



Ameliorative Effect of *Rauwolfia vomitoria* Ethanol Extract on the Erectile Dysfunction Complicated with Coronary Artery Disease: An In-Vivo and Molecular Docking Approach

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Abstract

Erectile dysfunction in men may result as a side effect of the use of serotonin reuptake inhibitors such as paroxetine. Enzymes like phosphodiesterase 5 (PDE-5) and arginase are promising therapeutic targets for managing erectile dysfunction while creatinine kinase-myocardial band (CK-MB) serves as a marker for coronary artery disease. To manage these conditions, it is necessary to seek options in medicinal herbs. *Rauwolfia vomitoria* (RV) is a plant that has been used as an aphrodisiac but the inhibitory mechanism against these enzymes remain unclear. The study used in-vivo enzymatic biomarkers and [molecular docking](#) approach to better understand their inhibitory mechanism. Forty-eight adult male Wistar rats were divided into six groups of eight rats: naive control, paroxetine (PXT, 10 mg/kg), PXT+sildenafil citrate (4 mg/kg), PXT + RVE (12.5, 25 and 50 mg/kg). Exposure to PXT lasted for twenty-one days, and treatment with sildenafil citrate and RVE took place for the next seven days. On day twenty-nine, the rats were sacrificed under anaesthesia and various biochemical assays (PDE-5, Arginase, nitric oxide (NO)) were carried out on penile tissue homogenate while CK-MB, lipid profile and testosterone were assayed in the serum of rats. This study also employed gas chromatography–flame ionization detection (GC-FID) to identify the phytoconstituents in RV. From our findings, PXT significantly increased PDE-5, Arginase activities with a concomitant decrease in NO concentration. *Rauwolfia vomitoria* extract (RVE) decreased the activities of the penile PDE 5 and arginase activities, and increased NO concentrations in dose-dependent ways (12.5, 25, and 50 mg/kg body weight). RVE showed an increase in testosterone and a decrease in CK-MB activities. Moreover, the result of lipid profile revealed the significant reversal of the changes caused by PXT administration, indicating the potential of the extract in ameliorating paroxetine-induced dyslipidemia. All of the phytochemicals found by GC-FID docked against PDE-5 had the lowest binding energies (−9.4 to −7.0 kcal/mol) when likened to that of sildenafil citrate (−7.4 kcal/mol). The phytochemicals were also docked against arginase which released the lowest binding energy between −10.5 and −9.0 kcal/mol when compared with sildenafil citrate (−9.4 kcal/mol). This study is relevant in the design of new treatment option for ED and coronary artery disease.

Keywords Coronary artery disease · Ethanol extract · Erectile dysfunction · in-vivo, *Rauwolfia vomitoria* · Molecular docking

Introduction

Male sexual dysfunction is a condition brought on by a variety of circumstances, including lifestyle choices, long-term illnesses, and adverse pharmacological reactions [1]. It typically presents as pain during sexual activity, atypical desire, abnormal ejaculation, and erectile dysfunction (ED) [2]. The inability of the penis to attain and/or sustain adequate erectile hardness to accomplish a fulfilling sexual life is known as ED [3]. It is anticipated that by 2025, there will

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be 322 million ED sufferers globally, with over 150 million men already suffering from the disorder [4]. ED is a condition that has several risk factors, such as diabetes, atherosclerosis, neurological disorders, and cardiovascular diseases [5]. The primary mediator of penile erection, nitric oxide (NO), is produced by the action of nitric oxide synthase (NOS), which is expressed in endothelial and neuronal cells [6]. Evidence suggests that compromised endothelial function decreased antioxidant status and nitric oxide (NO) levels in the cavernosal smooth muscles. It also markedly decreased levels of other crucial signalling molecules such as cyclic guanosine monophosphate (cGMP), adenosine, and acetylcholine (ACh) [7].

Erectile dysfunction and coronary artery disease (CAD) are two extremely common disorders that can coexist [8]. Diabetes mellitus (DM), high blood pressure, hyperlipidemia, obesity, and tobacco use are among the risk factors they have in common [9]. The incidence of CAD and ED rises in tandem with the number of cardiovascular risk factors [10]. Although phosphodiesterase 5 inhibitors (PDE5) are essential for the overall treatment of ED, PDE5 inhibition is not the only therapeutic option. According to published research, co-inhibition of phosphodiesterase 5 and other important enzymes (adenosine deaminase, acetylcholinesterase, and arginase) that regulate biomolecules essential to penile erection may have pharmacological importance in the treatment of ED [11].

Penile erection is regulated by phosphodiesterase 5 (PDE-5). For smooth muscle relaxation and blood flow to the penis, it hydrolyzes cyclic guanosine monophosphate (cGMP). Because they raise cGMP levels, known PDE5 inhibitors like sildenafil citrate are helpful in treating erectile dysfunction (ED) [12]. Another essential component for penile erection is nitric oxide (NO). The endothelial cells of the penile corpora cavernosa generate it, and it promotes the synthesis of cGMP, which relaxes smooth muscles and increases blood flow [13]. The enzyme arginase degrades L-arginine, a substrate for the synthesis of NO. Elevated arginase levels can contribute to ED by reducing NO production [14]. Testosterone is the primary anabolic steroid and sex hormone in men. The development of the prostate, testes, and other male reproductive organs depends on human testosterone. Additionally, it encourages the formation of body hair and secondary sexual characteristics such as greater muscle and bone mass [15]. Creatinine kinase-MB (CK-MB) is an enzyme found in the heart tissue, but its levels can also be elevated in cases of ED. It is thought to be related to the muscle damage and inflammation associated with ED [16]. Lipid profile is also an important biomarker for ED. Excessive levels of triglycerides and low-density lipoprotein (LDL) cholesterol can lead to ED, whereas high levels of HDL (high-density lipoprotein) cholesterol may be beneficial [17]. The atherogenic index, which is the ratio of

HDL to LDL cholesterol, may also indicate the risk of ED and cardiovascular disease [18].

A type of extremely selective serotonin re-uptake inhibitor (SSRI) is paroxetine (PXT). ED, diminished libido, and irregular ejaculation have all been linked to long-term usage of PXT, according to numerous studies [19]. Consequently, PXT is typically utilized as a modeling drug to create a mouse sexual dysfunction model in order to assess how well plants can treat sexual dysfunction [20]. However, sildenafil citrate (Sc), a PDE5 inhibitor that is frequently used to treat sexual dysfunction, can have a number of negative effects, including indigestion, headache, nausea, vomiting, and facial congestion [21]. Therefore, it is vital to use natural active components that have non-toxic adverse effects to manufacture safe and effective remedies for preventing and eradicating male sexual dysfunction. Numerous plant extracts have been found to include active components, including triterpenes, alkaloids, steroids, phenolics, flavonoids, and saponins. These substances can be employed as PDE5 inhibitors and have a significant positive impact on enhancing male sexual performance [22].

One of the medicinal plants that has been used for centuries to treat and maintain human health is *Rauwolfia vomitoria* Afzel (Apocyanaceae) [23]. This shrub from the rainforest has straight venation, oval leaves, and clusters of small blooms that bear red berries. According to Alade and Attah [24], it grows in forests of tropics in the Pacific, South America, Asia, and Africa. Common names for the plant include swizzle stick, serpent wood, and serpent root. In Nigeria, it is referred to as “utoenyin” in Efik, “asofeyeje” in Yoruba, “wada” in Hausa, “akanta” in Ibo, and “akata” in Bini [25]. Roots, root bark, leaves, and stem bark are the portions that are frequently utilized in herbal medicines [26]. Numerous investigations into the plant’s chemical makeup revealed that it contains over 50 active indole alkaloids, each of which had exceptional pharmacological capabilities [25]. The pharmaceutical derivatives are mostly utilized as sedatives and antihypertensive medications. Its calming qualities are ascribed to its capacity to enhance oxygen transport to the brain and balance the body’s reaction to stress and anxiety [27]. Traditionally, the tea made from the roots and leaves of *Rauwolfia vomitoria* has been used to cure cholera, lunacy, and hypertension [28].

The root extract of *Rauwolfia vomitoria* contained alkaloids, saponins, tannins, and flavonoids, according to preliminary phytochemical investigations. In accordance with studies, the plant’s flavonoid concentration may be a factor in its sexually stimulating properties because flavonoids have been demonstrated to change testosterone levels, which are crucial for the stimulation of sexual activity [29]. The phytochemistry of *Rauwolfia vomitoria* root extract further revealed the presence of saponins. Saponins are known to increase sexual drive or libido. Hence, plants with

these secondary metabolites or ingredients enhance sexual activity when consumed by humans [30]. It has been reported that alkaloids possess good aphrodisiac potential by increasing sexual desire or libido in male rats [31]. Libido-boosting substances work by raising the levels of serum testosterone and a number of anterior pituitary hormones [32].

The mechanism via which *R. vomitoria* stem bark and its related plant extracts elicit these changes in reproductive function has not been elucidated, despite the fact that their effects on the reproductive organs of men and function are empirically recognized. Utilizing in silico studies, such as molecular docking projections of secondary metabolites from *Rauwolfia vomitoria* extract, and in vivo enzymatic biomarkers to determine the best way for inhibitors to bind with different chemical scaffolds and to clarify their shared pharmacophore concept as the primary inhibitors for PDE5, arginase, and creatine kinase-MB, has inspired the current investigation. Testosterone is the primary anabolic steroid and sex hormone in men. The development of the prostate, testes, and other male reproductive organs depends on human testosterone. Additionally, it encourages the formation of body hair and secondary sexual characteristics, such as greater muscle and bone mass [23]. The goal of this research is to show how the plant extract may be used to treat coronary artery disease and erectile dysfunction. This study should be a direction towards finding new drug candidates with good efficacy and provide more findings on plant-based compounds that could be further detailed in their promising use in both erectile dysfunction and coronary artery disease therapy.

Materials and Methods

Sample Collection and Preparation

The stem bark of *Rauwolfia vomitoria* was gathered from Dongari Iju, a tiny town in Asa Local Government of Kwara State, Nigeria. The authentication was carried out by the herbarium unit at the Department of Plant Biology, Faculty of Life Sciences, University of Ilorin, Nigeria. The voucher sample was put in the institution's herbarium and given reference number UILH/001/0402/2022. After carefully cleaning the stem bark under running tap water to remove any dirt, it was allowed to dry completely at room temperature. A household blender was then used to grind up the dried stem bark. For 48 h, 400 ml of distilled water was added to 100 g of powdered *R. vomitoria* stem bark in a beaker, and the mixture was continuously agitated. The homogenate was filtered through a piece of pure white cotton. The filtrate was lyophilized, and the residue was stored in an airtight container at 4 °C. The extract's yield as a percentage was 32%. When necessary, a fresh stock was

made from the residue and reconstituted in distilled water to obtain concentrations of 12.5, 25, and 50 mg/kg body weight of rats.

Care of Animals and Experimental Design

The animal breeding facility of the Department of Biochemistry, Faculty of Life Sciences, University of Ilorin, Ilorin, Nigeria, provided forty-eight (48) adult male Wistar rats weighing 180 ± 20 g. The animals were fed a commercial diet and had unrestricted access to water. When working with experimental animals, the ethical standards of the US National Institutes of Health (NIH) and the institution's ethical committee were adhered to. The rats in the experiment were housed in stainless steel cages in a room that was between 25 and 28 °C and had a 12-h light/dark cycle.

In order to cause erectile dysfunction, 40 male rats were given an oral dose of 10 mg/kg paroxetine suspension for 21 days after they had acclimated for two weeks. To confirm erectile dysfunction, tissues were examined for elevated phosphodiesterase 5 levels and nitric oxide depletion. Every day, the paroxetine suspension was prepared using saline solution and Tween-80. At random, the rats were divided into six (6) groups of eight ($n = 8$). The Naive Control group of (non-induced) rats received 0.75 ml of physiological saline solution as a baseline for comparison. The effects of paroxetine alone were measured by the Paroxetine Control Group (PCG), which consisted of induced rats that were not given any medication. As a positive control to compare the effects of the extract, the Paroxetine Standard Group (PSG) was made up of induced rats given sildenafil citrate. *R. vomitoria* stem bark ethanol extract was administered in varying quantities to the remaining three groups: 12.5 mg/kg, 25 mg/kg, and 50 mg/kg, respectively. Paroxetine + 12.5 mg/kg Extract Group, Paroxetine + 25 mg/kg Extract Group, and Paroxetine + 50 mg/kg Extract Group were the names given to these groups. While Ademosun et al. [33] suggested the dosage of paroxetine, the dosages of *Rauwolfia vomitoria* extract were selected in accordance with previous studies by Akanbi et al. [34] and Alabi et al. [35]. The experiment lasted for 28 days. On day 29, diethyl ether was used to put the rats to sleep. The heart and penile tissues were extracted, homogenized using a Teflon glass homogenizer, and centrifuged for biochemical testing. The supernatant was stored at -20 °C in order to prepare it for biochemical analysis.

Biochemical Assays

Phosphodiesterase 5 (PDE 5) activity assay

Muritala and Bewaji [36] slightly modified Butcher and Sutherland's [37] method to determine phosphodiesterase 5

activity when cyclic guanosine monophosphate (cGMP) was present as the substrate. Using the following formula, the phosphodiesterase 5 enzyme activity (P) was determined:

$$P = \frac{V\Delta C}{V_3} (\text{units/ml})$$

P = enzyme activity, V = total reaction volume, ΔC = Reaction velocity (Pi/incubation period of 20 min), V_3 = the enzyme source's volume, Pi = Amount of inorganic phosphate released.

Arginase activity assay

The experiment's outcome was reported to be consistent with the study conducted by Ademosun et al. [33]. In a nutshell, arginase activity was measured separately in heart and penile tissues. In order to hydrolyze the substrate, the mixture of activated arginase and 50 μL L-arginine (0.5 M) was incubated for one hour after the homogenate had been pre-incubated for ten minutes at room temperature with Tris-HCl (75 μL , 50 mmol/l, pH 7.5) containing 10 mM MnCl_2 . This was completed by adding 400 μL of the acid solution mixture [$\text{H}_2\text{SO}_4/\text{H}_3\text{PO}_4/\text{H}_2\text{O}$ at ratio 1:3:7 (v/v/v)]. To increase the urea concentration, the mixture was heated for 45 min after adding 25 μL of α -isonitrosopropiophenone, which is 9% in absolute ethanol [33]. At 550 nm, the urea content was measured using spectrophotometry.

