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Original Article

Molecular Docking Analysis of Onion Bioactives and Amino Acids to PDE-5, iNOS, AR, and D2R in Diabetic Erectile Dysfunction: A Multi-Targeted Approach

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ABSTRACT

Background: Diabetic erectile dysfunction is a complex disorder involving impaired nitric oxide bioavailability, endothelial dysfunction, altered androgen signaling, and neurohormonal dysregulation. Conventional phosphodiesterase-5 inhibitors show reduced efficacy in diabetic patients and do not adequately target these interconnected molecular pathways. A multitarget strategy using natural bioactives and amino acids may provide broader therapeutic coverage. **Objectives:** To investigate the multitarget binding potential of selected onion-derived bioactives and amino acids against key molecular targets implicated in diabetic erectile dysfunction. **Materials and Methods:** An *in silico* molecular docking analysis was performed using quercetin, allicin, diallyl trisulfide, citrulline, and norvaline. Docking was carried out against phosphodiesterase-5, inducible nitric oxide synthase, androgen receptor, and dopamine D2 receptor. Binding energies and interaction profiles at functional domains were analyzed to assess target affinity and stability. **Results:** Quercetin, citrulline, and norvaline demonstrated notable binding affinities toward phosphodiesterase-5, ranging from -6.9 to -7.9 kcal/mol, with interactions at key active site residues. Quercetin showed the strongest affinity for the androgen receptor with a binding energy of -9.4 kcal/mol. Citrulline and norvaline exhibited favorable interactions with inducible nitric oxide synthase and dopamine D2 receptor, indicating potential modulation of nitric oxide signaling and neurohormonal pathways. Allicin and diallyl trisulfide displayed weak or negligible interactions across the studied targets. **Conclusion:** The docking outcomes suggest that quercetin, citrulline, and norvaline possess complementary multitarget potential relevant to diabetic erectile dysfunction. These findings justify further experimental validation through *in vivo* and clinical investigations.

Keywords: Amino acids, Androgen Receptor (AR), Diabetic erectile dysfunction, Dopamine D2 Receptor (D2R), Inducible Nitric Oxide Synthase (iNOS), Molecular docking, Onion bioactives, Phosphodiesterase-5 (PDE-5).

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INTRODUCTION

Diabetes Mellitus (DM) affects more than 500 million adults worldwide and is projected to rise to 783 million by 2045 (Hashim *et al*., 2024; Kumar *et al*., 2025). Beyond micro and macrovascular sequelae, one of the most distressing yet underaddressed complication is male sexual dysfunction. Epidemiological surveys indicate that 35-75 % of men with diabetes experience some degree of Erectile Dysfunction (ED), occurring 10-15 years earlier and with greater severity than in nondiabetic populations (Esposito *et al*., 2014). Hyperglycaemiadriven oxidative stress, endothelial Nitric Oxide Synthase (eNOS) uncoupling, autonomic neuropathy, and hypogonadism converge to impair the Nitric Oxide (NO)-cyclic Guanosine Monophosphate (cGMP) cascade that governs penile smoothmuscle relaxation (Dilixiati *et al*., 2024). Psychogenic factors-particularly blunted central dopaminergic signalling-further compound the problem, underscoring the need for therapies that act on vascular, endocrine, and neurogenic axes simultaneously.

Phosphodiesterase5 Inhibitors (PDE5i) such as sildenafil remain firstline pharmacotherapy. Although highly effective in the general ED population, PDE5i show diminished efficacy in men with poorly controlled diabetes, require intact NO bioavailability, and are contraindicated in patients taking nitrates (Swiecicka, 2023). Moreover, they address only a single biochemical bottleneck (cGMP degradation) and carry doselimiting sideeffects (headache,

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flushing, visual disturbance). Intracavernosal prostaglandin injection, vacuum erection devices, and penile implants offer second or thirdline options but are invasive, costly, or associated with poor compliance. These limitations have catalysed interest in botanical and nutraceutical interventions that can enhance NO production, attenuate oxidative stress, and modulate hormonal or central pathways, ideally with a superior safety profile.

Allium cepa (onion) has been used in traditional medicine for cardiovascular and reproductive ailments. Its bioactivity is chiefly attributed to organosulfur constituents-allicin and Diallyl Trisulfide (DATS)-and the flavonol quercetin. Allicin and DATS upregulate eNOS expression, activate Nuclear FactorErythroid2-Related Factor 2 (Nrf2), and inhibit NADPH oxidase, collectively augmenting NO output while curbing reactive oxygen species (Li *et al*., 2020; Yang *et al*., 2023). Quercetin exerts complementary actions: it is a potent antioxidant, suppresses arginase, mildly inhibits PDE5, and improves endothelial function in diabetic models (Adefegha *et al*., 2018). Together, these compounds could target both production and preservation of NO, a critical prerequisite for erectile physiology.

Alongside phytochemicals, lamino acids that interface with the NO pathway have attracted considerable attention. Citrulline is a nonproteinogenic amino acid converted by renal argininosuccinate synthase/lyase into larginine-the obligate substrate for all NOS isoforms. Oral citrulline elevates plasma arginine more efficiently than arginine itself, bypassing firstpass hepatic metabolism and intestinal arginase degradation (Schwedhelm *et al*., 2008). Norvaline is a naturally occurring arginase inhibitor; by limiting arginine catabolism to ornithine and urea, it increases substrate availability for NOS, restoring NOmediated vasodilation in diabetic vasculature (De *et al*., 2016). Preliminary human and rodent studies demonstrate improved erection hardness or intracavernosal pressure after supplementation with either amino acid, but the molecular underpinnings of their synergy with onion phytochemicals remain unexplored.

To rationalise a multitarget nutraceutical approach, this study focused on four key proteins implicated in the pathophysiology of diabetic Erectile Dysfunction (ED). Phosphodiesterase 5 (PDE-5) is a critical enzyme that degrades cyclic Guanosine Monophosphate (cGMP) in the smooth muscle of the corpus cavernosum; its inhibition sustains NO-mediated vasodilation and forms the mechanistic basis for current PDE-5 inhibitor drugs (Kaltsas *et al*., 2025). Inducible Nitric Oxide Synthase (iNOS), responsible for catalysing the conversion of l-arginine to Nitric Oxide (NO), plays a vital role in endothelial function, and restoring its activity is essential in diabetic vasculopathy (Wu *et al*., 2021). The Androgen Receptor (AR) governs the actions of testosterone, and its dysfunction in type 2 diabetes mellitus-often manifesting as hypoandrogenism-contributes to reduced libido, diminished erectile capacity, and overall sexual dysfunction (Heald *et al*., 2021). Finally, the Dopamine D2 Receptor (D2R) serves as a central modulator of sexual motivation and arousal within the hypothalamic-mesolimbic pathway (Melis *et al*., 2022). Together, these targets encompass the vascular, hormonal, and neurogenic dimensions of diabetic sexual dysfunction, providing a comprehensive basis for molecular docking investigations into potential natural therapeutics. Objectives of the present study were therefore to evaluate, *in silico*, the binding propensities of allicin, DATS, quercetin, citrulline, and norvaline toward PDE5, AR, D2R, and iNOS. By illuminating molecular avenues through which these natural agents engage multiple erectile targets, our work lays the groundwork for subsequent experimental validation and the rational design of a polyphytochemical-aminoacid therapeutic.

MATERIALS AND METHODS

Ligand preparation

The chemical structures of five selected bioactive compounds allicin, diallyl trisulfide, quercetin, citrulline, and norvaline were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). These ligands were selected based on their reported pharmacological activities, particularly in modulating inflammatory and neurological pathways. The structures were prepared using the LigPrep module of the Schrödinger suite 2021 v12.8 (Schrödinger, LLC, New York, NY, USA). The LigPrep tool was used to generate low-energy, 3D conformations of the compounds, incorporating proper protonation states and stereochemical configurations (Mukhtar *et al*., 2023). A pH of 8.0 was specified to reflect physiological conditions relevant to the target proteins, while all other parameters were maintained at their default settings. The software performed tautomeric and ionization state generation, optimization of geometries using the OPLS force field, and ensured proper chirality where applicable. Only the most relevant stereoisomers and conformers were retained for docking to minimize redundancy.

