation of docking results for compound interaction with β2 adrenergic.

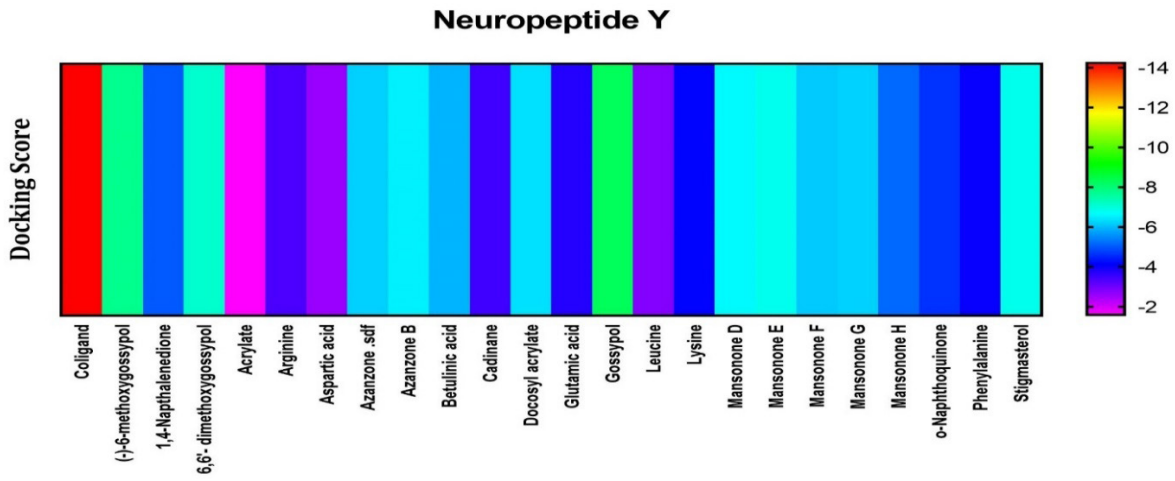

Figure 5: Heat map representation of docking result for compound interaction with Neuropeptide Y.

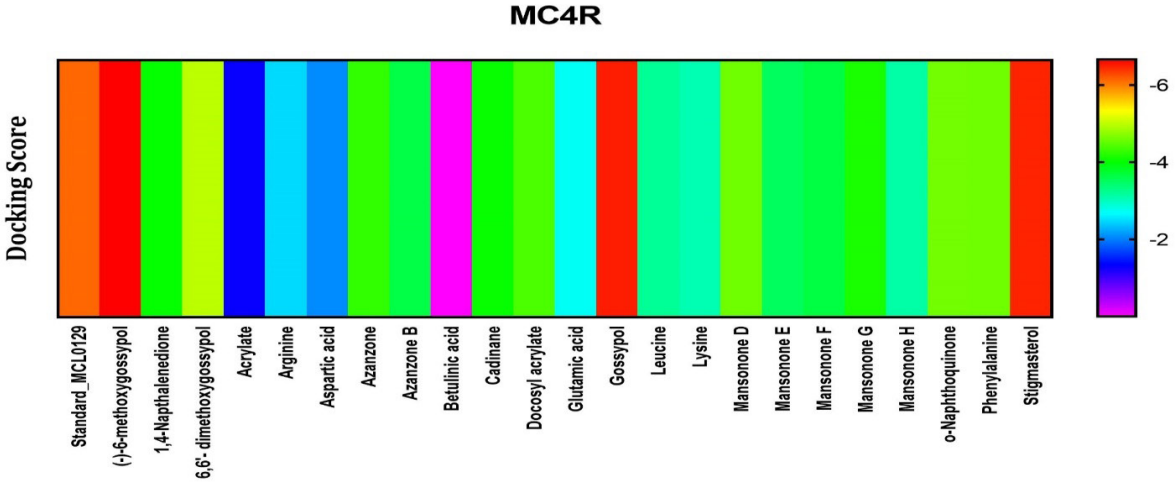

Figure 6: Heat map representation of docking results for compound interaction with Melarnocortin 4.