Determination of nitric oxide concentration

The nitric oxide concentration of penile and cardiac tissue homogenate was measured using a medium that contained 400 milliliters of 2% vanadium chloride (VCl_3) in 5% HCl, 200 milliliters of 0.1% N-(1-naphthyl) ethylenediamine dihydrochloride, and 200 milliliters of 2% sulfanilamide (in 5% HCl). Following an incubation time of 60 min at 37 °C, the nitrite content, which corresponds to an estimation level of NO, was measured spectrophotometrically at 540 nm in accordance with the reduction of nitrate to nitrite by VCl_3 , as reported by Ademosun et al. [33].

Determination of serum testosterone concentration

Using the method described in the instruction manual provided by the manufacturer of the human testosterone enzyme immunoassay (EIA) kit, the plasma testosterone concentration in the animals was measured. This was founded on the idea that human testosterone enzyme immunoassay (EIA) conjugate and testosterone in the test specimen (plasma) would bind competitively for a fixed quantity of human anti-testosterone [38, 39]. A competitive ELISA-based direct human testosterone enzyme immunoassay (EIA) kit was

used to measure the levels of serum testosterone. Absorbance was read at 450 nm, and testosterone concentration was extrapolated from a calibration curve as described by Gholib et al. [40].

Serum creatine kinase-MB activity assay

Economically accessible ELISA (enzyme-linked immunosorbent assay) kits were used to measure creatine kinase (CK-MB) in compliance with the manufacturer's instructions.

Determination of serum lipid profile

Total cholesterol determination Sukowati et al. [41] state that total cholesterol was measured using the colorimetric enzymatic cholesterol p-aminophenazone cholesterol technique (CHOD-PAP, DiaSys). After homogenizing a serum with 0.01 mL and 1 mL of cholesterol solution using a vortex, it was left to stand at room temperature for 20 min. The mixture's absorbance at 500 nm was evaluated in comparison to the blank, which consisted of 0.01 mL of pure water and 1 mL of cholesterol reagent. Cholesterol standards were used in place of the serum.

Triglyceride (TG) determination In order to use GPO-PAP (DiaSys) to measure triglycerides, 0.01 mL of serum was mixed with 1 mL of TG reagent, vortexed, and left to stand at room temperature for 20 min. The reagents comprised glycerocination, 4-aminoantipyrin, glycerol 3-phosphate-oxidase, peroxidase, lipoprotein lipase, ATP, Mg^{2+} , pH 7.2 buffers, and 4-chlorophenol. As blanks, 0.01 milliliters of pure water and one milliliter of triglyceride reagent were added. The absorbance of the mixture was measured at 500 nm and compared to the blank.

HDL determination The process of determining HDL began with the precipitation of chylomicron, VLDL, and LDL cholesterol. 0.02 mL of serum was combined with 0.5 mL of sediment solution. The mixture was then centrifuged for 20 min at 4500 rpm. The 0.01 milliliter supernatant was mixed with one milliliter of cholesterol reagent. The CHOD-PAP (DiaSys) method was used to assess HDL cholesterol after the clear supernatants were separated, using the identical procedures as for total cholesterol. The sample's absorbance at 500 nm was evaluated in relation to the blanks, which were 1 mL of cholesterol reagent and 0.01 mL of distilled water.

LDL determination The Friedewald formula was used to determine the levels of LDL cholesterol:

$$\text{LDL} = \text{total cholesterol} - \text{HDL} - (\text{TG}/5).$$

Atherogenic index

The atherogenic index was calculated as the molar ratio of total cholesterol, triglycerides, or LDL-C to HDL-C, providing a predictive value for coronary heart disease risk.

Gas Chromatography-Flame Ionization Detection (GC-FID) Identification and Quantification of Phytochemical Constituents

For the GC-FID analysis, of the ethanol extract of *R. vomitoria* was placed in a test tube. The analysis was performed using a Shimadzu GC-2010 equipped with an automated sampler and a FID. The separation was carried out on a Shimadzu capillary column with a split ratio of 25:1, an injection volume of 0.2 μ l, a FID temperature of 280 °C, and an input temperature of 250 °C. The temperature program included a three-minute initial hold at 25 °C, a 40 °C/min ramp to 120 °C, a 50 °C/min ramp to 230 °C, and a two-minute final hold at 230 °C. The retention lengths of the phytochemical components were compared with the NIST05 mass spectral library and standards, and their levels were calculated as a percentage of the total peak area.

In-Silico Molecular Docking Experiment

3D-Protein target retrieval

The crystal structures of PDE-5 (PDB ID: 2h42), arginase (PDB ID: 2ef4), and CK-MB (PDB ID: 1i0e) were made available in .pdb format by the Protein Data Bank (<https://www.rcsb.org/>). PDB is a global database of three-dimensional structures of biological macromolecules [42, 43]. This study used a single chain of target proteins (PDE-5 and arginase) for molecular docking analysis. The MGLTools were used to prepare proteins. Following the removal of water molecules and co-crystallized ligands from the macromolecule target proteins, polar hydrogens were added.

Ligand preparation

The SDF files of the reference drug and twenty-two (22) GC-FID-identified bioactive ingredients from *Rauwolfia vomitoria* stem bark aqueous extract were downloaded from PubChem. Before the PDB files were created using O-BABEL (2.3.1 version), the ligand SDF files were acquired from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>).

Molecular docking study

Molecular docking can be used to clarify the relationships between a protein and ligand. In order to understand the mechanism of substrate/inhibitor selectivity as it was

discussed in previous research, this technique was utilized to view the ligand orientation in the α -amylase and α -glucosidase active site pocket [44–46]. AutoDock 1.5.6 and AutoDock Vina were utilized to convert the PDB data of proteins and ligands into an improved PDB format known as PDBQT for molecular docking investigations. The “TXT” file included all of the data on the target proteins, ligand, grid size, and geometry, and the “Grid” of AutoDock 1.5.6 was used to establish the grid settings.

Additionally, the grid box size was set to 46 $\times$ 44 $\times$ 44; 62 $\times$ 56 $\times$ 42; and 78 $\times$ 64 $\times$ 42. The grid center was designated at dimensions (x, y, and z) of 33.71, –23.48, –1.73; 21.16, 125.01, 16.97, and –1.23, 28.58, 192.07 for PDE-5 and arginase, respectively. The exhaustiveness parameter in the Vina software was set to 8 Å by default. A maximum of ten binding variants were produced, and the best and worst binding modes had an energy difference of no more than 3 kcal/mol. To confirm the molecular docking technique and protocol, a redocking experiment was performed using the co-crystal reference chemicals (sulfate and nitrate ions) to duplicate the native binding poses into the template’s binding pocket. The outcomes of the redocking experiment between docked and co-crystallized reference molecules were superimposed using Pymol. Then, at the crystal structure, the RMSD value for docked ligands relative to reference ligands was computed. The biggest conformation cluster with the lowest binding free energy (kcal/mol) was chosen after AutoDock Vina was estimated to yield the best result for each substrate. The output pdbqt files were stored in a config. (configuration) file. The conformation with the lowest binding energy was considered to be the most stable for the targeted proteins. The data were examined using the free edition of the Biovia Discovery Studio 2020 client (Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 2017, San Diego: Dassault Systèmes, 2016).

Statistical Analysis

The data were expressed using the mean $\pm$ SEM. To find significant differences between treatment groups, the statistical analysis included Tukey’s test and one-way ANOVA; $p < 0.05$ was deemed significant. All analyses were performed using GraphPad Prism 7.

Results

Effect of *Rauwolfia vomitoria* Extract on Penile Tissue phosphodiesterase 5 (PDE5) Activity

It was examined how *Rauwolfia vomitoria* extract affected the phosphodiesterase 5 (PDE5) activity in penile tissue

Fig. 1 Effect of *Rauwolfia vomitoria* ethanol extract on penile tissue phosphodiesterase 5 activity in paroxetine-treated rats. Bars represent mean $\pm$ standard error of the mean (n = 4)

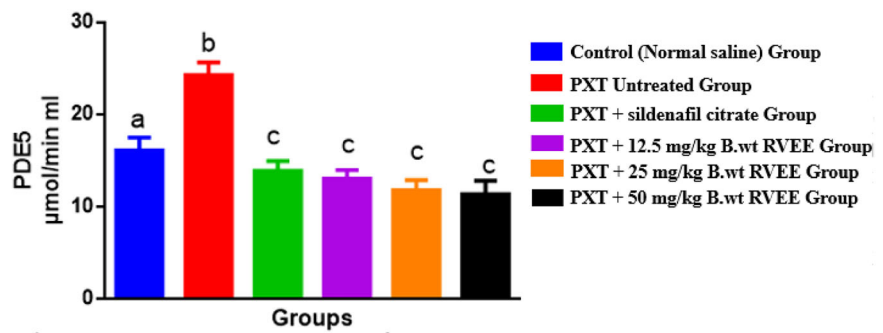


Fig. 2 Effect of *Rauwolfia vomitoria* extract on Concentration of Nitric Oxide (Penile Organ) in paroxetine-treated rats. Bars represent mean $\pm$ standard error of the mean (n = 4)

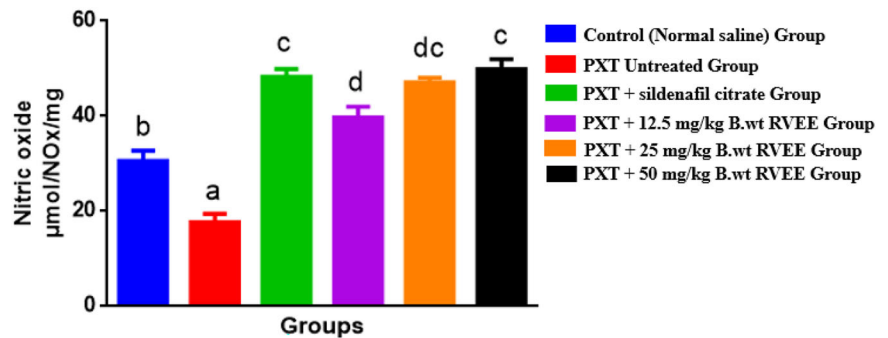
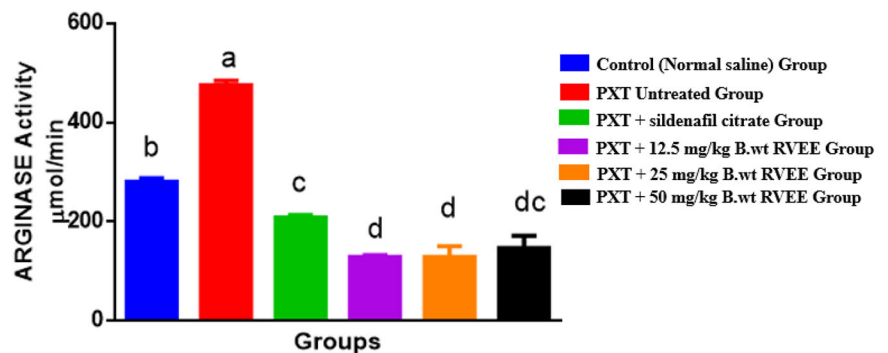


Fig. 3 Effect of *Rauwolfia vomitoria* extract on arginase activity (penile organ) in paroxetine-treated rats. Bars represent mean $\pm$ standard error of the mean (n = 4)



(Fig. 1). The study found no significant difference in PDE5 activity between the sildenafil citrate-treated group and the test groups (12.5, 25, and 50 mg/kg body weight). However, there was a significant drop ($p < 0.05$) when the test groups were compared to the control and paroxetine-treated groups.

Effect of *Rauwolfia vomitoria* Ethanol Extract on Nitric Oxide (NO) Concentration in Penile Tissue

Figure 2 shows how *Rauwolfia vomitoria* extract affects the amount of nitric oxide (NO) in penile tissue. There is no discernible difference in NO levels between the groups that received 25 mg and 50 mg/kg body weight of the extract and the group that received sildenafil citrate. However, when these groups were contrasted with the group that received 12.5 mg/kg body weight of the extract, a substantial rise ($p < 0.05$) in NO concentration was noted.

Furthermore, NO concentrations in all test groups were significantly increased ($p < 0.05$) when compared with the control group and the paroxetine-treated group.

Effect of *Rauwolfia vomitoria* Ethanol Extract on Arginase Activity in Penile Tissue

The current investigation assessed the impact of *Rauwolfia vomitoria* extract on penile tissue's arginase activity (Fig. 3). In comparison to the sildenafil citrate group, the analysis showed a substantial ($p < 0.05$) decrease in arginase activity in the groups of rats who received 12.5 and 25 mg/kg body weight of the extract. However, there was no discernible change in the group that got 50 mg/kg body weight. In addition, the arginase activity of all test groups was significantly lower ($p < 0.05$) than that of the control and paroxetine-treated groups.

Fig. 4 Effect of *Rauwolfia vomitoria* extract on serum testosterone concentration in paroxetine-treated rats. Bars represent mean $\pm$ standard error of the mean ($n = 4$)

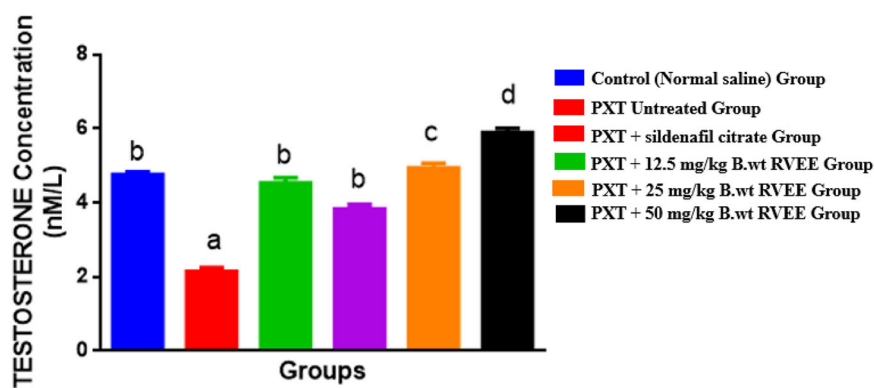
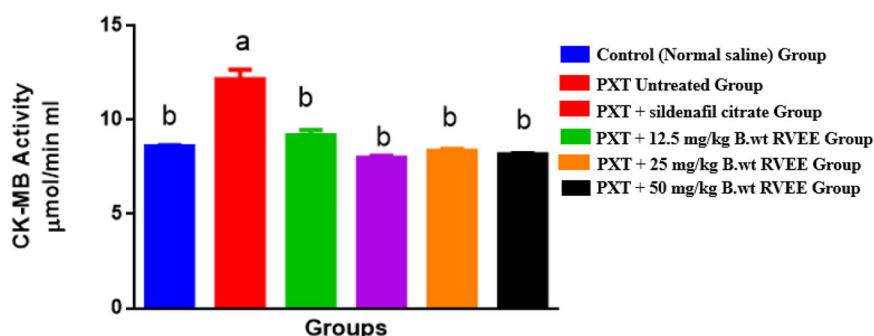


Fig. 5 Effect of *Rauwolfia vomitoria* extract on serum CK-MB activity in paroxetine-treated rats. Bars represent mean $\pm$ standard error of the mean ($n = 4$)



Effect of *Rauwolfia vomitoria* extract on plasma testosterone concentration

Test subjects' serum testosterone levels were examined in relation to *Rauwolfia vomitoria* extract (Fig. 4). The findings showed that the group of rats that got 12.5 mg/kg body weight of the extract and the group that received sildenafil citrate did not significantly differ in their testosterone concentrations. However, when compared with the control group and paroxetine-treated group, the testosterone concentrations of the rats that received 25 and 50 mg/kg body weight increased significantly ($p < 0.05$).