Protein preparation

The crystal structures of four therapeutic protein targets were retrieved from the Protein Data Bank (PDB) (https://www.rcsb.org/): Phosphodiesterase-5 (PDE5) - PDB ID: 2H42; Inducible nitric oxide synthase (iNOS) - PDB ID: 4CX7; Androgen receptor - PDB ID: 1E3G; Dopamine receptor D2 - PDB ID: 6CM4. Protein structures were prepared using the Protein Preparation Wizard in the Schrödinger suite. This process involved assigning proper bond orders, removing water molecules located more than 5 Å away from heteroatoms, adding missing side chains and loops (if required), and optimizing the hydrogen-bond network. Protonation states were assigned using Epik at pH 8.0. All proteins were then energy-minimized using the OPLS force field, converging to a Root Mean Square Deviation (RMSD) of 0.3 Å to remove steric clashes and optimize the geometry for docking.

Molecular docking simulations

Molecular docking studies were conducted using the Glide module in Schrödinger to predict the binding affinities and interactions of the prepared ligands with the target proteins (Ejeje *et al.*, 2024). For each protein, a receptor grid was generated by defining the active site residues based on co-crystallized ligands or known functional residues. The grid box was centered on these active regions to ensure accurate ligand positioning. Docking was performed using the Extra Precision (XP) mode of Glide, which offers enhanced scoring functions and more stringent sampling compared to Standard Precision (SP) mode. The XP mode allows for more reliable differentiation between potential binders and non-binders, making it suitable for high-affinity lead identification. The GlideScore (GScore) was used as the primary scoring metric to evaluate the binding affinity of ligands. In addition to the docking scores, ligand-protein interaction profiles were analyzed to assess hydrogen bonding, hydrophobic interactions, π-π stacking, and salt bridge formations. The top-ranked poses from XP docking were selected for each ligand and subjected to visual inspection. All molecular visualizations and interaction analyses were carried out using Maestro, the graphical interface of the Schrödinger suite. The binding orientation and key interactions of each ligand within the active site were studied to gain mechanistic insight into their potential inhibitory effects.

Ethical Statement

Not applicable. This study utilizes *in silico* molecular docking techniques and does not involve human participants or animal experimentation.

Statistical Analysis

Not applicable. This study relies on computational algorithms (GlideScore, Glide Emodel) to predict binding affinity and molecular interactions; no statistical hypothesis testing (e.g., ANOVA, *t*-tests) was performed on biological replicates.

RESULTS

Docking results for PDE-5

The docking outcomes for all five compounds (allicin, diallyl trisulfide, quercetin, citrulline, and norvaline) against PDE-5 are summarized in Table 1. Both the Docking Score and Glide Score columns are presented, alongside the Glide Emodel, key residue interactions (hydrogen bonds, hydrophobic contacts, metal coordination, and polar interactions), and qualitative assessments of binding stability.

Allicin

Allicin showed a docking score of -2.879 and a Glide Score of -2.879, with a relatively low Glide Emodel value (-24.685). Minimal hydrogen bonding was observed, and only limited hydrophobic interactions with residues PHE 786, PHE 787, and LEU 804 were identified. Metal coordination with MG 506 was weak, and no significant polar interactions were noted. Overall, the binding stability of allicin was deemed weak (Figure 1A).

Diallyl trisulfide

Diallyl trisulfide displayed the least favorable scores among the tested compounds, with a Docking Score and Glide Score of 0.130. It formed minimal or no hydrogen bonds and engaged in moderate hydrophobic interactions with VAL 782, PHE 786, and PHE 787. No metal coordination was detected for diallyl trisulfide, and only weak polar interactions occurred with GLN 817. As a result, binding stability was ranked very weak (Figure 1B).

Quercetin

Quercetin demonstrated a more favorable interaction profile, with a Docking Score of -6.962 and a Glide Score of -6.994, as well as a notably strong Glide Emodel value (-70.078). It formed multiple hydrogen bonds with ASN 662, GLU 682, and HIS 613, as well as significant hydrophobic interactions involving PHE 786, TYR 612, PHE 820, and LEU 725. A strong metal coordination was observed with MG 506, and polar interactions were noted with nearby residues THR 723 and MET 681. Collectively, these interactions contributed to moderate binding affinity and strong stability within the PDE-5 active site (Figure 1C).

Citrulline

Citrulline recorded a Docking Score and Glide Score of -7.909, alongside a Glide Emodel of -59.434. Hydrogen bonds were noted with ASN 662, ASN 661, and ASP 724, while weak hydrophobic contacts occurred with TYR 664, LEU 725, and ALA 726. Coordination with MG 506 was observed, although no additional polar interactions were detected. Overall, citrulline exhibited moderate binding stability, supporting the notion that it may aid in enhancing nitric oxide pathways for PDE-5 modulation (Figure 1D).

Norvaline

Norvaline showed comparable performance to citrulline, with a Docking Score and Glide Score of -7.863 and a Glide Emodel of -49.213. It formed hydrogen bonds with ASP 724, GLU 682, and ASN 662, and hydrophobic interactions with LEU 725, TYR 664, and ALA 726. Coordination with MG 506 was noted, and weak polar interactions with HIE 657 and HIE 685 were also observed. This resulted in a moderate to strong binding capacity, indicative of a stable conformation within the PDE-5 active site (Figure 1E).

Docking results for Androgen Receptor

The five test compounds: allicin, diallyl trisulfide, quercetin, citrulline, and norvaline were docked against the androgen receptor to explore their binding affinity and potential

modulatory effects on androgen signaling. Table 2 presents the precise Docking Score, Glide Score, Glide Emodel, and observed binding interactions for each compound.

Allicin

Allicin displayed a Docking Score and Glide Score of -3.239, with a corresponding Glide Emodel of -24.760. No hydrogen bonds were formed, though moderate hydrophobic interactions were observed with MET 749, MET 780, MET 787, LEU 873, and VAL 746. No significant polar interactions or metal coordination were identified, and electrostatic interactions with ARG 752 were limited. As a result, allicin's binding stability within the androgen receptor was classified as weak (Figure 2A).

Diallyl Trisulfide

Diallyl trisulfide had relatively unfavorable scores (Docking Score = -0.416, Glide Score = -0.416, Glide Emodel = -23.170), with no direct hydrogen bonds. Minimal hydrophobic contacts occurred with VAL 746, MET 742, MET 749, LEU 873, and MET 787. A weak polar interaction was detected with GLN 711, and ARG 752 was in the vicinity but did not contribute a strong electrostatic effect. This ligand thus exhibited very weak binding and negligible stability (Figure 2B).

Quercetin

Quercetin emerged as the strongest binder against the androgen receptor, registering a Docking Score of -9.434, a Glide Score of -9.466, and a Glide Emodel of -54.361. It formed multiple hydrogen bonds with ASN 705, PHE 764, and PHE 770, while also engaging in extensive hydrophobic interactions with LEU 701, LEU 704, LEU 873, LEU 880, and PHE 764. No metal coordination was detected; however, polar interactions with GLN 711 and proximity to ARG 752 likely contributed to additional stabilization. Taken together, these factors supported quercetin's high binding stability within the androgen receptor (Figure 2C).

Citrulline

Citrulline demonstrated moderate binding affinity, with Docking Score = -6.043 and Glide Score = -6.043, along with a Glide Emodel of -43.199. Hydrogen bonding occurred with ASN 705, GLN 711, and ARG 752, alongside hydrophobic contacts with LEU 701, LEU 707, LEU 880, VAL 746, and MET 780. Although polar interactions with GLN 711 were noted, no metal coordination was observed. Overall, this profile indicated moderate stability within the androgen receptor binding site (Figure 2D).

Norvaline

Norvaline showed a Docking Score and Glide Score of -5.205, with a Glide Emodel of -26.794. Hydrogen bonds were established with GLN 711 and ARG 752, and hydrophobic contacts involved VAL 746, MET 742, MET 749, MET 780, and LEU 873. No metal coordination was identified, but polar interactions with GLN 711 and nearby ARG 752 contributed to a moderate level of binding stability (Figure 2E).

Table 1: Docking results for PDE-5.