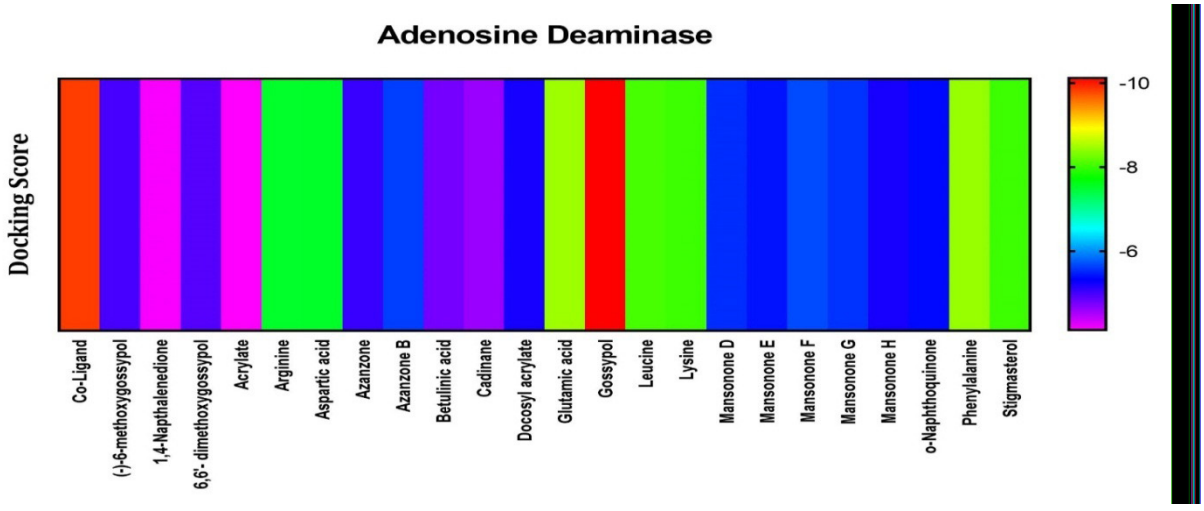

Figure 7: Heat map representation of docking results for compound interaction with Neprilysin.

in the form of a heat map. (The scale is a spectrum from blue (-4 kcal/mol) to red (-16 kcal/mol).

Scores of identified phytochemical compounds docked into the substrate-binding sites of adenosine deaminase

Among the compounds docked into the substrate-binding sites of adenosine deaminase in comparison with a coligand, gossypol looked to have the highest affinity for the enzyme. Indicating that it may well have some viable activity on inhibition of adenosine deaminase. Results showed that Phenylalanine, lysine, leucine, stigmasterol, and glutamic acid also look to have good affinities for the enzyme (Figure 8).

The free energy of binding of phytochemicals of *A. garckeana* docked into the substrate-binding sites of Adenosine deaminase is represented in the form of a heat map. (The scale is a spectrum from blue (-6 kcal/mol) to red (-10 kcal/mol) (Table 4).

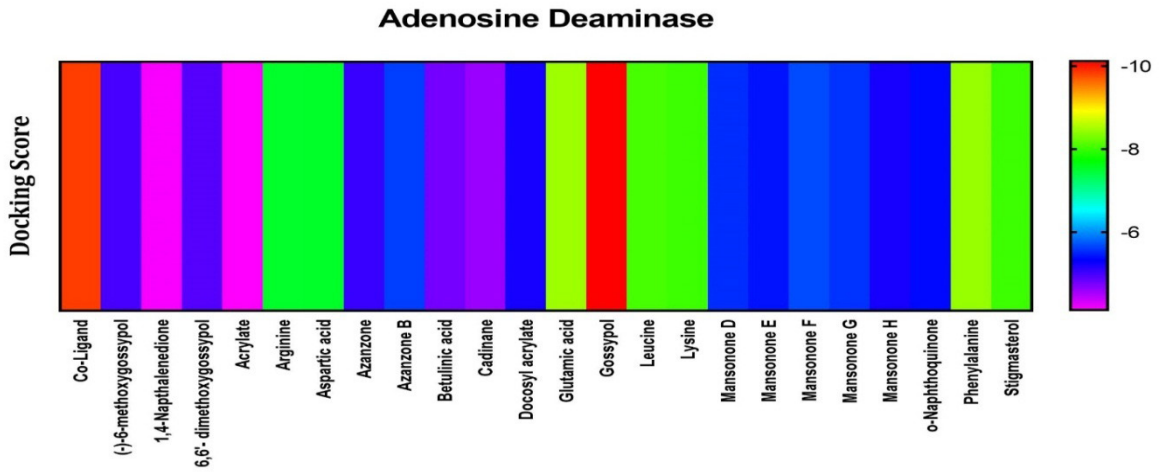

Figure 8: Heat map representation of docking results for compound interaction with Adenosine deaminase.

Table 4: Showing the pharmacokinetic/toxicological properties of compounds present in *A. garckeana*.