Effect of *Rauwolfia vomitoria* Ethanol Extract on Creatine Kinase-MB Activity of Rats

The present study investigated the effect of *Rauwolfia vomitoria* extract on plasma CK-MB activity in test subjects (Fig. 5). CK-MB (creatine kinase-MB) is an important enzyme that serves as a biomarker for cardiac tissue damage, commonly used to diagnose myocardial infarction (Heart Attack) and other heart-related conditions. In contrast to sildenafil citrate and control groups, the results showed no discernible change in plasma CK-MB activity between the groups treated with *Rauwolfia vomitoria* extract at doses of 12.5, 25, and 50 mg/kg body weight. All treatment groups, however, showed a substantial

decrease ($p < 0.05$) when compared to the paroxetine-treated group.

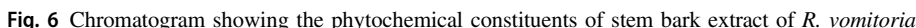
Effect of *Rauwolfia vomitoria* Stem Bark Ethanol Extract on Lipid Profile of Rats

The results of an investigation into the effects of an ethanol extract of the stem bark of *Rauwolfia vomitoria* on the lipid profile of male Wistar rats treated with paroxetine are displayed in Table 1. It is well recognized that the selective serotonin reuptake inhibitor (SSRI) paroxetine negatively impacts lipid metabolism, raising levels of triglycerides, total cholesterol, and low-density lipoprotein (LDL) while lowering levels of high-density lipoprotein (HDL). These alterations contribute to an increased atherogenic index, which is a marker of cardiovascular risk. The study found that treatment with *Rauwolfia vomitoria* extract at doses of 12.5, 25, and 50 mg/kg body weight significantly reversed these changes, indicating the potential of this extract in ameliorating paroxetine-induced dyslipidemia.

GC-FID Analysis of the Ethanol Extract of *Rauwolfia vomitoria*

The GC-FID analysis of the ethanolic extract of *Rauwolfia vomitoria* stem bark as shown in Fig. 6 and Table 2 revealed a complex mixture of bioactive alkaloids, including reserpine, reserpiline, tetraphyllicine, nortetraphyllicine, calycanthine,

Values are mean of six determinations $\pm$ SEM; values along a column with different superscripts 'a–f' are significantly different from each other. Key: *PXT* Paroxetine, *RVEE* *Rauwolfia vomitoria* ethanol extract, *TAG* Triglyceride, *HDL* High density lipoprotein, *LDL* Low density lipoprotein



Molecular Docking Analysis

affinities and interactions of compounds (identified by GC-FID) with the active sites of tested enzymes were approximated using a blind docking approach [48]. The ligands (bioactive compounds) were literally able to cooperate freely with all of the protein's binding sites (enzymes such as PDE5, arginase, and CK-MB) thanks to this blind docking technique, providing pertinent information on likely ligand-protein binding interactions that may be competitive, non-competitive, or mixed inhibition [47].

The ethanol extract of *Rauwolfia vomitoria* stem bark included twenty-two chemicals that were identified and docked to the PDE5 enzyme (Table 3). The binding energies of fifteen docked compounds with PDE-5 were lower than those of sildenafil citrate (-7.4 kcal/mol), ranging from

Table 2 Phytochemicals present in *R. vomitoria* showing retention time, area and height

Component	Retention	Area	Height
Reserpine	2.633	2293.5550	118.417
Reserpiline	3.533	277.2220	16.670
Tetraphyllicine	4.200	287.8490	14.708
Nortetraphyllicine	4.683	547.1290	27.187
Corynanthine	5.133	284.6140	23.138
Aricine	5.383	664.1310	55.131
Raubasine	6.050	1271.9800	52.890
Raucaffricine	6.583	1887.3300	87.856
Rauwolscline	7.050	868.6465	78.783
Rauhimbine	7.300	1558.4450	147.715
Vomilenine	7.566	492.3070	50.524
Yohimbine	7.766	1495.6240	67.539
Allo-Yohimbine	8.416	2144.6540	56.632
Ajmaline	9.133	1790.6800	150.380
Norajmaline	9.416	562.7535	42.464
Ajmalicine	9.733	953.3425	50.097
Ajmalidine	10.133	1105.8890	44.952
Deserpidine	10.850	1854.5650	115.011
Papaverine	11.100	583.6545	50.173
Canescine	11.383	573.8820	27.712
Recanescine	12.050	1112.7785	43.368
Rescinnamine	12.450	1380.9200	81.136

−7.5 to −9.4 kcal/mol, while four compounds (Ajmaline, Rescinnamine, Reserpiline and Reserpine) predict the lower binding affinity (7.0 – 7.2 kcal/mol) and three compounds (Canescine, Rauhimbine and Yohimbine) showed the same binding energies as sildenafil citrate (Table 3). With binding energies (ΔG) of −9.3 and −9.4 kcal/mol, respectively, for Raucaffricine and Ajmalidine, Table 5 shows that PDE-5 had substantial binding attractions for both compounds. In contrast to its binding affinity for sildenafil citrate ($\Delta G = -7.4$ kcal/mol), a common medication for erectile dysfunction and a PDE5 inhibitor, the binding energies of AlloYohimbine, Aricine, Corynanthine, Rauwolscline, and Tetraphyllicine were −8.4, −8.3, and −8.1 kcal/mol, respectively, while those of Tetraphyllicine, Vomilenine, Recanescine, Raubasine, Ajmalicine and Deserpidine, Norajmaline, and Papaverine were −7.6 and −7.5 kcal/mol, respectively (Table 3). This suggests that there is a good chance that the drugs and the PDE-5 enzyme will interact molecularly.

Molecular docking against arginase enzyme

With each of the twenty-two chemicals that were discovered from the extract, molecular docking of the arginase was also carried out. The results were computed as binding energies

in kcal/mol (Table 4). Arginase activity was found to diminish in experimental studies, including ethanolic extracts of our plant. Fourteen compounds with a stronger negative binding energy value (−9.7 to −10.5 kcal/mol) than sildenafil citrate (−9.4 kcal/mol) for arginase inhibition were found when we docked the key compounds discovered via GC-FID. The binding energies were shown in Table 4. The docking of ligands Aricine and Norajmaline, Reserpine, Vomilenine and Papaverine resulted in higher binding energy of −9.3, −9.1, 9.0 and 8.4 kcal/mol, respectively, when compared with Sildenafil citrate (−9.4 kcal/mol) as shown in Table 4. When Ajmalidine, Deserpidine, and Recanescine were docked with arginase, we saw the same pattern as when arginase was docked with the reference drug, Sildenafil citrate (−9.4 kcal/mol). As a result, many of the docked ligands identified from our plant's ethanolic extracts had lower binding energies than the reference drug, which demonstrated stronger aphrodisiac activity and a higher affinity of docked ligands with arginase active sites.

Understanding the mechanism of mild to moderate inhibition of this enzyme and the constituents of the ethanolic extract of *Rauwolfia vomitoria* was made easier by the outcomes of molecular docking responsibility. Figure 7 displayed the ligand-arginase binding interactions that were determined by GC-FID. Notably, sildenafil citrate connected with these important amino acid residues in the catalytic site by van der Waals, hydrophobic-Pi interactions, and conventional hydrogen bonds (Val256, Tyr41, Gly87) (Fig. 7a). Whereas majority of identified complexes (Ajmalicine, Ajmalidine, Ajmaline, AlloYohimbine, Aricine, Corynanthine, Deserpidine, Norajmaline, Nortetraphyllicine, Deserpidine, Raubasine, Rauwolscline, Rescinnamine, Reserpine, Tetraphyllicine and Yohimbine) interacted with arginase with either 1 or 2 hydrogen bonds which were either the same or different from identified catalytic amino acids in arginase-sildenafil citrate complex and other bonds as shown in Fig. 7b–f, h–k, m, p, r, t, u & w. Similar interactions were also observed for the reference drug (Sildenafil citrate) and Canescine, Papaverine, Rauhimbine, Recanescine, Reserpiline, Vomilenine with three hydrogen bonds (Fig. 7g, l, o, q, s & v) while Raucaffricine showed 4 conventional hydrogen bonds. Interestingly, however, few compounds interacted with one or two same key amino acid residues as standard drug (Sildenafil citrate) which are involved in catalysis at the active site of arginase (Fig. 7b, e–h, k, o & p).

Molecular docking against creatine kinase-myocardial band (CK-MB) enzyme

Table 5 displays the findings of docking studies as well as the docked conformations of the top-scoring ligands in the CK-MB catalytic region. According to these docking data,

Table 3 Predicted binding affinity and comprehensive docking interactions of PDE-5 with the bioactive chemicals discovered by GC-FID in the ethanol extract of the stem bark of *Rauwolfia vomitoria* and Sildenafil citrate

Identified phytochemicals	Binding energy	H-Bond (H-Bond distance)	Residual interactions (Van der Waals, Electrostatic and Hydrophobic interactions)	Electrostatic (salt bridge, attractive charge) and Hydrophobic- (Pi-Donor H-Bond, Pi sigma, Pi-Pi T-shaped, Pi-Pi Stacked, Alkyl, Pi-alkyl, Pi-Sulfur & C-H Bond)
Ajmalicine	-7.6	His613 (2.55)	Ile778, Gln775, Ala779, Gln817, Ser663, Asn662	Asp764, Asn661, Leu725, Leu765, Ile665, Phe786, Ile768, Tyr612, Phe820, Ala767, Val782
Ajmalidine	-9.4	His613 (2.18)	Try612, Leu765, Asp725, Thr723, Arg667, Asn662, Asn661, Gln817, Ile778, Ala767	Leu725, Phe786, Phe820, Val782
Ajmaline	-7.0	His613 (2.18)	Ile665, Gln717, Leu765, His617, Asp764, Asp724, Asn661, Thr723	Phe786, Phe820, Val782, Tyr612, Leu725
AlloYohimbine	-8.4	Gln817 (2.36)	Ala779, Gln775, Ile778, Ile824, Gly819	Val782, Ala767, Ile768, Tyr612, Phe820, Leu804, Met816, Phe786
Aricine	-8.3	Gln817 (2.75)	Leu804, Gly819, Asp764, Leu765, Ile768, Ile778, Gln775, Ala779	Met816, Phe820, Ile665, Ile824, Leu725, Tyr612, Ala767, Val782
Canescine	-7.4	Arg667 (2.21, 2.80), His657 (2.24)	Ile665, Leu804, Met816, Gln817, Leu765, His613, Asp764, Thr723, Asn661, Leu725, Asn662, Ser679, Asp724, Ser663	Phe786, Phe820, Val782, His685, Met816, Glu682, Val660
Corynanthine	-8.1	His613 (2.25), His657 (2.32), Asp724 (2.65), Glu682 (2.76), Leu725 (2.72)	Val660, Asp764, Ala676, Phe786, Asn661, Asp662, Arg667, Ala726, His653	Val782, Tyr612, Phe820, Leu765, Asp654, Thr723
Deserpidine	-7.5	Leu804 (2.85)	Leu725, Ile824, Leu765, Gln817, Asp803, Thr802, Ser663	Ile665, Phe820, Val782, Phe786, Met816, Lys812
Norajmaline	-7.5	His613 (2.29)	Ile665, Gln817, Val782, Leu765, Tyr612, His617, Asp764, Asn661, Thr723	Phe786, Phe820, Leu725
Nortetraphyllidine	-7.5	Asn661 (2.73)	Thr723, Asp745, Leu765, Ile778, Phe820, Phe786, Asn662, Arg667, Asp724	His613, Ala767, Tyr612, Val782, Leu725
Papaverine	-7.5	Gln817 (2.18)	Tyr612, Leu765, Asp764, His613, His617, Leu725, Ile768	Val782, Ala779, Ala783, Ile813, Leu804, Met816, Phe786, Phe820
Raubasine	-7.6	Gln817 (2.18)	Ala779, Gln775, Ile778, Leu765, Leu725, Ser663, Asn662, Phe786, Leu804	Val782, Ala767, Ile768, Tyr612, Phe820, Ile665, Met816
Raucaffricine	-9.3	His657 (3.06), Glu682 (2.97), Asp654 (2.37), Thr723 (2.24), His613 (2.19)	Ile768, Ala779, Gln817, Leu804, Leu725, Ile667, Asp764, His653, Asp724, His685, Met681, Asn661, Asn662, Arg667	Phe786, Phe820, Val660, Tyr612, Leu765, His617, Val782
Rauhimbine	-7.4	His613 (2.71), His657 (2.09), Asp724 (2.41), Leu725 (2.62)	Asp764, Ala767, Phe786, Asn662, Glu682, Arg667, Ala726, Asp654, His653, Val660, Asn661	Val782, Tyr612, Phe820, Leu765, Thr723
Rauwolfscine	-8.1	Leu725 (2.98), Asn661 (2.94)	Leu765, Gln817, Ile665, Asn662, His657, Val660	Val782, Phe820, Phe786, Thr723, Asp764, His613

Table 3 (continued)