Compound	Docking Score	Glide Score	Glide Emodel	Hydrogen Bonds	Hydrophobic Contacts	Metal Coordination	Polar Interaction	Electrostatic Environment	Binding Stability
Allicin	-2.879	-2.879	-24.685	- Minimal or no hydrogen bonds	PHE 786, PHE 787, LEU 804	Limited with MG 506	None identified	Nearby LYS 809, LYS 810, LYS 812	Weak binding, minimal stability
Diallyl Trisulfide	0.13	0.13	-22.387	- Minimal or no hydrogen bonds	VAL 782, PHE 786, PHE 787	None	Weak with GLN 817	Nearby LYS 809, LYS 810, LYS 812	Very weak binding, negligible stability
Quercetin	-6.962	-6.994	-70.078	ASN 662, GLU 682, HIS 613	PHE 786, TYR 612, PHE 820, LEU 725	Strong with MG 506	Nearby THR 723, MET 681	N/A	Moderate binding with strong stability
Citrulline	-7.909	-7.909	-59.434	ASN 662, ASN 661, ASP 724	Weak TYR 664, LEU 725, ALA 726	Present with MG 506	None identified	N/A	Moderate stability, supportive interactions
Norvaline	-7.863	-7.863	-49.213	ASP 724, GLU 682, ASN 662	LEU 725, TYR 664, ALA 726	Present with MG 506	Weak HIE 657, HIE 685	N/A	Moderate to strong binding, stable conformation

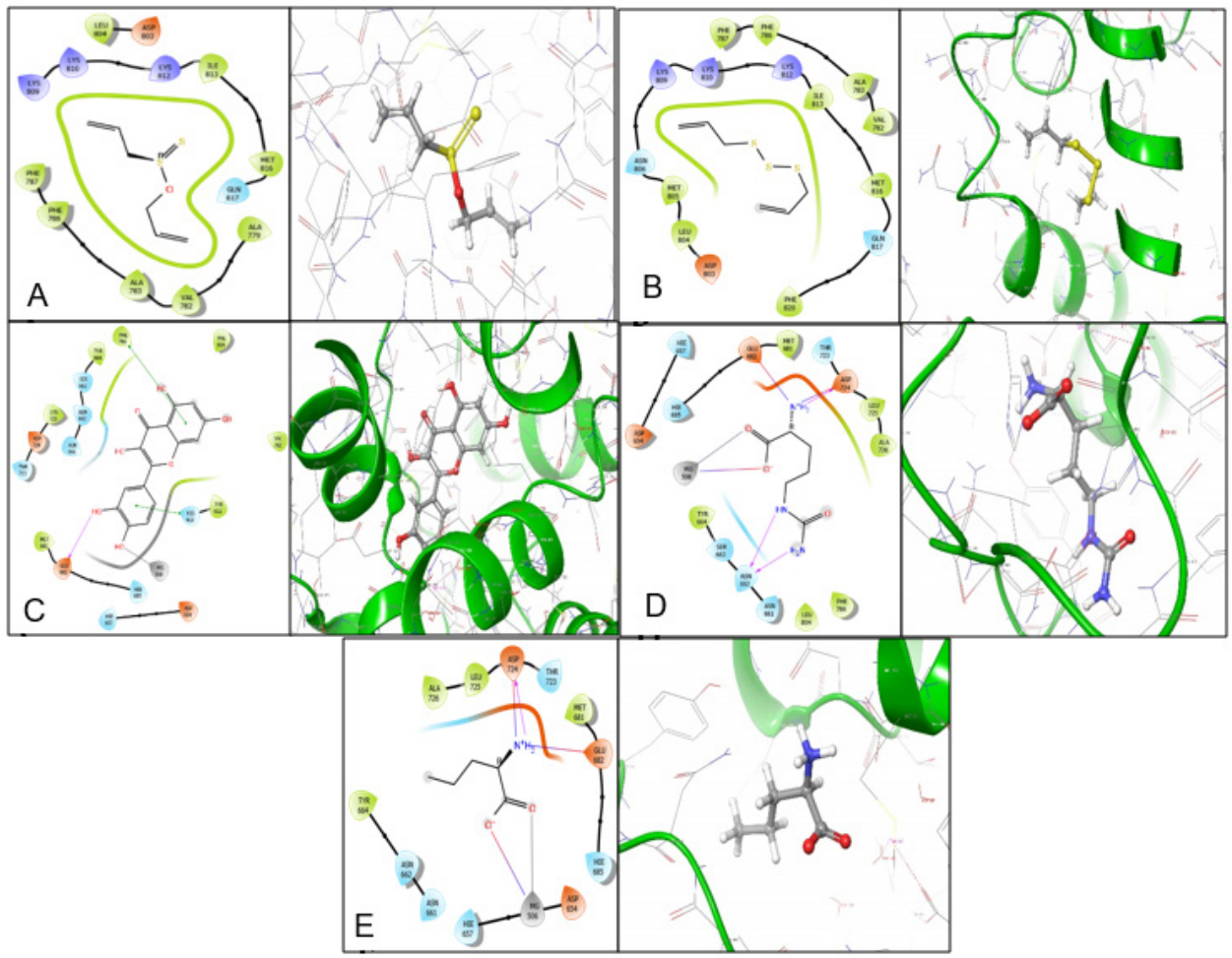

Figure 1: (A-E) Two-dimensional interaction profiles (left) and three-dimensional docking conformations (right) of (A) Allicin, (B) Diallyl trisulfide, (C) Quercetin, (D) Citrulline, and (E) Norvaline within the PDE-5 active site, illustrating key binding residues and interaction patterns.

Among the tested compounds, quercetin displayed the highest binding affinity and strongest stability within the androgen receptor, suggestive of its potential to modulate androgen signaling. Citrulline and norvaline also exhibited moderate binding stability, hinting at potential supportive roles in modulating androgen-dependent processes. In contrast, allicin and diallyl trisulfide showed weak binding, with few direct hydrogen bonds and limited hydrophobic or polar interactions. These data collectively underscore the variable capacity of these onion-derived phytochemicals and amino acids to interact with the androgen receptor, laying the groundwork for subsequent functional assays aimed at elucidating their therapeutic relevance in diabetic sexual dysfunction.

Docking results for Dopamine Receptor (D2)

In addition to PDE-5 and the androgen receptor, all five test compounds: allicin, diallyl trisulfide, quercetin, citrulline, and norvaline were docked against the Dopamine Receptor D2 (D2R) to investigate their potential interactions and implications in sexual function and reward pathways. Table 3 presents a summary of the Docking Score, Glide Score, Glide Emodel, and key binding interactions for each compound within the D2 receptor active site.

Allicin

Allicin exhibited a Docking Score and Glide Score of -2.200, with a corresponding Glide Emodel of -24.270. Although it formed no hydrogen bonds, it engaged in hydrophobic interactions primarily with TRP 386, PHE 189, PHE 389, PHE 390, TYR 412, and VAL 115. Polar interactions were noted with SER 193 and SER 197, but there was no direct metal coordination. ASP 114 in the vicinity may offer a limited electrostatic environment. Overall, these findings indicate weak binding and minimal stability for allicin at the D2 receptor (Figure 3A).

Diallyl Trisulfide

Diallyl trisulfide showed a Docking Score and Glide Score of 0.196, with a Glide Emodel of -23.239-a relatively weak binding profile. No hydrogen bonds were observed, though hydrophobic interactions occurred with TRP 386, PHE 389, PHE 382, PHE 390, VAL 115, and ALA 116. Polar contacts with SER 197 and SER 193 were present, but no metal coordination. Overall, diallyl

trisulfide exhibited very weak binding and negligible stability in the D2 receptor site (Figure 3B).

Quercetin

Quercetin displayed a favorable Docking Score of -6.245 and Glide Score of -6.245, with a notably low Glide Emodel of -61.971, suggesting moderate binding affinity. It formed hydrogen bonds with MET 155 and ILE 130, while additional hydrophobic contacts involved ILE 158, VAL 159, LEU 123, LEU 162, and CYS 126. ALA 127 was identified nearby for potential polar interactions, yet the electrostatic environment was characterized as neutral. Collectively, quercetin's profile indicates moderate binding and reasonable stability within the D2 receptor (Figure 3C).

Citrulline

Citrulline recorded Docking Score and Glide Score values of -4.418, along with a Glide Emodel of -38.574. It established hydrogen bonds with ASP 114, SER 409, and TRP 413, and formed additional hydrophobic contacts with TRP 100, TYR 416, PHE 389, and PHE 110. Polar interactions with GLU 95 and THR 412 were also noted, reinforcing the notion of moderate stability. Overall, the presence of ASP 114 for electrostatic interactions likely contributes to citrulline's moderate binding behavior at the D2 receptor (Figure 3D).