Entry Name	mol MW	donorHB	accptHB	QPlogPo/w	HOA	ROF
(-)-6-methoxygossypol	532.589	3	6.5	4.41	1	1
1,4-Napthalenedione	158.156	0	4	0.908	3	0
1'-OH-4-Keto-gamma-carotene	568.881	1	2.75	11.804	1	2
6,6'- dimethoxygossypol	546.616	2	6.5	5.094	1	2
Acrylate	72.063	1	2	0.128	2	0
Arginine	174.202	7	5	-3.529	1	1
Aspartic acid	133.104	3	4	-3.886	1	0
Azanzone	244.29	1	4.75	1.75	3	0
Azanzone B	258.273	1	5.5	1.315	3	0
Betulinic acid	456.707	2	3.7	6.345	1	1
Cadinane	208.386	0	0	7.049	1	1
Docosyl acrylate	380.653	0	2	8.909	1	1
Glutamic acid	147.13	4	5	-3.015	1	0
Gossypol	518.562	4	6.5	3.667	1	2
Leucine	131.174	3	3	-1.521	2	0
Lysine	146.189	5	4	-3.187	1	0
Mansonone D	242.274	0	4.75	1.646	3	0
Mansonone E	242.274	0	4.75	1.708	3	0
Mansonone F	240.258	0	4.5	1.765	3	0
Mansonone G	244.29	1	4.75	1.854	3	0
Mansonone H	258.273	1	5.5	1.354	3	0
o-Naphthoquinone	158.156	0	4	0.663	3	0
Phenylalanine	165.191	3	3	-1.145	2	0
Stigmasterol	412.698	1	1.7	7.564	1	1

MW: Molecular Weight; R.V.=130-725; donorHB: Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution; R.V.=0.0-6.0; accptHB: Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution; R.V.=2.0-20.0; QPlogPo/w: Predicted octanol/water partition coefficient; HOA: Human Oral Absorption level 1, 2, 3; 1=low, 2=medium, 3=high; ROF: The number of violations of Lipinski's rule of five

DISCUSSION

This study evaluated and validated the claim of high efficacy of *A. garckeana*, in the treatment of female sexual arousal disorder. Sexual dysfunction affects about 30%-40% of women and the lack of sexual desire is the most common complaint among them [29]. In women, sexual dysfunction tends to increase as women age, but can affect women at any stage of life [30]. It may be chronic or temporary. Factors that can lead to arousal disorders include, use of some medications such as antidepressants, drugs of addiction and alcohol abuse, conditions that impair blood flow to the vagina, gynecological conditions such as, ovarian cyst, endometrial hormonal changes, chronic disease states, and debilitating conditions such as menopausal changes, vaginal atrophy, and conditions that lead to it. These conditions may contribute to vaginismus, painful sex (dyspareunia), and low sexual desire [31].

Manifestations of hypoactive female sexual arousal disorder may include low libido or loss of interest in sexual activity, lack of pleasurable sensations even when the sexually sensitive areas are

stimulated, difficulty getting pleasure from actual sexual activities, few or no sexual fantasies at all [32]. More often than not, male sexual dysfunction and its remedy is given much more attention, while, very little attention is paid to female sexual dysfunction and its possible remedies.

In this study, the increase in vagina width in treated groups proves without doubt, that *A. garckeana* has a unique property of increasing vaginal lubrication and inducing sexual arousal and justifies its use in the traditional medicine setting to treat female sexual arousal problems.

The mechanism of *A. garckeana* female sexual arousal action is unknown, but it is likely to involve the activation of female sexual excitatory systems and inhibition of those that depress female sexual arousal, or a combination of both. These systems might include either one or more of the following: the enhancement or potentiation of the physiological actions of adenosine through the L-Arginine-Nitric oxide syntheses pathway, which induces relaxation of the female corpora and increases levels of PDE-5 in the female vagina, clitoral and labial smooth muscles, accounting for the lengthening of the width of the vagina or the activation of Melanocortin receptor. This receptor has been associated with central control of sexual behavior and is known to increase penile erection in males and receptivity in females.

Over 20 compounds had previously been identified in the plant as indicated above. Upon molecular docking with related targets to the subject of interest, it was observed that gossypol looked to have potential drug activity on the targets of consideration. It is pertinent to say that, molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding conformation of small-molecule ligands to the appropriate binding sites. Characterization of the binding behavior play important role in the rationale designs of drug and it helps to elucidate fundamental biochemical processes [33]. Gossypol is a polyphenolic aldehyde present in *A garckeana* [12,13].

This compound may well be responsible for the sexual arousal and vaginal lubrication properties of the plant, as it showed a high-affinity level to the various targets of concern.

However, previous research works have shown that gossypol may produce sterility or act as a contraceptive in males, as it is likely to inhibit spermatogenesis [34-36]. In females, gossypol administration may promote degeneration of ovarian follicles, but it is unknown whether this effect is direct or indirect [37].

The female aphrodisiac activity of this plant is somewhat a novel discovery in terms of scientific documentation, as all claims laid to it are anecdotal. This study is proposed to draw attention to the sexual arousal and vaginal lubrication properties of *A. garckeana* seed even though it justifies the use of *A. garckeana* seed as a female aphrodisiac both socially and in traditional medicine.

CONCLUSION

This study has shown that the extract of *A. garckeana* significantly enhances vaginal muscle relaxations and vaginal secretions upon sexual stimulation in rabbits, by a mechanism that may likely involve activation of female sexual excitatory systems and inhibition of those that depress female sexual arousal, or a combination of both. It is, therefore, logical to infer that it enhances the same in humans, and the likely active component for this activity in the plant is gossypol.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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