Identified phytochemicals	Binding energy	H-Bond (H-Bond distance)	Residual interactions (Van der Waals, Electrostatic and Hydrophobic interactions)
			Van der Waals and Electrostatic (salt bridge, attractive charge) and Hydrophobic- (Pi-Donor H-Bond, Pi sigma, Pi-Pi T-shaped, Pi-Pi Stacked, Alkyl, Pi-alkyl, Pi-Sulfur & C-H Bond)
Recanescine	-7.6	Asn662 (1.86), His (2.71)	Tyr612, Asp764, Ser663, Leu804, Ile665, His657, Arg667, Ser679, Met681, Ile680, Thr723 Asp724, Glu682, Asp654
Rescinnamine	-7.3	His613 (1.84), Ile (2.77)	Ser663, His657, Asn661, Arg667, Met681, Ser679, Asn662, Asp724, Val660, His653, Ala779, Gln817, Ile768
Reserpiline	-7.3	Tyr612 (2.50)	Gln775, Gln817, Leu804, Leu725, Asn662, Asn661, Arg667
Reserpine	-7.2	Asn662 (2.97), His613 (1.86)	Asp764, Thr723, Tyr612, Ile768, Gln817, Leu804, Ser663, Ile665, His657, Met681, Ser679, Ile680
Tetraphyllicine	-7.6	Tyr612 (2.35), Asp764 (2.35)	His617, Ile778, Gln775, Gln817, Ala779, Phe786, Thr723, His613
Vornilenine	-7.6	Asn662 (2.30)	Leu725, Gln817, Met816, Tyr612, His613, Asn661, Arg667, Ser663, Ile665
Yohimbine	-7.4	Asn662 (2.38)	Phe786, Gln817, Gln775, His617, Asp764, His613, Arg667
Sildenafil citrate	-7.4	Gln817 (1.87, 2.10)	Leu765, Tyr612, Ala767, Gln775, Ile768, Ala779, Ala783, Ser663, Arg667, Ile665, Leu725, Ile824, Asn661
			Val782, Ala767, Ile768, Phe820, Asn661, Leu725, Leu765 Phe820, Val782, Phe786, Leu804 Phe820, Val782, Tyr612, Ala767, Leu765, Ile768, Leu725, Asn661, Ile665, Ser663 His613, Val782, Phe820, Ile813, Leu804, Met816, Phe786, Asn662

Table 4 Predicted binding affinity and thorough docking interactions of arginase with the bioactive substances found by GC-FID in the ethanolic extract of stem bark of *Rauwolfia vomitoria* and the Sildenafil citrate

Identified phytochemicals	Binding energy	H-Bond (H-Bond distance)	Residual interactions (Van der Waals, Electrostatic and Hydrophobic interactions)	
			Van der Waals and	Electrostatic (salt bridge, attractive charge) and Hydrophobic- (Pi-Donor H-Bond, Pi sigma, Pi-Pi T-shaped, Pi-Pi Stacked, Alkyl, Pi-alkyl, Pi-Sulfur & C-H Bond)
Ajmalicine	-10.5	Gly87 (2.50), Val256 (1.96)	Gln257, Arg255, Arg111, Pro212, Glu86, Arg3, Glu2, Tyr41	Phe89
Ajmalidine	-9.4	Ser132 (2.22)	Asn134, His136, Thr232, Arg18, Ala122, Glu175, Asp123, Gly137, Asn125	Asp172, His121
Ajmaline	-9.8	His136 (2.65)	Asn134, Ser132, Thr232, Arg18, Ser170, Ala122, Glu175, Asp123, Asn125, Gly137	Asp172, His121
AlloYohimbine	-9.9	Tyr41 (2.51)	Val256, Pro212, Arg111, Gln257, Gly87, Val88, Glu2, Leu285, Ala251, Gly287, Gly254	Leu286, Phe89
Aricine	-9.3	Tyr41 (2.58)	Ala251, Leu285, Glu2, Gly87, Glu86, Arg109, Arg111, Pro212, Gln257, Arg255	Gly254, Val256, Leu286, Phe89, Val4
Canescine	-9.7	Tyr41 (2.99), Arg31 (2.33), Gln35 (2.12)	Arg241, Leu226, Arg273, Val279, Ala30, Tyr29, Gly280, Lys288	His244, Met277, Glu276
Corynanthine	-9.8	Arg111 (2.54), Val254 (2.68)	Gly254, Tyr41, Glu2, Val88, Gly87, Glu86, Pro212, Gln257	Phe89
Deserpidine	-9.4	Arg31 (3.37), Gln35 (2.07)	Arg241, Leu226, Arg273, Val279, Ala30, Tyr29, Gly280, Lys288, Leu283	His244, Tyr240, Met277, Glu276
Norajmaline	-9.3	His136 (2.55)	Thr232, Asp123, Gly137, Asn134, Asn125, Ser132, Ser170	His121, Asp172, Pro131
Nortetraphyllicine	-10.0	Val256 (1.94), Gly87 (2.42)	Gln257, Gly254, Arg255, Tyr41, Glu2, Arg3, Val88, Glu86, Arg111, Gly254, Gln257,	Phe89, Pro212
Papaverine	-8.4	Asn125 (1.94), Asp172 (2.50), Thr232 (2.22, 2.12)	Asp218, Arg18, Ser170, Ser132, Glu175, Gly137, Asp123, Asp218	Asp220, Glu263, His136, His121, Pro131
Raubasine	-10.1	Arg18 (2.76), Thr232 (2.31)	His97, Glu263, Asn16, Ser132, Asp172, His136, His97, Glu263, Gly137	Asp220, As123, Asp218
Raucaffricine	-9.7	Arg109 (2.61, 2.77), Gln257 (2.82, 2.73), Glu2 (2.41), Gly254 (2.14)	Tyr41, Leu286, Leu285, Ala251, Arg255, Pro212, Arg111, Glu86, Val88, Gly87, Phe89, Pro85	Val256
Rauhimbine	-9.8	Gln257 (2.29), Arg111 (2.43), Val256 (2.70)	Gly254, Tyr41, Glu2, Glu86, Pro212, Arg255	Phe89, Gly87
Rauwolscline	-9.8	Leu285 (2.57), Val256 (2.76)	Arg255, Pro212, Gln257, Arg111, Gly87, Glu2, Ala251	Gly254, Tyr41, Leu286, Phe89
Recanescine	-9.4	Arg31 (2.31), Gln35 (2.04), Tyr240 (3.00)	Arg241, Leu226, Arg273, Val279, Ala30, Tyr29, Gly280, Lys288	His244, Met277, Glu276
Rescinnamine	-9.8	Glu2 (2.06)	Leu285, Gly287, Tyr41, Val88, Glu86, Gly87, Phe89, Gln257	Leu286, Ala251, Val256, Pro212, Arg255, Arg111

Table 4 (continued)

Identified phytochemicals	Binding energy	H-Bond (H-Bond distance)	Residual interactions (Van der Waals, Electrostatic and Hydrophobic interactions)	
			Van der Waals and	Electrostatic (salt bridge, attractive charge) and Hydrophobic (Pi-Donor H-Bond, Pi sigma, Pi-Pi T-shaped, Pi-Pi Stacked, Alkyl, Pi-alkyl, Pi-Sulfur & C-H Bond)
Reserpiline	-9.9	Thr232, (2.81), His136 (2.31), Arg18 (2.93)	Asp218, Gly231, Ser132, Asp172, Gly137	Asp123, Asn16, Asn134, His121
Reserpine	-9.1	Tyr240 (2.03)	Arg273, Thr239, Gly280, Leu283, Lys288, Val279, Gln35, Tyr29, Ala30	Met277, Arg241, Leu226, His244, Arg31
Tetraphyllicine	-10.3	His136 (2.76)	Asn125, Asp123, Glu175, Ala122, Ser170, Ala15, Ser132, Thr232, Asn134, asn16Gly137	Asp172, His121
Vomilenine	-9.0	Asp123 (2.02), Asp172 (2.09), Ser132 (3.07)	Arg18, Asn134, Asn125, Ala122, Glu175, Gly137, Thr232	Pro131, His136, His121
Yohimbine	-10.2	Arg111 (2.45)	Val256, Gln257, Gly254, Pro212, Glu86, Gly87, Val88, Glu2, Tyr41	Phe89
Sildenafil citrate	-9.4	Val256 (3.08), Tyr41 (2.74), Gly87	Glu2, Arg255, Gln257, Arg111, Glu86, Val88, Leu286, Phe89, Ala251, Gly254	Pro212, Leu286

the majority of the compounds that were found had strong binding affinities for the CK-MB structure (-6.6 kcal/mol to -8.7 kcal/mol), and their energy ranges were similar to those of the reference compound, sildenafil citrate (-7.7 kcal/mol) (5). In contrast, the reference drug showed a high binding affinity for Ajmaline (7.1 kcal/mol), Aricine (7.4 kcal/mol), Corynanthine (7.3 kcal/mol), Norajmaline (7.4 kcal/mol), Papaverine (6.6 kcal/mol), Rauhimbine (7.4 kcal/mol), and Rauwolscine (7.6 kcal/mol) (Table 5).

Using the free edition of Biova Discovery Studio Visualizer 2020, the detailed interaction of the best conformation of the docking data was visualized and analyzed. This showed the bioactive compounds' optimal docking positions (Fig. 8), their binding sites on CK-MB, the amino acid residues that were engaged in their interaction, and the different bonds that were involved (such as carbon-hydrogen bonds, conventional hydrogen bonds, pi-sigma, pi-pi, and pi-alkyl, among others). We also found that all of these bioactive substances were attached to the enzyme close to the catalytic site domain where sildenafil citrate binds, based on binding pose/binding site occupied (Fig. 8). This implies once more that these substances may contribute to the overall CK-MB inhibitory effect of the *Rauwolfia vomitoria* ethanol extract through a competitive method of inhibition similar to that of sildenafil citrate (Fig. 8a–k, m–t, v & w). On the contrary, although compounds Nortetraphyllicine and Tetraphyllicine ($\Delta G = -7.9$ kcal/mol, -8.2 kcal/mol, respectively) are more towards the enzyme (CK-MB) than the reference drug (Sildenafil citrate, $\Delta G = -7.7$ kcal/mol) (Table 5), the reference medication, sildenafil citrate, is not in competition with these bioactive chemicals for the enzyme's active site because the latter was bound to the protein with a different binding residual interaction than hydrogen formation (Fig. 8l & u). This suggests that it has the potential to use a non-competitive form of inhibition to assist in the overall CK-MB inhibitory action of the *Rauwolfia vomitoria* ethanol extract. It should be emphasized that these drugs bind to these enzymes at their non-catalytic site as well, which is a distinct binding pose and site from the reference medication, sildenafil citrate (Fig. 8). Fascinatingly, the ethanol extract of *Rauwolfia vomitoria* examined in this work contained all of these bioactive chemicals that interacted with CK-MB mostly by a combination of van der Waals forces, conventional hydrogen bonds, pi-sigma, pi-alkyl, pi-cation, pi-anion, and pi-pi interactions (Table 5 & Fig. 8).

Discussion

Numerous studies have demonstrated the link between sexual dysfunction and certain selective serotonin reuptake inhibitors (SSRIs) such as paroxetine [49, 50]. An alteration

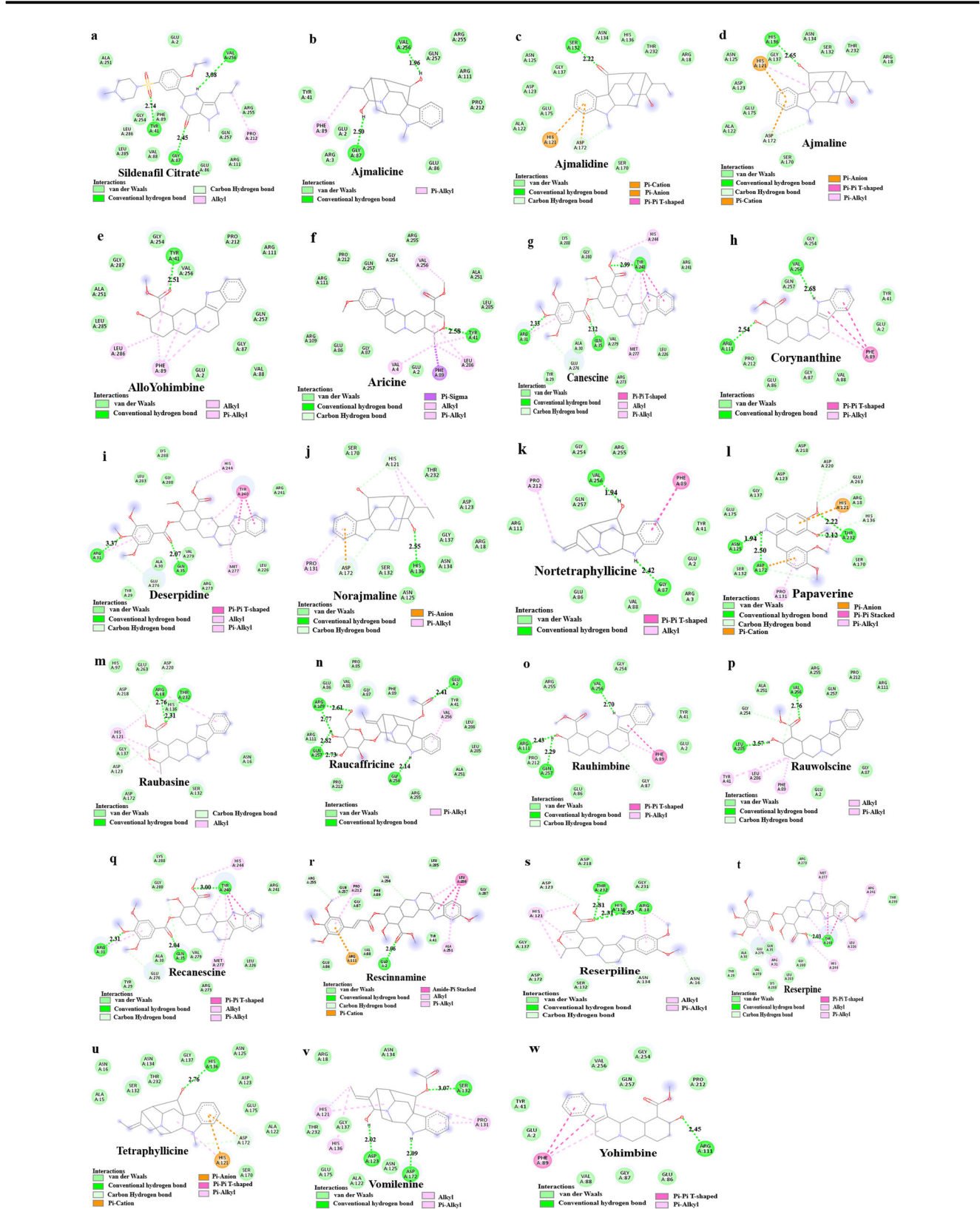


Table 5 Predicted binding affinity and thorough docking interactions between CK-MB and the bioactive substances found by GC-FID in the ethanolic extract of the stem bark of *Rauwolfia vomitoria* and Sildenafil citrate