Norvaline

Norvaline similarly demonstrated moderate binding, with a Docking Score of -4.846, Glide Score of -4.846, and a Glide Emodel of -24.172. It formed a hydrogen bond with ASP 114 and showed extensive hydrophobic contacts involving TRP 386, PHE 189, PHE 389, PHE 390, VAL 115, and PHE 382. Polar interactions with HIE 393 and SER 193 were also identified. Interactions at ASP 114 further reinforce the compound's moderate binding stability (Figure 3E).

The Dopamine Receptor D2 docking results indicate that quercetin, citrulline, and norvaline each display moderate binding affinity and stability, characterized by various hydrogen bonds and hydrophobic interactions, including notable interactions with ASP 114. In contrast, allicin and diallyl trisulfide show weaker binding profiles, reflecting limited hydrogen bonding and fewer stabilizing interactions. These data provide insight into the potential neuromodulatory effects of onion bulb-derived phytochemicals and amino acids on dopaminergic pathways, warranting further *in vitro* or *in vivo* validation.

Docking results for Nitric Oxide Synthase (iNOS)

All five test compounds-allicin, diallyl trisulfide, quercetin, citrulline, and norvaline were investigated for their binding potential against Nitric Oxide Synthase (iNOS), an enzyme central to the production of Nitric Oxide (NO). Dysregulation of NO production is a known contributing factor to diabetic complications and erectile dysfunction. Table 4 summarizes the Docking Score, Glide Score, Glide Emodel, and key interactions observed for each compound with iNOS.

Table 2: Docking results for Androgen Receptor.

Compound	Docking Score	Glide Score	Glide Emodel	Hydrogen Bonds	Hydrophobic Contacts	Metal Coordination	Polar Interaction	Electrostatic Environment	Binding Stability
Allicin	-3.239	-3.239	-24.76	None	MET 749, MET 780, MET 787, LEU 873, VAL 746	None	None identified	ARG 752 nearby	Weak binding, minimal stability
Diallyl Trisulfide	-0.416	-0.416	-23.17	None	VAL 746, MET 742, MET 749, LEU 873, MET 787	None	Weak with GLN 711	ARG 752 nearby	Very weak binding, negligible stability
Quercetin	-9.434	-9.466	-54.361	ASN 705, PHE 764, PHE 770	LEU 701, LEU 704, LEU 873, LEU 880, PHE 764	None	GLN 711 nearby	ARG 752 nearby	Strong binding with high stability
Citrulline	-6.043	-6.043	-43.199	ASN 705, GLN 711, ARG 752	LEU 701, LEU 707, LEU 880, VAL 746, MET 780	None	GLN 711 nearby	ARG 752 nearby	Moderate binding with moderate stability
Norvaline	-5.205	-5.205	-26.794	GLN 711, ARG 752	VAL 746, MET 742, MET 749, MET 780, LEU 873	None	GLN 711 nearby	ARG 752 nearby	Moderate binding, stable conformation

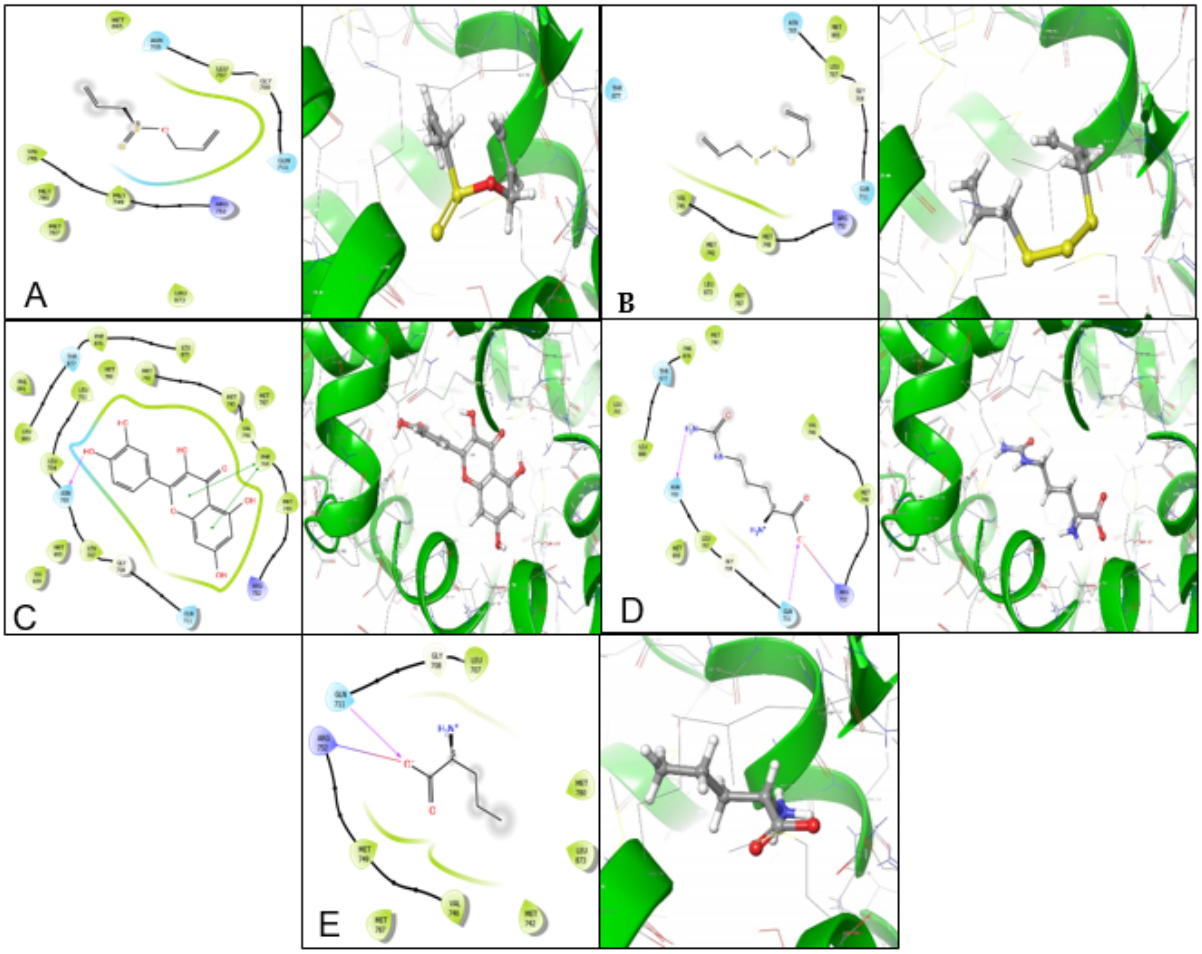

Figure 2: (A-E) Two-dimensional interaction profiles (left) and three-dimensional docking poses (right) of (A) Allicin, (B) Diallyl trisulfide, (C) Quercetin, (D) Citrulline, and (E) Norvaline docked within the Androgen Receptor (AR) ligand-binding site, illustrating key binding residues and interaction patterns.

Allicin

Allicin exhibited a Docking Score and Glide Score of -2.901, with a Glide Emodel of -32.614. It formed no hydrogen bonds but showed notable hydrophobic contacts with TRP 372, LEU 209, and ILE 244, alongside coordination with HEM 550. Polar interactions were observed at ASN 370 and SER 242, and CYS 200 appeared in the electrostatic environment. Despite these interactions, allicin's overall binding stability remained weak (Figure 4A).

Diallyl Trisulfide

Diallyl trisulfide had a Docking Score and Glide Score of 0.472, and a Glide Emodel of -20.684, reflecting weak binding affinity. No hydrogen bonds were identified, although hydrophobic contacts with TRP 372, LEU 209, and ILE 244 were noted, as well as minimal heme (HEM 550) coordination. ASN 370 and SER 242 provided limited polar interactions, with CYS 200 as a nearby residue in the electrostatic environment. Consequently, diallyl trisulfide exhibited very weak binding to iNOS (Figure 4B).

Quercetin

Quercetin demonstrated a more favorable interaction profile, with a Docking Score of -6.693 and Glide Score of -6.725, plus a Glide Emodel of -73.034-the lowest among the tested ligands. Hydrogen bonds were established with SER 118, GLN 478, and TRP 461, accompanied by hydrophobic contacts involving TRP 463, ILE 462, and MET 120. Additionally, it coordinated with HEM 550 and formed polar interactions with GLU 479, while ARG 381 was identified in the electrostatic environment. These synergistic interactions contributed to quercetin's moderate binding stability within iNOS (Figure 4C).