Identified phytochemicals	Binding energy	H-Bond (H-Bond distance)	Residual interactions (Van der Waals, Electrostatic and Hydrophobic interactions)	
			Van der Waals and	Electrostatic (salt bridge, attractive charge) and Hydrophobic- (Pi-Donor H-Bond, Pi sigma, Pi-Pi T-shaped, Pi-Pi Stacked, Alkyl, Pi-alkyl, Pi-Sulfur & C-H Bond)
Ajmalicine	-8.0	Arg130 (2.88), Arg132 (2.43), Arg292 (2.62)	Arg320, Leu202, Phe194, Asp195, His191	Glu231, Glu232, Arg236, Pro197, Trp228
Ajmalidine	-7.8	Arg130 (1.90), Asp335 (2.77)	His191, His192, Trp228, Leu226, Arg320	Ile238, Met240, Arg132, His296
Ajmaline	-7.1	Arg130 (2.41)	Phe192, Leu193, Phe194, Asp195, Arg236, Arg132, Arg292, Ile238, His296	Trp228, Met240, His191
AlloYohimbine	-7.8	Arg292 (2.23), Arg132 (2.32), Arg341 (2.41), Glu232 (2.55)	Val75, Ser205, Leu201, Val72, Ser285, Arg96, Arg236, Arg320, Asn286	Leu202, Cys283, Met207
Aricine	-7.4	Thr52 (2.02), Asp55 (2.15), Asn8 (2.21)	Arg43, Asp54, Glu46, Phe10	His145, Lys9, Gly50, Phe10
Canescine	-8.6	Asp195 (3.01), Arg132 (2.29)	Phe192, Glu231, Pro197, Gln184, Leu193, Phe194, Arg236, Arg292, Ile238	Lys196, Ile188, Arg292, His296, Met240, Trp228, Leu226His191
Corynanthine	-7.3	Phe271 (3.03), Trp273 (2.47), Glu261 (2.74), Tyr279 (2.22)	Glu79, Met272, Thr108, Leu110, Lys265	Pro270, Lys138
Deserpidine	-8.4	Asp195 (2.38), Arg132 (3.03)	Trp228, Glu231, Pro197, Lys196, Gln184, Leu193, Phe194, Arg236, Arg292, Ile238	Ile188, His296, Met240, Leu226, His191
Norajmaline	-7.4	Arg292 (2.24), Arg130 (3.02), Arg132 (2.42), His191 (2.77)	Arg236, Leu226, Met240, Phe192	Ile238, Trp228
Nortetraphyllicine	-7.9	—	Arg132, Arg236, Arg320, His296, Met240, Phe192	Arg292, Arg130, Ile238, Trp228, Leu226
Papaverine	-6.6	Ser128 (2.28)	Leu187, Leu193, Phe192, Trp228, Leu226, Ile238, Arg132	Ile188, Met240, Lys242, His296, Arg130, His191
Raubasine	-7.9	Asp195 (2.72), Leu193 (2.24), Phe192 (2.72)	Phe194, Trp228, Arg236, Arg132, Met240, Gln184	His191, Ile238, Leu226, Ile188
Raucaffricine	-7.8	Arg130 (2.60), Glu231 (2.27)	Val198, Asp195, Leu202, Phe194, Trp228, Leu193, His191, Leu226, Ile238, Met240, Arg236, Arg292	Pro197, Ile188
Rauhimbine	-7.4	Asn8 (1.80), Asp55 (2.95)	Lys9, Thr52, Glu46, Gly50, Arg209, Gly206	Phe51, Pro144, Ser205, His145
Rauwolscline	-7.6	Arg130 (2.45, 2.56), Arg292 (2.69), Arg132 (2.84), Arg236 (2.73)	Trp228, Phe194, Asp195, Ile238	Ile188, Leu193, His191, Met240
Recanescine	-8.7	Ser128 (2.57), Lys242 (2.80), Arg130(2.05)	Leu193, Phe194, Asp195, Trp228, Leu202, Glu232, Arg236, Arg292, Arg132, Ile238	Glu231, Pro197, His296, His191, Met240
Rescinamine	-7.7	Lys242 (1.99, 2.72), Arg236 (2.21, 2.61)	Leu193, Ile188, Phe194, Arg292, Arg130, Ser128	Met240, Trp228, Asp195, His191, Val198
Reserpiline	-7.6	Arg130 (1.86), Asp195 (2.13)	Phe194, His296, Gln184	Trp228, Ile238, Arg132, His191, Met240, Ile188, Leu193, Glu231

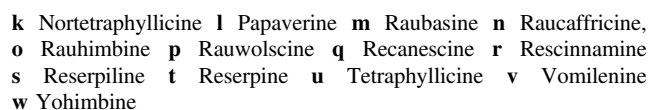
Table 5 (continued)

Identified phytochemicals	Binding energy	H-Bond (H-Bond distance)	Residual interactions (Van der Waals, Electrostatic and Hydrophobic interactions)
			Van der Waals and Electrostatic (salt bridge, attractive charge) and Hydrophobic (Pi-Donor H-Bond, Pi sigma, Pi-Pi T-shaped, Pi-Pi Stacked, Alkyl, Pi-alkyl, Pi-Sulfur & C-H Bond)
Reserpine	-8.3	Arg132 (2.37), Arg292 (3.00), Asp195 (2.96)	Leu193, Gln184, Phe194, Pro197, Glu231, Arg236, Ile188, Lys196, Ile238, Trp228, Leu226, His191, Met240, His296, Arg130
Tetraphyllicine	-8.2	—	Arg320, Met240, Phe192, Arg132
Vomilenine	-8.2	Arg236 (2.21), Leu193 (2.73)	Met240, Leu226, Phe192, His191, Phe194, Ile188, Asp195, Arg132
Yohimbine	-7.8	Arg96 (2.01, 3.08), Gln318 (2.48)	Glu309, Leu317, Thr313, Asp340, His97
Sildenafil citrate	-7.7	Arg130 (2.42), Phe192 (2.40)	Leu312, Lys319, Ala339, Arg341, Arg236, Glu231, Phe194, Asp195, Leu193, Ile188, Leu187, His191, Met240, Arg132, Arg191

in sexual behavior, erectile dysfunction, and endothelial cell oxidative impairment are some of the pathophysiological signs of male sexual dysfunction [51]. Since there are several causes of ED, treatment may involve a variety of approaches and call for several regimens. Additionally, flushing, visual impairment, and dyspepsia are common adverse effects of the majority of conventional medications used to treat ED. However, the majority of these adverse effects can be avoided by treating ED using natural herbs that have aphrodisiac properties.

These results imply that, like sildenafil citrate, *Rauwolfia vomitoria* extract can successfully lower PDE-5 activity in penile tissue. Comparing the test groups to the control and paroxetine-treated groups revealed a substantial decrease in PDE-5 activity. This illustrates the potential use of *Rauwolfia vomitoria* extract as a natural remedy for erectile dysfunction (ED). By blocking the breakdown of cyclic guanosine monophosphate (cGMP), which promotes smooth muscle relaxation and enhanced blood flow in the corpus cavernosum, PDE5 inhibitors, such as sildenafil citrate, are well known for their use in the treatment of erectile dysfunction (ED) [11]. *Rauwolfia vomitoria* extract may improve erectile performance by increasing the accumulation of cGMP levels, as evidenced by its capacity to similarly reduce PDE5 activity. The results of this investigation are consistent with a number of earlier studies that looked at the effects of natural extracts on PDE5 activity. In their review of natural aphrodisiacs, Rahman et al. [52] emphasized the potential of plant-based compounds to inhibit PDE5, providing new treatment options for erectile dysfunction. The idea that natural extracts can be useful in regulating the activity of this enzyme is supported by the notable decrease in PDE5 activity seen with *Rauwolfia vomitoria* extract in the current study. This is in line with the findings of Oboh et al. [53], who discovered that *R. vomitoria* inhibited PDE5 in a dose-dependent manner.

In a related study, Akuamoah et al. [54] demonstrated that ginseng extract could inhibit PDE5 activity and improve erectile function in animal models. The present study's findings that *Rauwolfia vomitoria* extract can decrease PDE5 activity are consistent with these results, suggesting that various natural extracts may share similar mechanisms of action in enhancing erectile function. Moreover, studies on *Epimedium* extract (Horny Goat Weed) have shown its potential to inhibit PDE5 and enhance erectile responses in animal models [55]. The mechanisms by which *Rauwolfia vomitoria* extract reduces PDE5 activity are not entirely understood, but several hypotheses can be proposed. One possibility is that the extract contains bioactive compounds that directly inhibit PDE-5 activity. Research supports this theory by showing that various phytochemicals, such as flavonoids and alkaloids, can inhibit PDE-5 [56]. Another potential mechanism is the modulation of signalling



pathways involved in cGMP production and degradation. A study conducted by Puşcaşu et al. [12] emphasized the importance of the NO-cGMP pathway in erectile function. *Rauwolfia vomitoria* extract may enhance NO production or inhibit cGMP degradation, thereby reducing PDE5 activity and promoting smooth muscle relaxation and vasodilation in penile tissue.

The observed increase in NO concentration in penile tissue following administration of *Rauwolfia vomitoria* extract is significant because in both vasodilation and erectile function, NO is essential. NO plays a vital role in the relaxation of the corpus cavernosum's smooth muscle, which promotes erection and improved blood flow [57]. The significant increase in NO concentration at higher doses of the extract suggests that *Rauwolfia vomitoria* may potentiate erectile function through enhanced NO production, comparable to the effects of the popular phosphodiesterase type 5 (PDE5) inhibitor sildenafil citrate. The enzyme endothelial NO synthase (eNOS), which produces NO in endothelial cells, is activated by *Rauwolfia vomitoria* extract [58]. This is consistent with Hsuan et al. [59] study, which showed that *Glossogyne tenuifolia* extract significantly increased NO production and improved erectile function in animal models.

Rauwolfia vomitoria extract's capacity to regulate enzyme activity involved in NO production is demonstrated by the notable reduction in arginase activity seen in the groups that got 12.5 and 25 mg/kg body weight of the extract. Arginase and Nitric Oxide Synthase (NOS) compete for L-arginine, a common substrate, thereby regulating NO availability [60]. By inhibiting arginase activity, *Rauwolfia vomitoria* extract may increase L-arginine availability for NO synthesis, thereby improving endothelial function and erectile response. The results of this study are reliable with earlier investigations on the modulation of arginase activity by natural extracts. According to Shin et al. [61] study demonstrated that Korean red ginseng extracts significantly inhibited arginase activity, resulting in increased NO production and improved erectile function in rats. Li et al. [62] study found that arginase inhibition led to enhanced NO production and improved vascular function in erectile tissue. The significant decrease in arginase activity observed with *Rauwolfia vomitoria* extract supports the hypothesis that arginase inhibition can be a therapeutic strategy for improving erectile function. *Rauwolfia vomitoria* extract may contain polyphenolic compounds, which have been shown to inhibit arginase activity in various tissues [63]. These compounds may interact with the active site of arginase or modulate its expression, thereby reducing its activity.

Testosterone plays a crucial role in male reproductive health, influencing libido, muscle mass, bone density, and overall well-being [64]. The observed rise in plasma

testosterone levels in the groups administered 25 and 50 mg/kg body weight of *Rauwolfia vomitoria* extract raises the possibility that the extract possesses androgenic qualities, enhancing testosterone production and/or release. This could be particularly beneficial for individuals with testosterone deficiency or related conditions, improving their quality of life and physical health. These findings align with previous research, which highlighted the testosterone-boosting effects of various herbal extracts. Koloko et al. [31] showed that extracts from *Rauwolfia vomitoria* roots markedly raised testosterone levels in male rats.

Similarly, the present study indicates that *Rauwolfia vomitoria* extract may have comparable effects, supporting the potential use of herbal extracts in managing testosterone deficiency [65]. Furthermore, a study by Qureshi et al. [66] showed that extracts from *Tribulus terrestris* significantly increased testosterone levels in male rats, corroborating the present findings that certain herbal extracts can effectively enhance plasma testosterone concentration. These studies, combined with the current research, underscore the therapeutic potential of herbal extracts in boosting testosterone levels. One potential mechanism is the stimulation of the hypothalamic-pituitary-gonadal (HPG) axis, leading to increased secretion of luteinizing hormone (LH) and subsequent stimulation of testosterone production by the testes [67]. Additionally, bioactive compounds in *Rauwolfia vomitoria*, such as alkaloids, may directly stimulate Leydig cells in the testes to produce more testosterone [68].

The absence of significant differences in plasma CK-MB activity between the *Rauwolfia vomitoria* treated groups and the sildenafil citrate and control groups suggest that the extract does not induce additional cardiac stress or damage. In contrast, the significant decrease in CK-MB activity compared to the paroxetine-treated group indicates a potential cardioprotective effect. Paroxetine, an SSRI, has been associated with various cardiovascular side effects, including an increase in cardiac enzyme levels, indicating stress or damage to cardiac tissues [69].

The findings of the present study imply that *Rauwolfia vomitoria* extract could counteract these adverse effects, offering a protective mechanism against SSRI-induced cardiac stress. A study by Lobay [70] demonstrated that *Rauwolfia vomitoria* extract exhibited significant anti-hypertensive and antiarrhythmic effects in experimental animal models, suggesting its potential in protecting cardiac tissue from damage. Furthermore, a study by Xue et al. [71] stated that ginger extract significantly reduced CK-MB levels in rats with induced myocardial infarction, corroborating the cardioprotective effects observed in the present study. These studies, combined with the current research, underscore the therapeutic potential of herbal extracts in managing cardiac health and preventing tissue damage. The extract's antioxidant qualities, which might lessen oxidative

stress and stop heart cell damage, are one possible method [72]. Antioxidants are crucial for counteracting reactive oxygen species (ROS) and conserving cellular integrity, and oxidative stress is a known cause of heart injury [73]. By reducing oxidative stress, *Rauwolfia vomitoria* extract may help preserve cardiac tissue and reduce the release of CK-MB. Additionally, the extract's anti-inflammatory properties may contribute to its cardioprotective effects. Inflammation is a key factor in cardiac tissue damage and the progression of cardiovascular diseases [74]. By inhibiting inflammatory pathways, *Rauwolfia vomitoria* extract may reduce cardiac inflammation and subsequent enzyme release, offering further protection to the heart.