Citrulline

Citrulline also showed promising results, registering Docking Score and Glide Score values of -6.655, with a Glide Emodel of -68.121. Key hydrogen bonds were observed with GLN 478, HIE 477, and SER 118, and hydrophobic interactions involved TRP 463, ILE 462, and MET 120. Coordination with HEM 550, along with polar interactions with GLU 479 and proximity to ARG 381,

supported good binding stability for citrulline in the iNOS active site (Figure 4D).

Norvaline

Norvaline recorded Docking Score and Glide Score values of -6.514, alongside a Glide Emodel of -42.734. It formed hydrogen bonds with SER 118 and GLN 478, complemented by hydrophobic contacts with TRP 463, ILE 462, and MET 120. Its coordination with HEM 550, in addition to polar interactions with GLU 479 and the presence of ARG 381, contributed to moderate binding stability (Figure 4E).

Among the tested ligands, quercetin, citrulline, and norvaline demonstrated stronger affinities and more stable interactions with nitric oxide synthase, largely driven by multiple hydrogen bonds, hydrophobic contacts, and heme coordination. By contrast, allicin and diallyl trisulfide showed weaker binding, featuring fewer stabilizing interactions and minimal heme coordination. These results suggest that certain onion-derived phytochemicals (especially quercetin) and amino acids (notably citrulline and norvaline) may positively modulate iNOS activity and nitric oxide production, which has implications for improving vascular function and erectile capacity in diabetic models.

DISCUSSION

Molecular docking of the five bioactives (allicin, diallyl trisulfide, quercetin, citrulline, norvaline) with the four targets (PDE-5, androgen receptor, dopamine D2 receptor, and nitric oxide synthase) revealed distinct interaction profiles. In PDE-5, the amino acids Citrulline and Norvaline showed the most favorable docking scores (approximately -7.9 kcal/mol), suggesting stronger binding affinity compared to the other compounds (Sulyman *et al.*, 2025). Both citrulline and norvaline engaged in multiple hydrogen bonds with the PDE-5 active site (e.g., interactions with ASN-662, ASN-661, ASP-724) and coordinated with the Mg^{2+} cofactor in the catalytic pocket, contributing to stable binding. They also made hydrophobic contacts with residues like LEU-725 and TYR-664, indicating that these small amino acids can sit in the substrate pocket. Quercetin, a larger polyphenol, also docked reasonably well to PDE-5 (docking score ~-7.0 kcal/mol) and formed several hydrogen bonds (with ASN-662, GLU-682, HIS-613) along with π-π stacking or hydrophobic interactions with aromatic residues (PHE-786, TYR-612, PHE-820). Notably, quercetin strongly coordinated with the active-site metal (Mg^{2+}), which enhanced its docking energy and stability. In contrast, the onion-derived organosulfur compounds, allicin and Diallyl Trisulfide (DATS), showed poor docking to PDE-5 (scores around -2.9 and +0.13 kcal/mol, respectively) and made few or no hydrogen bonds. Their binding was supported only by weak hydrophobic contacts (e.g., with PHE-786, PHE-787) and minimal polar or metal interactions, leading to negligible predicted stability. This pattern suggests that polar and multidentate ligands (like citrulline, norvaline, quercetin) can better satisfy the PDE-5 binding pocket's interaction requirements than highly lipophilic, flexible molecules like allicin and DATS.

Table 3: Docking results for Dopamine Receptor (D2).

Compound	Docking Score	Glide Score	Glide Emodel	Hydrogen Bonds	Hydrophobic Contacts	Metal Coordination	Polar Interaction	Electrostatic Environment	Binding Stability
Allicin	-2.2	-2.2	-24.27	None	TRP 386, PHE 189, PHE 389, PHE 390, TYR 412, VAL 115	None	SER 193, SER 197	ASP 114 nearby	Weak binding, minimal stability
Diallyl Trisulfide	0.196	0.196	-23.239	None	TRP 386, PHE 389, PHE 382, PHE 390, VAL 115, ALA 122	None	SER 197, SER 193	ASP 114 nearby	Very weak binding, negligible stability
Quercetin	-6.245	-6.245	-61.971	MET 155, ILE 130	ILE 158, VAL 159, LEU 123, LEU 162, CYS 126	None	ALA 127 nearby	Neutral environment	Moderate binding with reasonable stability
Citrulline	-4.418	-4.418	-38.574	ASP 114, SER 409, TRP 413	TRP 100, TYR 416, PHE 389, PHE 110	None	GLU 95, THR 412 nearby	ASP 114 interaction	Moderate binding with moderate stability
Norvaline	-4.846	-4.846	-24.172	ASP 114	TRP 386, PHE 189, PHE 389, PHE 390, VAL 115, PHE 198	None	HIE 393, SER 193 nearby	ASP 114 interaction	Moderate binding due to hydrophobic contacts

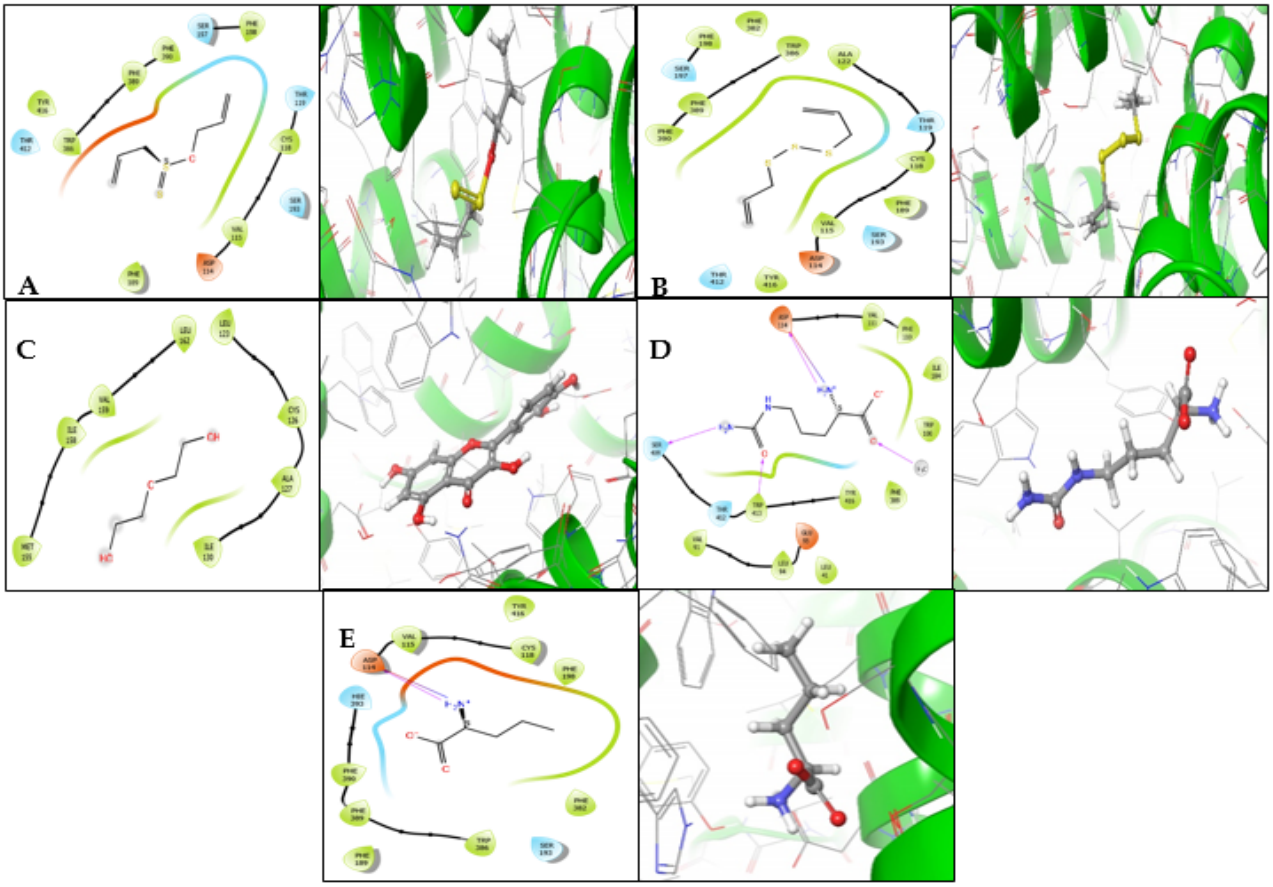

Figure 3: (A-E) Two-dimensional interaction profiles (left) and three-dimensional docking conformations (right) of (A) Allicin, (B) Diallyl trisulfide, (C) Quercetin, (D) Citrulline, and (E) Norvaline docked with the binding site of dopamine D2 Receptor (D2R), illustrating key interactions.

For the Androgen Receptor (AR) ligand-binding domain, quercetin emerged as the strongest binder among the tested compounds. It achieved a docking score of about -9.4 kcal/mol and displayed multiple hydrogen bonds with key polar residues in the AR pocket, namely ASN-705, GLN-711, and even PHE-764 (the last likely via a π-π stacking interpreted as a hydrogen bond in the software). Quercetin's planar multi-ring structure enabled it to snugly fit in the hydrophobic hormone-binding pocket of AR, contacting residues such as LEU-701, LEU-704, and PHE-764. The binding mode of quercetin notably involved the same anchoring residues that natural androgens use - the docking poses showed quercetin interacting with GLN-711 and ARG-752, which are known to form a hydrogen-bond network with the 3-keto and 17β-hydroxyl groups of Dihydrotestosterone (DHT). Indeed, in the AR crystal structure with DHT, the hormone's 3-keto group forms bidentate hydrogen bonds with GLN-711 and ARG-752 (van de Wijngaart *et al.*, 2010), and our docking indicates quercetin can mimic this interaction. L-citrulline and L-norvaline also occupied the AR binding site with moderate affinity (scores ~-6.0 and -5.2 kcal/mol, respectively). They each hydrogen-bonded to GLN-711 and ARG-752 as well, essentially inserting their polar termini into the same pocket that binds the androgen carbonyl group. However, being much smaller molecules, citrulline and norvaline made fewer hydrophobic contacts than quercetin (confined to a subset of the pocket's leucine and methionine residues) and thus had lower overall stability. Allicin and DATS again showed minimal binding to AR (scores near -3 and -0.4 kcal/mol). They formed no hydrogen bonds with the ligand pocket and only transiently occupied a hydrophobic cleft formed by residues like MET-749, LEU-873, and VAL-746. These weak interactions resulted in very unstable docking poses, implying that allicin and DATS are unlikely to directly modulate AR through strong binding.

In the dopamine D2 receptor (D2R) docking, quercetin had a moderate predicted affinity (around -6.2 kcal/mol). Interestingly, quercetin's binding pose in the D2 receptor was distinct from a typical dopamine-like ligand: it formed hydrogen bonds with backbone atoms of MET-155 and ILE-130 in the receptor's extracellular loop or top of the transmembrane region, rather than interacting with the conserved Asp in the binding pocket. It also packed against hydrophobic residues like ILE-158, LEU-162, and CYS-126 located in the receptor's binding site crevice. These contacts suggest quercetin sits in the orthosteric site but perhaps in an orientation not identical to dopamine. By contrast, L-citrulline and L-norvaline, despite being highly polar, did show some ability to dock in the D2R orthosteric site (docking scores ~-4.4 and -4.8 kcal/mol). Both made a key polar contact with ASP-114 on transmembrane helix 3. This

Table 4: Docking results for Nitric Oxide Synthase.

Compound	Docking Score	Glide Score	Glide Emodel	Hydrogen Bonds	Hydrophobic Contacts	Metal Coordination	Polar Interaction	Electrostatic Environment	Binding Stability
Allicin	-2.901	-2.901	-32.614	None	TRP 372, LEU 209, ILE 244	HEM 550	ASN 370, SER 242	CYS 200	Weak binding; minor hydrophobic and heme interactions
Diallyl Trisulfide	0.472	0.472	-20.684	None	TRP 372, LEU 209, ILE 244	HEM 550	ASN 370, SER 242	CYS 200	Very weak binding; slight heme coordination
Quercetin	-6.693	-6.725	-73.034	SER 118, GLN 478, TRP 461	TRP 463, ILE 462, MET 120	HEM 550	GLU 479	ARG 381	Moderate binding stability through H-bonds and heme coordination
Citrulline	-6.655	-6.655	-68.121	GLN 478, HIE 477, SER 118	TRP 463, ILE 462, MET 120	HEM 550	GLU 479	ARG 381	Good stability with favorable hydrogen bonds and heme coordination
Norvaline	-6.514	-6.514	-42.734	SER 118, GLN 478	TRP 463, ILE 462, MET 120	HEM 550	GLU 479	ARG 381	Moderate stability; H-bonds, hydrophobic interactions, and heme coordination

interaction is noteworthy because ASP-114$^{3.32}$ is the pivotal residue that forms a salt bridge with dopamine's protonated amine in all catecholamine receptors. Indeed, in the D2 receptor, the carboxylate of ASP-114 forms a tight salt bridge (~2.6 Å) with the primary amine of dopamine (Kalani *et al.*, 2004). The docking indicates citrulline's α-NH_3^+ and norvaline's α-NH_3^+ can similarly engage ASP-114, effectively mimicking dopamine's anchoring interaction. Norvaline, in particular, showed a direct ASP-114 contact and also hydrophobic interactions with aromatic residues (TRP-386, PHE-389, PHE-390) lining the binding site. This suggests norvaline might sit deep enough in the pocket to behave as a minimalist dopamine analog. However, neither citrulline nor norvaline can form the extensive network of hydrophobic and aromatic interactions that a typical D2 ligand does (they lack the bulky ring systems of dopamine agonists/antagonists). Thus, their binding is likely much weaker and possibly not sufficient to trigger receptor activation. Allicin and DATS fared poorest in D2R docking (scores ~-2.2 and +0.2 kcal/mol). They failed to form any hydrogen bonds or salt bridges with the receptor, and only transiently interacted with a few lipophilic residues (such as PHE-389 and VAL-115). This indicates that neither garlic compound can properly occupy or stabilize within the dopamine D2 binding site.

Finally, for Nitric Oxide Synthase (iNOS), citrulline, norvaline, and quercetin all showed moderate binding (docking scores ~-6.5 to -6.7 kcal/mol). The active site of iNOS contains a heme prosthetic group (with an Fe^{2+} center) and a pocket that normally binds L-arginine. Docking results suggest quercetin, citrulline, and norvaline each entered the L-arginine binding region and made contacts with both the heme and surrounding residues. Quercetin formed hydrogen bonds with SER-118, GLN-478, and TRP-461 in the iNOS enzyme, while also π-stacking or hydrophobically interacting with TRP-463 and ILE-462 near the heme pocket. The planar quercetin likely lies against the heme porphyrin (the docking noted coordination with HEM-550, the heme group) and may chelate the heme iron or at least π-stack with it (Zhang *et al.*, 2015). Citrulline and norvaline, being analogs

of L-arginine or its byproduct, adopted a pose very similar to substrate/inhibitor binding: both formed multiple H-bonds with residues in the arginine-binding site (GLN-478 and HIE-477 for citrulline; GLN-478 for norvaline) and also showed bidentate coordination to the heme iron (as implied by the noted heme interaction). Their carboxylate and amino groups likely bridge the active-site pocket, similar to how L-arginine's guanidinium engages iNOS. This resulted in "favorable heme coordination" for citrulline, which in docking terms means citrulline could potentially bind to the heme iron akin to an enzyme substrate or inhibitor. Norvaline too maintained hydrogen bonds plus hydrophobic contacts (with MET-120, ILE-462) near the heme, indicating a stable fit. Allicin and DATS, on the other hand, showed very weak binding to iNOS (scores ~-2.9 and +0.47). They did not form any hydrogen bonds with the enzyme's active site residues and interacted only weakly with the heme prosthetic group. The docking notes that allicin and DATS stayed near a hydrophobic region (contacts with TRP-372, LEU-209) and made only "minor hydrophobic and heme interactions". In essence, the garlic compounds did not effectively occupy the L-arginine binding site of iNOS, whereas citrulline/norvaline (and to a degree quercetin) bound in a manner resembling known iNOS substrates or inhibitors.