The significance of these findings lies in the ability of *Rauwolfia vomitoria* extract to modulate lipid profiles adversely affected by paroxetine. Dyslipidemia is a critical risk factor for cardiovascular diseases [75], considering the extract's capacity to lower triglyceride, low-density lipoprotein cholesterol (LDLc) and total cholesterol levels while increasing high-density lipoprotein (HDL) levels suggests its therapeutic potential for managing SSRI-induced lipid disorders [76]. The dose-dependent effects observed, with the 50 mg/kg body weight group showing the most pronounced improvements, highlight the extract's efficacy and the importance of dosage in achieving optimal therapeutic outcomes.

The cardioprotective effects of *Rauwolfia vomitoria* observed in this study aligned with previous research highlighting the lipid-lowering properties of various natural extracts. Faponle et al. [77] demonstrated that *Rauwolfia vomitoria* extract exhibited significant antihypertensive and lipid-lowering effects in experimental animal models, supporting its use in managing cardiovascular risk factors. In a similar vein, Khosravani et al. [78] found that ginger extract dramatically raised HDL levels in rats while lowering total cholesterol and LDL levels, corroborating the lipid-modulating effects observed with *Rauwolfia vomitoria*. The present study's findings are consistent with these results, indicating that natural extracts can effectively manage dyslipidemia. The lipid-modulating effects of *Rauwolfia vomitoria* extract may be attributed to several mechanisms. One possible route is the suppression of 3-hydroxyl-3-methylglutaryl-CoA (HMG-CoA) reductase, which is crucial for the production of cholesterol. Inhibition of this enzyme can lead to reduced cholesterol production [79], which may explain the significant decrease in total cholesterol and LDL levels observed in the study. Additionally, the extract's antioxidant properties could reduce oxidative stress, a known contributor to lipid peroxidation and dyslipidemia [80]. Furthermore, the anti-inflammatory properties of *Rauwolfia vomitoria* may play a role in modulating lipid profiles [81]. Chronic inflammation is associated with alterations in lipid metabolism, and by

reducing inflammation, the extract could help restore normal lipid levels. These combined effects underscore the multifaceted nature of the extract's action on lipid metabolism.

Reserpine, Reserpiline Tetraphyllicine, Tetraphyllicine, Coryanthine (Rauhimbine), Aricine, Ajmaline and Raubasine are a class of phytomedicinal compounds called alkaloids [82]. A minimum of one nitrogen atom is present in this group of basic, organic compounds that occur naturally. Alkaloids are utilized in the production of medications because they have a significant metabolic impact on living things, altering their physiology and providing protection for animals. The Discovery Studio 2020 software was used to visualize the docking results, revealing the compounds' ideal docking positions (Table 3), the PDE5 binding sites with amino acid deposits involved in their cooperation with PDE5, and the various bonds (Fig. 9) involved (Pi-Pi, Pi-alkyl, Pi-sigma, carbon-hydrogen bond, conventional hydrogen bond, etc.). The affinity for binding between ligands and proteins in complexes was evaluated using the H-bonds, binding energy, residual interactions, such as the Van der Waals interaction, electrostatic contacts, and hydrophobic interactions (Table 3). Figure 9 shows compounds that were present binding with one or more of the catalytic amino acid residues of PDEs, which are Ala, Asn, Gln, His, Ile, Leu, Lys, Phe, and Tyr [47]. Prior research indicated that Arg667, Asn662, Gln817, Leu804, Ser663, and Phe786 would be the catalytic amino acid residues of PDE-5 [47]. Overall, the compounds suppressed PDE-5 by a mechanism of action comparable to that of sildenafil citrate, despite the fact that each of them connected with one or more main catalytic site amino acid deposits using a conventional hydrogen bond, van der Waals forces, or Pi-Alkyl interactions [47]. It is important to remember that most of the substances interacted with different PDE-5 amino acids, unlike Sildenafil Citrate (Fig. 9). Meanwhile, a small number of compounds (Papaverine, Raubasine, AlloYohimbine, and Aricine) present in the extract may compete with the substrate for the enzyme's active spot in a style similar to how sildenafil citrate acts (Fig. 9a, e, f, l, & m). This suggests that the chemicals' attempt to inhibit PDE-5 generally through extract may use both competitive and non-competitive inhibition methods. This finding supports earlier studies that Heinrich et al. [83], reported. The results of the in-silico molecular interactions between PDE-5 (PDB ID: 2h42) and the compounds found (Fig. 1) are therefore generally consistent with the results of our in-vivo PDE-5 inhibition experiment, in which the extract significantly decreased the activity of PDE-5 extract conveying a relatively better PDE-5 inhibitory outcome as compared to sildenafil citrate both in penile and cardiac tissues.

This suggests that these bioactive substances may competitively inhibit arginase by a mechanism akin to that of

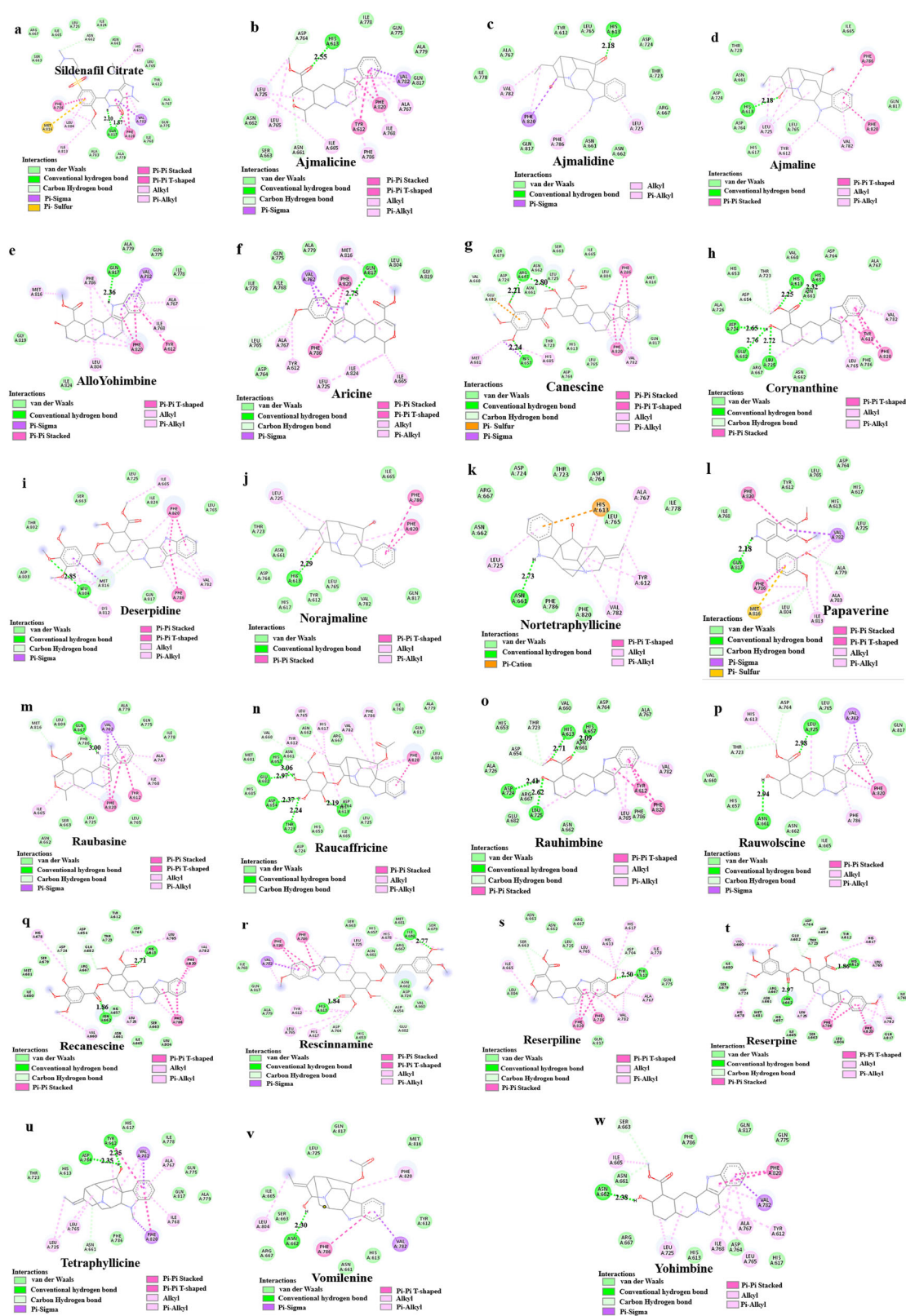


Fig. 9 Model of the Interaction and the 2D Structure of PDE-5 protein showing catalytic amino acids in PDE-5 with **a** Sildenafil citrate **b** Ajmalicine **c** Ajmalidine **d** Ajmaline **e** AlloYohimbine **f** Aricine **g** Canescine **h** Corynanthine, **i** Deserpidine **j** Norajmaline

k Nortetraphyllicine **l** Papaverine **m** Raubasine **n** Raucaffricine, **o** Rauhimbine **p** Rauwolsine **q** Recanescine **r** Rescinnamine **s** Reserpiline **t** Reserpine **u** Tetraphyllicine **v** Vomilenine **w** Yohimbine

sildenafil citrate. On the other hand, it was observed that some identified phytochemicals did not interact with arginase via conventional hydrogen bond using identified catalytic amino acids (Val256, Tyr41, Gly87) with Sildenafil citrate (Table 4), however, they interact with predicted catalytic amino acids thru other types of bonds like van der Waals and other hydrophobic-Pi interactions as shown in Fig. 7c, d, i, j, l, m, n, q, r–w. These substances are typically connected with one or two of the vital amino acid residues of the enzyme's catalytic site by weak van der Waals forces, traditional hydrogen bonds, pi-sigma, pi-alkyl, pi-cation, pi-anion, or Pi-Pi interactions. Resilient hydrogen bonding between proteins and ligands is suggested by the bioactive chemicals in the target proteins (arginase) being smaller than 3.5 Å. Our in vivo and in silico results corroborated with other reported analysis. According to Omojokun et al. [84] reported that alkaloids inhibit erectile dysfunction markers (Arginase and PDE5) with considerable antioxidant activity in a concentration-dependent manner. Also, alkaloids work as dopamine agonists because they look similar [85]. By binding to receptors in the paraventricular nucleus of the hypothalamus, alkaloids improve the central pro-erectile mechanism and transmit signals to the spinal cord's erection-generating area [84]. By increasing the activity of nitric oxide synthase, releasing nitric oxide, widening blood vessels, and relaxing the corpus carvenosum smooth muscles of the penis, all of these phytoconstituents present in the ethanol extract of *R. vomitoria* stem bark contributes to improved penile erection [30].

Creatine kinase-MB (CK-MB) is a significant enzyme that serves as a biomarker for cardiac tissue damage, commonly used to diagnose myocardial infarction (heart attack) and other heart-related conditions, but its levels can also be elevated in cases of ED. The docking approach allowed the bioactive chemicals (ligands) to freely access all possible binding sites on the protein (CK-MB). According to Oyewusi et al. [47], this provided them with relevant information regarding possible ligand-protein binding interactions that could result in competitive, non-competitive, or mixed inhibition. The formed complexes' binding energies showed that the chemicals discovered and sildenafil citrate, a medication used to treat erectile dysfunction, had good inhibitory effects on CK-MB activity. The efficiency of both compounds to prevent the hydrolytic activity of CK-MB was really reflected in the approved bond gaps of less than 3.5 Å between the hydrogen-acceptor and hydrogen-donor atoms [86–88]. According to literature, Ajmaline and its structurally related compounds discovered in stem bark extract *R. vomitoria* have been reported to be good antihypertensive agents and are used to develop drugs for high blood pressure [89]. Also, Recanescine, is recently isolated from *Rauwolfia canescens* and showed pharmacological properties similar to reserpine and rescinnamine with

potential hypotension, bradycardia, and sedation properties by characteristic alteration in cardiovascular responses [90]. Therefore, the findings of this study supported the use of *R. vomitoria* as an aphrodisiac which is liable to treat erectile dysfunction.

Conclusion

The first step in the drug development process is identifying the right drug target. Such targets must be validated in order to demonstrate a sufficient degree of confidence and to determine their pharmacological effectiveness in connection to the condition being studied. In order to find interesting drug targets for the creation of new medications suited for in silico clinical trials and clinical applicability, researchers can now investigate and interact with a variety of drug targets using in silico drug design, which has grown in importance. The *in-silico* method offers a significant benefit in terms of reducing the time and expense associated with the drug discovery process. As the first in vivo and in silico investigation of the phytochemicals found in the ethanol extract of *Rauwolfia vomitoria*'s inhibitory activity against PDE 5, arginase, and CK-MB as a restorative target for the treatment of erectile dysfunction, this study is, to the best of our knowledge, unique and noteworthy. Comparing the extract to the reference medication sildenafil citrate, it is also important to note that it has a significant inhibitory effect on both the penile and cardiac tissues. Additionally, the inhibitory effect of the extract independently in the penile and cardiac samples demonstrated remarkable inhibition capacity. The discovery of many types of phytochemicals in the plant may be the cause of this. The findings from this study indicated that the ethanol extract of *R. vomitoria* stem bark inhibited the enzymes in dose-dependent ways, and the phytochemicals investigated may be a promising therapeutic agent that is more advantageous over selective PDE-5 inhibitors (sildenafil citrate). It may also be a prospective aphrodisiac mediator with effective inhibitory action against PDE-5 and arginase. The natural compounds identified in RVE could be used to design and develop new treatment options not only for ED but also for coronary artery disease.

Data Availability

No datasets were generated or analysed during the current study.

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Author contributions H.F.M.: conceptualization, methodology, validation, formal analysis, investigation, data curation, writing (original

draft) & editing, supervision; H.A.O.: methodology, software, data analysis, supervision writing—review & editing, visualization; A.R.A.: project administration, resources, data analysis, writing—original draft; M.H.N.: review & editing; all authors have read and agreed to the published version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

References

- Anderson, D., Laforge, J., Ross, M. M., Vanlangendonck, R., Hasoon, J., Viswanath, O., Kaye, A. D., & Urits, I. (2022). Male sexual dysfunction. *Health Psychology Research*, 10(3), 37533. <https://doi.org/10.52965/001c.37533>.
- Leslie, S. W., & Sooriyamoorthy, T. (2024). Erectile dysfunction. *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/book/NBK562253/> Available from.
- Wang, C. M., Wu, B. R., Xiang, P., Xiao, J., & Hu, X. C. (2023). Management of male erectile dysfunction: From the past to the future. *Frontiers in Endocrinology*, 14, 1148834. <https://doi.org/10.3389/fendo.2023.1148834>.
- Care, U., Tiwari, A., Chandra, P. K., Awasthi, R., Chaudhary, S., Gupta, N., Agarwal, V., Chaubey, S., Ansari, S., Pande, A., Kumar, D., & Awasthi, A. (2022). Assessment of erectile dysfunction and other sexual dysfunction in men with type 2 diabetes mellitus: A multicenter observational study in North India. *Clinical Epidemiology and Global Health*, 18, 101136. <https://doi.org/10.1016/j.cegh.2022.101136>.
- Yannas, D., Frizza, F., Vignozzi, L., Corona, G., Maggi, M., & Rastrelli, G. (2021). Erectile dysfunction is a hallmark of cardiovascular disease: Unavoidable matter of fact or opportunity to improve men's health? *Journal of Clinical Medicine*, 10(10), 2221. <https://doi.org/10.3390/jcm10102221>.
- Melis, M. R., & Argiolas, A. (2021). Erectile function and sexual behavior: A review of the role of nitric oxide in the central nervous system. *Biomolecules*, 11(12), 1866. <https://doi.org/10.3390/biom11121866>.
- Olabiyyi, A. A., Tope-Eniola, O. S., Oluwatuyi, A. O., Alabi, O., Ademola, O. G., Oguntimehin, O. M., & AlliSmith, Y. R. (2022). Quercetin boosts nitric oxide levels and modulates the activities of arginase, acetylcholinesterase, and adenosine deaminase in the corpus cavernosum of cyclosporine-treated rats. *Andrologia*, 54(6), e14404. <https://doi.org/10.1111/and.14404>.
- Sayadi, M., Elmafshar, R., Razeghian-Jahromi, I., & Zibaeenezhad, M. J. (2021). Detection of coronary artery disease by an erectile dysfunction questionnaire. *Cardiology Research and Practice*, 2021, 6647995. <https://doi.org/10.1155/2021/6647995>.
- Brown, J. C., Gerhardt, T. E., & Kwon, E. (2023). Risk factors for coronary artery disease. *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK554410/> Available from.
- Ahmed, M. S., Adil, M., Raja Khan, F., Ullah, S., Rehmat, S., & Zad Gul, N. (2022). Association between erectile dysfunction, cardiovascular risk factors, and coronary artery disease: Role of exercise stress testing and International Index of Erectile Function (IIEF-5) questionnaire. *International Journal of Cardiology. Heart & Vascularity*, 40, 101033. <https://doi.org/10.1016/j.ijcha.2022.101033>.
- Dhaliwal, A., & Gupta, M. (2023). PDE5 inhibitors. *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK549843/> Available from.
- Puşcaşu, C., Zănfirescu, A., Negreş, S., & Şeremet, O. C. (2023). Exploring the multifaceted potential of sildenafil in medicine. *Medicina*, 59(12), 2190. <https://doi.org/10.3390/medicina59122190>.
- Mirone, V., Fusco, F., Cirillo, L., & Napolitano, L. (2023). Erectile dysfunction: From pathophysiology to clinical assessment. In C. Bettocchi, G. M. Busetto, G. Carrieri, & L. Cormio (Eds.), *Practical clinical andrology* (pp. 47–62). Springer, Cham. https://doi.org/10.1007/978-3-031-11701-5_3.
- Caldwell, R. W., Rodriguez, P. C., Toque, H. A., Narayanan, S. P., & Caldwell, R. B. (2018). Arginase: A multifaceted enzyme important in health and disease. *Physiological Reviews*, 98(2), 641–665. <https://doi.org/10.1152/physrev.00037.2016>.
- Nassar, G. N., & Leslie, S. W. (2023). Physiology, testosterone. *StatPearls*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK526128/>.
- Kurapati, R., & Soos, M. P. (2023). CPK-MB. *StatPearls*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK557591/>.
- Li, M., Ma, Z., Zhang, X. L., Guo, L. Q., & Yuan, M. Z. (2020). Significance of blood lipid parameters as effective markers for arteriogenic erectile dysfunction. *Andrology*, 8(5), 1086–1094. <https://doi.org/10.1111/andr.12776>.
- Cure, E., & Cumhuri Cure, M. (2020). Comment on “The relationship between erectile dysfunction and the atherogenic index of plasma. *International Journal of Impotence Research*, 32(5), 475–476. <https://doi.org/10.1038/s41443-020-0236-6>.
- Huang, Q., Wu, H., & Qin, X. (2023). Extract of Pfaffia glomerata ameliorates paroxetine-induced sexual dysfunction in male mice and the characterization of its phytoconstituents by UPLC-MS. *Foods*, 12(17), 3236. <https://doi.org/10.3390/foods12173236>.
- Saikia, Q., Hazarika, A., & Kalita, J. (2023). Isoliquiritigenin ameliorates paroxetine-induced sexual dysfunction in male albino mice. *Reproductive Toxicology*, 117, 108341. <https://doi.org/10.1016/j.reprotox.2023.108341>.
- Padda, I. S., & Tripp, J. (2023). Phosphodiesterase inhibitors. *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK559276/> Available from.
- Kunjiappan, S., Pandian, S. R. K., Panneerselvam, T., Pavadai, P., Kabilan, S. J., & Sankaranarayanan, M. (2023). Exploring the role of plant secondary metabolites for aphrodisiacs. In J. M. Mérillon & K. G. Ramawat (Eds.), *Plant specialized metabolites (Reference Series in Phytochemistry)*. Springer, Cham. https://doi.org/10.1007/978-3-031-30037-0_16-1.
- Bonheur, Y., Dzeufiet, P., Sanda, A., Fotsing, D., & Théophile, D. (2020). Acute and sub-acute toxicity of the aqueous extract of the stem bark of *Rauwolfia vomitoria* (Apocynaceae) in Wistar rats. *World Journal of Advanced Research and Reviews*, 8, 373–385. <https://doi.org/10.30574/wjarr.2020.8.3.0490>.
- Alade, G., & Attah, A. (2023). Pharmacognostic study and peptidomic analysis of the leaves of Nigerian *Rauwolfia vomitoria* Wennberg (Apocynaceae). *Proceedings of the Nigerian Academy of Science*, 16, 72–86. <https://doi.org/10.57046/CUOI3523>.
- Hilal, B., Khan, M. M., & Fariduddin, Q. (2024). Recent advancements in deciphering the therapeutic properties of plant secondary metabolites: phenolics, terpenes, and alkaloids. *Plant Physiology and Biochemistry*, 211, <https://doi.org/10.1016/j.pla.2024.108674>.
- Emencheta, S., Enweani, I., Oli, A., Ibezim, E., Ijeoma, E., & Imanyikwa, O. (2020). Antimicrobial evaluation of plant parts of *Rauwolfia vomitoria*. *Journal of Complementary and Alternative Medical Research*, 12, 11–20. <https://doi.org/10.9734/JOCAMR/2020/v12i130197>.
- Ugwu, P. C., Ozioko, P., & Okon, M. (2022). Vitamin composition of ethanol leaf extract of *Rauwolfia vomitoria*. <https://doi.org/10.13140/RG.2.2.31127.44969>.

28. Asoro, I. I., Ebuehi, O. A. T., & Igwo-Ezikpe, M. N. (2021). GC-MS analysis of the *Rauwolfia vomitoria* ethanol extracts. *European Journal of Medicinal Plants*, 32(6), 34–45. <https://doi.org/10.9734/ejmp/2021/v32i630398>.
29. Etim, E., Johnson, E., Bassey, U., Nwafor, P. A., & Johnson, E. (2018). Phytochemical and aphrodisiac studies of ethanol root extract of *Rauwolfia vomitoria* Afzel (Apocynaceae). *Journal of Biological Sciences*, 15(2), 134–145. <https://doi.org/10.4314/jb.v15i2.9>.
30. Johnson, E., Bassey, U., Nwafor, P. A., Johnson, E., & Etim, E. (2018). Phytochemical and aphrodisiac studies of ethanol root extract of *Rauwolfia vomitoria* Afzel (Apocynaceae). *Journal of Pharmacy & Bioresources*, 15(2), 160–165. <https://doi.org/10.4314/jpb.v15i2.9>.
31. Koloko, B. L., Bushra, I., Wankeu-Nya, M., Ngaha Njila, M. I., Kenmogne, H., Nyonseu Nzeubang, D. C., Nzangueu, C. B., Dimo, T., Dongmo, A. B., & Massoma Lembe, D. (2020). In vivo effects of *Rauwolfia vomitoria* (Apocynaceae) ethanolic extract on sexual performance and reproductive activity in male rats. *Andrologia*, 52(1), e13414 <https://doi.org/10.1111/and.13414>.
32. Khalid, M., Alqarni, M. H., Wahab, S., Annadurai, S., Alamri, M. A., Foudah, A. I., Aljarba, T. M., Akhtar, J., Badruddeen, & Ahmad, S. (2022). Ameliorative sexual behavior and phosphodiesterase-5 inhibitory effects of *Spondias mangifera* fruit extract in rodents: in silico, in vitro, and in vivo study. *Journal of Clinical Medicine*, 11(13), 3732.
33. Ademosun, A. O., Adebayo, A. A., & Oboh, G. (2019). Anogeiussus leiocarpus attenuates paroxetine-induced erectile dysfunction in male rats via enhanced sexual behavior, nitric oxide level and antioxidant status. *Biomedicine & Pharmacotherapy*, 111, 1029–1035.
34. Akanbi, O. M. (2019). Performance and health implication of feeding Fungi treated cocoa pod husk meal on broiler. *Bulletin of the National Research Centre*, 43, 1–8.
35. Alabi, Q. K., Akomolafe, R. O., Omole, J. G., Aturamu, A., Ige, M. S., Kayode, O. O., & Kajewole-Alabi, D. (2021). Polyphenol-rich extract of *Ocimum gratissimum* leaves prevented toxic effects of cyclophosphamide on the kidney function of Wistar rats. *BMC Complementary Medicine and Therapies*, 21, 1–14.
36. Muritala, H. F., & Bewaji, C. O. (2021). Paroxetine administration alter some biochemical parameters in male Wistar rats over a systemic period of thirty-five days. *Nigerian Journal of Pure and Applied Science*, 34(1), 3800–3816.
37. Butcher, R. W., & Sutherland, E. W. (1962). Adenosine 3', 5'-phosphate in biological materials. *Journal of Biological Chemistry*, 237(4), 1244–1250.
38. Tietz, N. W. (1995). *Clinical guide to laboratory tests*. 3rd ed. W.B. Saunders Company.
39. Huml, L., Tauchen, J., Rimpelová, S., Holubová, B., Lapčák, O., & Jurášek, M. (2021). Advances in the determination of anabolic-androgenic steroids: from standard practices to tailor-designed multidisciplinary approaches. *Sensors*, 22(1), 4.
40. Gholib, G., Wahyuni, S., Akmal, M., Hasan, M., Agil, M., & Purwantara, B. (2020). The validation of a commercial enzyme-linked immunosorbent assay and the effect of freeze-thaw cycles of serum on the stability of cortisol and testosterone concentrations in Aceh cattle. *F1000Research*, 8, 1220.
41. Sukowati, Y. K., Johan, A., & Murwani, R. (2019). Ethanol extracts of *Ficus carica* fruit and leaf normalize high serum lipid profile, TNF- α , and MDA due to high fat diet in Sprague Dawley rat. *Current Research in Nutrition and Food Science Journal*, 7(3), 772–782.
42. Oyewusi, H. A., Huyop, F., & Wahab, R. A. (2022). Molecular docking and molecular dynamics simulation of *Bacillus thuringiensis* dehalogenase against haloacids, haloacetates and chlorpyrifos. *Journal of Biomolecular Structure and Dynamics*, 40(5), 1979–1994.
43. Oyewusi, H. A., Akinyede, K. A., Abdul Wahab, R., & Huyop, F. (2023). In silico analysis of a putative dehalogenase from the genome of halophilic bacterium *Halomonas smyrnensis* AAD6T. *Journal of Biomolecular Structure and Dynamics*, 41(1), 319–335.
44. Oyewusi, H. A., Wahab, R. A., Akinyede, K. A., Albadrani, G. M., Al-Ghadi, M. Q., Abdel-Daim, M. M., Ajiboye, B. O., & Huyop, F. (2024a). Bioinformatics analysis and molecular dynamics simulations of azoreductases (AzrBmH2) from *Bacillus megaterium* H2 for the decolorization of commercial dyes. *Environmental Sciences Europe*, 36(1), 31.
45. Oyewusi, H. A., Adedamola Akinyede, K., Wahab, R. A., Susanti, E., Syed Yaacob, S. N., & Huyop, F. (2024b). Biological and molecular approaches of the degradation or decolorization potential of the hypersaline Lake Tuz *Bacillus megaterium* H2 isolate. *Journal of Biomolecular Structure and Dynamics*, 42(12), 6228–6244.
46. Adekilekun, H. A., Oyewusi, H. A., Wahab, R. A., Huyop, F., Albadrani, G. M., Al-Ghadi, M. Q., Abdel-Daim, M. M., Ajiboye, B. O., Igbinoba, S. I., Odoma, S., & Onohuean, H. (2024). A computational discovery of hexokinase 2 inhibitors from *Newbouldia laevis* for Hepatocellular carcinoma (HCC) treatment. *South African Journal of Botany*, 169, 12–26.
47. Oyewusi, H. A., Oladipo, O. O., Muritala, H. F., Olaleye, A. C., & Akinyede, K. A. (2024c). Ex-vivo antioxidant, enzyme inhibitory properties and computational analysis unveil the molecular mechanism of cardiac and penile phosphodiesterase-5 inhibition by bacterial strain HOKA1 extract as an aphrodisiac's agent. *International Journal of Biological Macromolecules*, 283, 137513.
48. Tze Lin, K., Mahat, N. A., Azman, A. R., Wahab, R. A., Oyewusi, H. A., & Abdul Hamid, A. A. (2023). Interaction of the nanobio-based reagent with sodium fluorescein and lipids via bioinformatics for forensic fingerprint visualisations. *Journal of Biomolecular Structure and Dynamics*, 41(24), 15045–15052.
49. Atmaca, M. (2020). Selective serotonin reuptake inhibitor-induced sexual dysfunction: current management perspectives. *Neuropsychiatric disease and treatment*, 16, 1043–1050.
50. Kaloğlu, H. A., Öztürk, G. S., & Dilekoz, E. (2024). Sexual dysfunctions (SD) and selective serotonin reuptake inhibitors (SSRIs): from preclinical studies to intervention strategies. *Anatolian Current Medical Journal*, 6(5), 341–348.
51. Kaltsas, A., Zikopoulos, A., Dimitriadis, F., Sheshi, D., Politis, M., Moustakli, E., Symeonidis, E. N., Chrisofos, M., Sofikitis, N., & Zachariou, A. (2024). Oxidative stress and Erectile Dysfunction: pathophysiology, impacts, and potential treatments. *Current Issues in Molecular Biology*, 46(8), 8807–8834.
52. Rahman, A. U., Alam, F., Khan, M., Sarfraz, M., Basit, A., Ahmad, T., Khokhar, M. A., Ali, S., & Khan, K. U. (2023). Evaluating the aphrodisiac potential of *Mirabilis jalapa* L. root extract: Phytochemical profiling and in silico, in vitro, and in vivo assessments in normal male rats. *Molecules*, 28(17), 6314 <https://doi.org/10.3390/molecules28176314>.
53. Oboh, G., Adebayo, A. A., & Ademosun, A. O. (2019). HPLC phenolic fingerprinting, antioxidant and anti-phosphodiesterase-5 properties of *Rauwolfia vomitoria* extract. *Journal of Basic and Clinical Physiology and Pharmacology*, 30(5), <https://doi.org/10.1515/jbcpp-2019-0059>.
54. Akuamo, F., Hoogenboom, R. L. A. P., Hamers, A., Rietjens, I. M. C. M., & Bovee, T. F. H. (2021). PDE-5 inhibitors in selected herbal supplements from the Ghanaian market for better erectile function as tested by a bioassay. *Toxicology in Vitro*, 73, 105130 <https://doi.org/10.1016/j.tiv.2021.105130>.