Molecular docking results from this study highlight promising therapeutic roles for citrulline, norvaline, and quercetin in managing diabetic sexual dysfunction, primarily by targeting Nitric Oxide (NO) pathways. Diabetes is known to impair NO production and signaling, leading to reduced cGMP levels and erectile difficulties. Citrulline and norvaline showed moderate binding affinity for Phosphodiesterase-5 (PDE-5), suggesting their potential as mild natural inhibitors that could help sustain cGMP levels and promote smooth muscle relaxation. Quercetin also demonstrated PDE-5 binding, consistent with reports of flavonoids having inhibitory effects on this enzyme. Additionally, citrulline (as a precursor to L-arginine) and norvaline (as an arginase inhibitor) may enhance NO bioavailability by supporting or preserving the L-arginine-iNOS pathway. Docking studies further revealed favorable interactions between these amino acids and Nitric Oxide Synthase (iNOS), reinforcing their potential to improve vasodilation in erectile tissues through NO production. Quercetin's strong binding to the Androgen Receptor (AR) suggests a potential to modulate hormonal aspects of diabetic ED, though its role may be double-edged. While quercetin may act as an AR antagonist-raising concern about suppressing testosterone signaling-it also serves as an antioxidant and vascular protector, potentially offsetting some diabetic complications. Norvaline, in

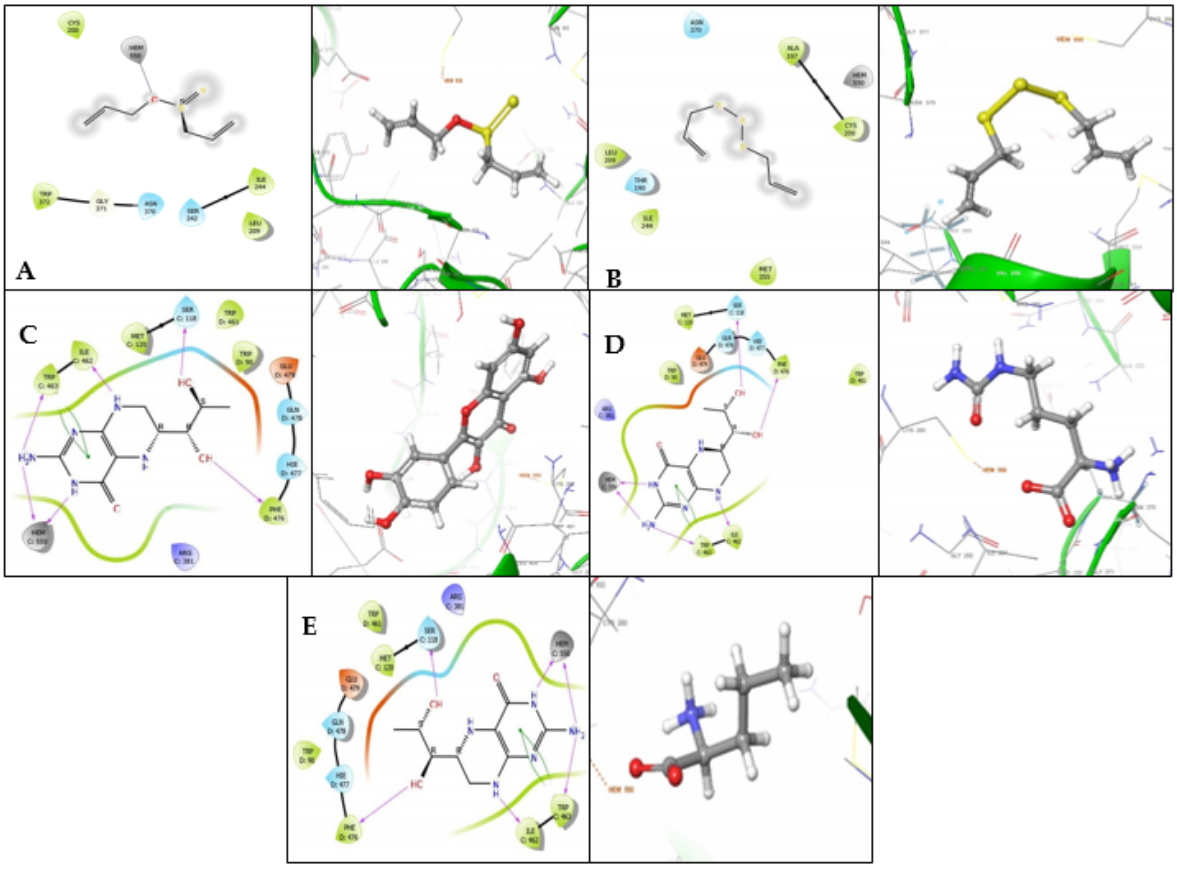

Figure 4: (A-E) Two-dimensional interaction profiles (left) and three-dimensional docking conformations (right) of (A) Allicin, (B) Diallyl trisulfide, (C) Quercetin, (D) Citrulline, and (E) Norvaline docked within the catalytic active site of inducible nitric oxide synthase (iNOS), illustrating key interactions.

contrast, may indirectly improve testosterone levels by restoring NO-dependent testicular function. The compounds' interactions with the Dopamine D2 Receptor (D2R), though weaker, suggest minimal direct neurological modulation, as their structures lack key features of dopamine agonists. Nevertheless, their indirect support of NO and hormonal balance may improve libido and mood through peripheral mechanisms. Overall, the findings support a multifaceted therapeutic potential of these natural compounds-especially quercetin, citrulline, and norvaline-in addressing the vascular, hormonal, and possibly psychogenic contributors to diabetic sexual dysfunction.

This study highlights a compelling synergistic potential between phytochemicals like quercetin and amino acids such as citrulline and norvaline in addressing diabetic sexual dysfunction. Quercetin's moderate inhibition of PDE-5 and ability to upregulate eNOS expression may enhance the efficacy of citrulline, which supplies arginine for Nitric Oxide (NO) production. Together, they not only promote NO synthesis but also preserve its bioavailability by countering oxidative stress, an important factor in diabetic pathology. Studies suggest that this combination improves endothelial NO function more effectively than either agent alone. Moreover, quercetin's slight PDE-5 inhibition may prolong citrulline-driven cGMP elevation, mimicking the clinically observed benefit of combining NO precursors with PDE-5 inhibitors like sildenafil. The combination of citrulline and norvaline also presents a promising synergy, as citrulline serves as a precursor for arginine, while norvaline inhibits arginase, preventing arginine depletion, a common issue in diabetes. This dual action could enhance NO production more efficiently than either compound alone. While garlic-derived compounds like allicin showed weak direct docking, they are known to boost eNOS activity and reduce ROS levels, suggesting that they may complement citrulline and quercetin through indirect NO-enhancing mechanisms. A combined regimen incorporating these agents could simultaneously address multiple aspects of diabetic ED: NO production, preservation, and downstream signaling. Although early clinical data, such as improved erection hardness with L-citrulline, are encouraging, these synergistic effects require validation through well-controlled human trials to confirm their therapeutic promise.

CONCLUSION

Molecular docking studies investigated the binding affinities and interactions of allicin, diallyl trisulfide, quercetin, citrulline, and norvaline with four key protein targets involved in diabetic erectile dysfunction: PDE-5, iNOS, androgen receptor, and dopamine D2 receptor. Quercetin, citrulline, and norvaline exhibited favorable binding affinities with PDE-5, forming multiple hydrogen bonds and engaging key residues. Quercetin strongly interacted with the androgen receptor ligand-binding domain, while citrulline and norvaline demonstrated stable interactions with iNOS and D2 receptor via critical residues and the heme prosthetic group. In contrast, allicin and diallyl trisulfide showed weak binding across all targets. The findings suggest a therapeutic potential for combining quercetin, citrulline, and norvaline to synergistically enhance nitric oxide bioavailability, preserve cGMP signaling, and support hormonal and neurogenic pathways in managing diabetic sexual dysfunction.