55. Edwards, S., Rocha, I., Williamson, E., & Heinrich, M. (2015). Horny goat weed. In *Handbook of Medicinal Herbs* (3rd ed., pp. 111–118). CRC Press. <https://doi.org/10.1002/9781118543436.ch58>.
56. Panklai, T., Suphrom, N., Temkitthawon, P., Totoson, P., Chootip, K., Yang, X. L., Ge, H. M., Yao, Z. J., Chaichamnong, N., Ingkaninan, K., & Girard, C. (2023). Phosphodiesterase 5 and arginase inhibitory activities of the extracts from some members of Nelumbonaceae and Nymphaeaceae families. *Molecules*, 28(15), 5821 <https://doi.org/10.3390/molecules28155821>.
57. de Souza, I. L. L., Ferreira, E. D. S., Vasconcelos, L. H. C., Cavalcante, F. A., & da Silva, B. A. (2022). Erectile dysfunction: Key role of cavernous smooth muscle cells. *Frontiers in Pharmacology*, 13, 895044 <https://doi.org/10.3389/fphar.2022.895044>.
58. Adebayo, A. A., Ademosun, A. O., & Oboh, G. (2023). Chemical composition, antioxidant, and enzyme inhibitory properties of *Rauwolfia vomitoria* extract. *Journal of Complementary and Integrative Medicine*, 20(3), 597–603. <https://doi.org/10.1515/jcim-2022-0390>.
59. Hsuan, C. F., Lee, T. L., Tseng, W. K., Wu, C. C., Chang, C. C., Ko, T. L., Chen, Y. L., & Hwang, J. Y. (2021). Glossogyne tenuifolia extract increases nitric oxide production in human umbilical vein endothelial cells. *Pharmaceuticals*, 14(6), 577 <https://doi.org/10.3390/ph14060577>.
60. Caldwell, R. B., Toque, H. A., Narayanan, S. P., & Caldwell, R. W. (2015). Arginase: An old enzyme with new tricks. *Trends in Pharmacological Sciences*, 36(6), 395–405. <https://doi.org/10.1016/j.tips.2015.03.006>.
61. Shin, W., Yoon, J., Oh, G. T., & Ryoo, S. (2013). Korean red ginseng inhibits arginase and contributes to endothelium-dependent vasorelaxation through endothelial nitric oxide synthase coupling. *Journal of Ginseng Research*, 37(1), 64–73. <https://doi.org/10.5142/jgr.2013.37.64>.
62. Li, Z., Wang, L., & Ren, Y., et al. (2022). Arginase: Shedding light on the mechanisms and opportunities in cardiovascular diseases. *Cell Death Discovery*, 8, 413 <https://doi.org/10.1038/s41420-022-01200-4>.
63. Minozzo, B. R., Fernandes, D., & Beltrame, F. L. (2018). Phenolic compounds as arginase inhibitors: New insights regarding endothelial dysfunction treatment. *Planta Medica*, 84(5), 277–295. <https://doi.org/10.1055/s-0044-100398>.
64. Nassar, G. N., & Leslie, S. W. (2024). Physiology, Testosterone. StatPearls [Internet]. PMID: 30252384
65. Kada, A. S., Aneng, E., Mbouh, M., Manfo, F. P., Ngimgoh, S. N., & Nantia, E. A. (2021). Testicular antioxidants and testosterone enhancing effects of the hydro-ethanolic extract of *Rauwolfia vomitoria* (Apocynaceae) in male Wistar rats. *Investigational Medicinal Chemistry and Pharmacology*, 4(2), 1–6.
66. Qureshi, A., Naughton, D. P., & Petroczi, A. (2014). A systematic review on the herbal extract *Tribulus terrestris* and the roots of its putative aphrodisiac and performance-enhancing effect. *Journal of Dietary Supplements*, 11(1), 64–79. <https://doi.org/10.3109/19390211.2014.887602>.
67. Acevedo-Rodriguez, A., Kauffman, A. S., Cherrington, B. D., Borges, C. S., Roepke, T. A., & Laconi, M. (2018). Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling. *Journal of Neuroendocrinology*, 30(10), e12590 <https://doi.org/10.1111/jne.12590>.
68. Chen, X., Ge, F., Liu, J., Bao, S., Chen, Y., Li, D., Li, Y., Huang, T., Chen, X., Zhu, Q., Lian, Q., & Ge, R. S. (2018). Diverged effects of piperine on testicular development: Stimulating Leydig cell development but inhibiting spermatogenesis in rats. *Frontiers in Pharmacology*, 9, 244 <https://doi.org/10.3389/fphar.2018.00244>.
69. Wu, S., Zhou, Y., Xuan, Z., Xiong, L., Ge, X., Ye, J., Liu, Y., Yuan, L., Xu, Y., Ding, G., Xiao, A., Guo, J., & Yu, L. (2021). Repeated use of SSRIs potentially associated with an increase on serum CK and CK-MB in patients with major depressive disorder: A retrospective study. *Scientific Reports*, 11(1), 13365 <https://doi.org/10.1038/s41598-021-92807-7>.
70. Lobay, D. (2015). *Rauwolfia* in the treatment of hypertension. *Integrative Medicine (Encinitas, Calif.)*, 14(3), 40–46.
71. Xue, Y., Zhang, M., Zheng, B., Zhang, Y., Chu, X., Liu, Y., Li, Z., Han, X., & Chu, L. (2021). [8]-Gingerol exerts anti-myocardial ischemic effects in rats via modulation of the MAPK signaling pathway and L-type Ca²⁺ channels. *Pharmacology Research & Perspectives*, 9(5), e00852 <https://doi.org/10.1002/prp2.852>.
72. Tihapi, D. B., Ramaite, I. D. I., Anokwuru, C. P., van Ree, T., & Hoppe, H. C. (2020). In vitro studies on antioxidant and anti-parasitic activities of compounds isolated from *Rauwolfia caffra* Sond. *Molecules (Basel, Switzerland)*, 25(17), 3781 <https://doi.org/10.3390/molecules25173781>.
73. Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., Squadrito, F., Altavilla, D., & Bitto, A. (2017). Oxidative stress: Harms and benefits for human health. *Oxidative Medicine and Cellular Longevity*, 2017, 8416763 <https://doi.org/10.1155/2017/8416763>.
74. Bonheur, Y. D. D., Désiré, D. D. P., Ernestine, N. Z., Stéphane, Z., Christophe, M., Oumarou, B. F. A., Francine, T. N., Anatole, P. C., & Théophile, D. (2015). Antiinflammatory and antioxidant effects of the stem bark aqueous extract of *Rauwolfia vomitoria* (Apocynaceae) in female Wistar rats. *European Journal of Pharmaceutical and Medical Research*, 2, 64–73.
75. Hedayatnia, M., Asadi, Z., Zare-Feyzabadi, R., Yaghooti-Khorasani, M., Ghazizadeh, H., Ghaffarian-Zirak, R., Nosrati-Tirkani, A., Mohammadi-Bajgiran, M., Rohban, M., Sadabadi, F., Rahimi, H. R., Ghalandari, M., Ghaffari, M. S., Yousefi, A., Pouresmaeli, E., Besharatlou, M. R., Moohebat, M., Ferns, G. A., Esmaily, H., & Ghayour-Mobarhan, M. (2020). Dyslipidemia and cardiovascular disease risk among the MASHAD study population. *Lipids in Health and Disease*, 19(1), 42 <https://doi.org/10.1186/s12944-020-01204-y>.
76. Owoade, O., Adetutu, A., Ogundipe, O., & Owoade, A. (2021). Hypolipidemic potentials of methanolic extract of *Rauwolfia vomitoria* leaves in rats fed with high cholesterol. *Asian Plant Research Journal*, 8, 15–25. <https://doi.org/10.9734/APRJ/2021/v8i430181>.
77. Faponle, A., Atunnise, A., Adegbesan, B., Ogunlabi, O., Odufuwa, K., & Ajani, E. (2015). Combined administration of *Rauwolfia vomitoria* extract and Vitamin C elicits hypolipidemic and antioxidative potentials in high-fat fed experimental rats. *IOSR Journal of Pharmacy and Biological Sciences*, 10, 52–60. <https://doi.org/10.9790/3008-10225260>.
78. Khosravani, M., Azarbayjani, M. A., Abolmaesoomi, M., Yusof, A., Zainal Abidin, N., Rahimi, E., Feizolah, F., Akbari, M., Seyedjalali, S., & Dehghan, F. (2016). Ginger extract and aerobic training reduces lipid profile in high-fat fed diet rats. *European Review for Medical and Pharmacological Sciences*, 20(8), 1617–1622.
79. Bansal, A. B., & Cassagnol, M. (2023). HMG-CoA reductase inhibitors. *StatPearls*. Treasure Island, FL: StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK542212/> Available from.
80. Humphery, E., Ikwuka, A., Udeh, F., & Abraham, J. C. (2023). Effects of ethanol extract of *Rauwolfia vomitoria* leaf on lipid profile and cerebellar histology in cisplatin-induced oxidative stress. *British Journal of Medical and Health Research*, 10, 16–39. <https://doi.org/10.5281/zenodo.8042521>.
81. Chinonye, I., Chijioko, C., Iwuji, S., Obiagwu, I., Lynda, U., Ukaoma, A., Chijioko-Okere, M., & Ezekoye, M. (2022). Chemical and medicinal properties of *Rauwolfia vomitoria* (Afzel) harvested from the South Eastern Nigeria. *Asian Journal of Chemical Sciences*, 10, 56–71. <https://doi.org/10.9734/ajocs/2021/v10i419103>.

82. Kashyap, P., Kalaiselvan, V., Kumar, R., & Kumar, S. (2020). Ajmalicine and reserpine: Indole alkaloids as multi-target directed ligands towards factors implicated in Alzheimer's disease. *Molecules (Basel, Switzerland)*, 25(7), 1609 <https://doi.org/10.3390/molecules25071609>.
83. Heinrich, M., Mah, J., & Amirkia, V. (2021). Alkaloids used as medicines: Structural phytochemistry meets biodiversity—An update and forward look. *Molecules (Basel, Switzerland)*, 26(7), 1836 <https://doi.org/10.3390/molecules26071836>.
84. Omojokun, O. S., Famurewa, A. J., Jaiyeoba, O. A., Oboh, G., & Agbebi, O. J. (2019). Alkaloid extracts from Bitter leaf (*Vernonia amygdalina*) and Black nightshade (*Solanum nigrum*) inhibit phosphodiesterase-5, arginase activities and oxidative stress in rats penile tissue. *Journal of Food Biochemistry*, 43(6), e12889 <https://doi.org/10.1111/jfbc.12889>.
85. Kempster, P., & Ma, A. (2022). Parkinson's disease, dopaminergic drugs and the plant world. *Frontiers in Pharmacology*, 13, 970714 <https://doi.org/10.3389/fphar.2022.970714>.
86. Romes, N. B., Abdul Wahab, R., Abdul Hamid, M., Oyewusi, H. A., Huda, N., & Kobun, R. (2021). Thermodynamic stability, in-vitro permeability, and in-silico molecular modeling of the optimal *Elaeis guineensis* leaves extract water-in-oil nanoemulsion. *Scientific reports*, 11(1), 20851.
87. Yunus, A. A. M., Wahab, R. A., Bahaman, A. H., Oyewusi, H. A., & Yaacob, S. N. S. (2021). In-silico alanine scanning analysis on the catalytic residues of a novel β -glucosidase from *Trichoderma asperellum* UC1. *Jurnal Teknologi*, 83(3), 61–73.
88. Khairul Anuar, N. F. S., Abdul Wahab, R., Huyop, F., Normi, Y. M., Oyewusi, H. A., & Susanti, E. (2024). In silico mutagenesis on active site residues of *Acinetobacter haemolyticus* lipase KV1 for improved binding to polyethylene terephthalate (PET). *Journal of Biomolecular Structure and Dynamics*, 1–23. <https://doi.org/10.1080/07391102.2024.2431655>.
89. Kumar, S., & Singh, B. (2022). An overview on bioactives and pharmacology of *Rauvolfia vomitoria* Afzel. <https://doi.org/10.1201/9781003281702-24>
90. Surendran, S., Raju, R., Prasannan, P., & Surendran, A. (2021). A comprehensive review on ethnobotany, phytochemistry and pharmacology of *Rauvolfia* L. (Apocynaceae). *The Botanical Review*, 87, 311–376.

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