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ABBREVIATIONS

AR: Androgen Receptor; **cGMP:** Cyclic Guanosine Monophosphate; **D2R:** Dopamine D2 Receptor; **DATS:** Diallyl Trisulfide; **DM:** Diabetes Mellitus; **DHT:** Dihydrotestosterone; **ED:** Erectile Dysfunction; **eNOS:** Endothelial Nitric Oxide Synthase; **GScore:** GlideScore; **iNOS:** Inducible Nitric Oxide Synthase; **NO:** Nitric Oxide; **Nrf2:** Nuclear Factor-Erythroid-2-Related Factor 2; **PDB:** Protein Data Bank; **PDE-5:** Phosphodiesterase-5; **PDE-5i:** Phosphodiesterase-5 Inhibitors; **RMSD:** Root Mean Square Deviation; **XP:** Extra Precision.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Anas Islam: Writing the article, Data analysis and interpretation, Final approval of the article. **Badruddeen:** Research concept and design, Final approval of the article. **Mohammad Irfan Khan:** Research concept and design, Final approval of the article. **Mohammad Mujahid:** Critical revision of the article, Final approval of the article. **Juber Akhtar:** Data analysis and interpretation, Final approval of the article. **Mohammad Ahmad:** Critical revision of the article, Final approval of the article. **Asad Ahmad:** Critical revision of the article, Final approval of the article

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES

During the preparation of this work the author(s) used Paperpal in order to make grammatical corrections. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

KEY FINDINGS

Quercetin demonstrated strong binding to the androgen receptor and PDE-5, potentially modulating hormonal and vascular pathways. Citrulline and norvaline exhibited robust interactions

with PDE-5, iNOS, and the dopamine D2 receptor, suggesting they may support nitric oxide production and neurohormonal signaling. Conversely, allicin and diallyl trisulfide showed weak direct binding to these specific targets.

IMPLICATION

The results support the rational design of a combinatorial nutraceutical therapy involving quercetin, citrulline, and norvaline to address the complex vascular, hormonal, and neural mechanisms underlying diabetic ED.

SUMMARY

This study explores the potential of onion-derived bioactives (quercetin, allicin, diallyl trisulfide) and amino acids (citrulline, norvaline) to combat diabetic Erectile Dysfunction (ED) using a multitarget molecular docking approach.

REFERENCES

Adefegha, S. A., Oyeleye, S. I., Dada, F. A., Olasehinde, T. A., and Oboh, G. (2018). Modulatory effect of quercetin and its glycosylated form on key enzymes and antioxidant status in rats penile tissue of paroxetine-induced erectile dysfunction. Biomedicine and Pharmacotherapy, 107, 1473-1479.

De, A., Singh, M. F., Singh, V., Ram, V., and Bisht, S. (2016). Treatment effect of l-Norvaline on the sexual performance of male rats with streptozotocin induced diabetes. European Journal of Pharmacology, 771, 247-254. https://doi.org/10.1016/j.ejphar.2015.12.008

Dilixiati, D., Waili, A., Tuerxunmaimaiti, A., Tao, L., Zebibula, A., and Rexiati, M. (2024). Risk factors for erectile dysfunction in diabetes mellitus: A systematic review and meta-analysis. Frontiers in Endocrinology, 15, 1368079.

Ejeje, J. N., Agbebi, E. A., Mathenjwa-Goqo, M. S., Oje, O. A., Agboinghale, P. E., Ebe, I. T., Obafemi, T. O., Adewole, E., Omaka, O. N., Onikanni, S. A., Ajiboye, B. O., Omotuyi, O. I., and Oyinloye, B. E. (2024). Computational Investigation of the Therapeutic Potential of *Detarium senegalense* in the Management of Erectile Dysfunction. International Journal of Molecular Sciences, 25(22), 12362. https://doi.org/10.3390/ijms252212362

Esposito, K., Maiorino, M. I., and Bellastella, G. (2014). Diabetes and sexual dysfunction: Current perspectives. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 95. https://doi.org/10.2147/DMSO.S36455

Hashim, M., Akhtar, J., Khan, M. I., Ahmad, M., Islam, A., and Ahmad, A. (2024). Diabetic neuropathy: An overview of molecular pathways and protective mechanisms of phytobioactives. Endocrine, Metabolic and Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine and Metabolic Disorders), 24(7), 758-776.

Heald, A. H., Livingston, M., Fachim, H., Lunt, M., Narayanan, R. P., Siddals, K., Moreno, G., Jones, R., Malipatil, N., Rutter, M., and others. (2021). Androgen receptor-reduced sensitivity is associated with increased mortality and poorer glycaemia in men with type 2 diabetes mellitus: A prospective cohort study. Cardiovascular Endocrinology and Metabolism, 10(1), 37-44.

Kalani, M. Y. S., Vaidehi, N., Hall, S. E., Trabanino, R. J., Freddolino, P. L., Kalani, M. A., Floriano, W. B., Kam, V. W. T., and Goddard, W. A. (2004). The predicted 3D structure of the human D2 dopamine receptor and the binding site and binding affinities for agonists and antagonists. Proceedings of the National Academy of Sciences of the United States of America, 101(11), 3815-3820. https://doi.org/10.1073/pnas.0400100101

Kaltsas, A., Dimitriadis, F., Zachariou, A., Sofikitis, N., and Chrisofos, M. (2025). Phosphodiesterase Type 5 Inhibitors in Male Reproduction: Molecular Mechanisms and Clinical Implications for Fertility Management. Cells, 14(2), 120.

Kumar, N., Kumar, B., Ashique, S., Yasmin, S., Venkatesan, K., Islam, A., Ghosh, S., Sahu, A., Bhui, U., and Ansari, M. Y. (2025). A critical review on SGLT2 inhibitors for diabetes mellitus, renal health, and cardiovascular conditions. Diabetes Research and Clinical Practice, 112050.

Li, C., Liu, X., Qiao, Y., Ning, L., Li, W., Sun, Y., Liu, D., Gao, W., and Ma, C. (2020). Allicin alleviates inflammation of diabetic macroangiopathy via the Nrf2 and NF-kB pathway. European Journal of Pharmacology, 876, 173052.

Melis, M. R., Sanna, F., and Argiolas, A. (2022). Dopamine, erectile function and male sexual behavior from the past to the present: A review. Brain Sciences, 12(7), 826.

Mukhtar, R. M., Abdelmoniem, N., Elrufaie, H. A., Edris, A., Ghaboosh, H., Mahgoub, M. A., Garelnabi, E. A. E., Osman, W., Sherif, A. E., Ashour, A., Ghazawi, K. F., Samman, W. A., Alhaddad, A. A., Bafail, R., Ibrahim, S. R. M., Mohamed, G. A., and Alzain, A. A. (2023). Unlocking the potential of approved drugs for the allosteric inhibition of tropomyosin-receptor kinase A using molecular docking and molecular dynamics studies. Frontiers in Chemistry, 11, 1205724. https://doi.org/10.3389/fchem.2023.1205724

Schwedhelm, E., Maas, R., Freese, R., Jung, D., Lukacs, Z., Jambrecina, A., Spickler, W., Schulze, F., and Böger, R. H. (2008). Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: Impact on nitric oxide metabolism. British Journal of Clinical Pharmacology, 65(1), 51-59.

Sulyman, A. O., Aliyu, O. M., Ajani, E. O., Abdulkareem, Y. F., Afe, I. A., Abdulyakeen, F. O., Lukman, H. Y., Sabiu, S., Singh, K., and Naidoo, K. (2025). Mechanisms of L-citrulline on phosphodiesterase 5 in erectile dysfunction intervention. Scientific African, 27, e02572. https://doi.org/10.1016/j.sciaf.2025.e02572

Swiecicka, A. (2023). The efficacy of PDE5 inhibitors in diabetic patients. Andrology, 11(2), 245-256.

van de Wijngaart, D. J., Molier, M., Lusher, S. J., Hersmus, R., Jenster, G., Trapman, J., and Dubbink, H. J. (2010). Systematic structure-function analysis of androgen receptor Leu701 mutants explains the properties of the prostate cancer mutant L701H. The Journal of Biological Chemistry, 285(7), 5097-5105. https://doi.org/10.1074/jbc.M109.039958

Wu, G., Meininger, C. J., McNeal, C. J., Bazer, F. W., and Rhoads, J. M. (2021). Role of L-arginine in nitric oxide synthesis and health in humans. In Amino acids in nutrition and health (pp. 167-187). Springer.

Yang, J., Si, H., Dong, B., and Qin, Q. (2023). Allicin alleviates coronary atherosclerosis of mice via endothelial nitric oxide synthase (eNOS)/nuclear factor erythroid 2-related factor (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway. Applied Biological Chemistry, 66(1), 28.

Zhang, Y., Huang, C., Liu, S., Bai, J., Fan, X., Guo, J., Jia, Y., Zhang, Z., Chen, X., Jia, Y., Zhang, P., Wang, B., and Zhang, X. (2015). Effects of quercetin on intracavernous pressure and expression of nitrogen synthase isoforms in arterial erectile dysfunction rat model. International Journal of Clinical and Experimental Medicine, 8(5), 7599-7605.

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