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Full Length Research Article

IN-SILICO ASSESSMENT OF POTENTIALS OF *CNIDOSCOLUS ACONITIFOLIUS* LEAF IN THE MANAGEMENT OF BENIGN PROSTATE HYPERPLASIA

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Abstract
Benign Prostatic Hyperplasia (BPH) is a non-cancerous enlargement of the prostate gland commonly affecting aging men. Conventional pharmacological treatments, while effective, are often associated with adverse effects, prompting the search for safer, plant-based alternatives. *Cnidoscolus aconitifolius*, has attracted attention due to its rich phytochemical profile and traditional medicinal applications. This study focuses on the in-silico assessment of the n-hexane leaf fraction of *Cnidoscolus aconitifolius*, aiming to identify bioactive compounds with potential inhibitory effects on key targets implicated in BPH. The leaf was prepared using standard operation procedure. Gas Chromatography – Mass Spectroscopy (GCMS) assay was carried out on the n-hexane fraction of the leaf extract. Molecular docking analysis was carried out on the identified bioactive components using PyRx, Chimera and Discovery Studio computer softwares. The structure and properties of the bioactive compounds, finasteride (standard anti-BPH drug) and 5α-reductase were downloaded from appropriate databases. The result obtained revealed 20 bioactive compounds present in the n-hexane leaf fraction. There were interactions of these bioactive compounds with 5α-reductase. Some of these compounds such as 9-Octadecenoic acid; 2,4,5-Trichlorophenyl propenoate; cis-9-Hexadecenoic acid and Cyclopropaneoctanal, 2-octylexhibited -6.7, -6.4, -6.4 and -6.4kcal/mol binding affinity respectively for the active site of 5α-reductase. These compounds showed anti-BPH comparable with the anti-BPH action of finasteride, a standard BPH drug. The 2D structure models showed the interactions of these compounds with the amino acids present at the binding pocket of 5-alpha reductase

enzyme. The properties, interactions and activities of these bioactive compounds indicate that the n-hexane leaf fraction of *Cnidoscolus aconitifolus* may have an anti-BPH effect and may be recommended for further scientific study as it may be a promising anti-BPH drug agent.
Keywords: *Cnidoscolus aconitifolius*, benign prostate hyperplasia, 5α-reductase, Gas Chromatography – Mass Spectroscopy (GCMS), finasteride

Introduction

Benign prostatic hyperplasia (BPH), a common condition affecting the prostate gland in aging men, is characterized by the enlargement of the prostate, leading to urinary obstruction and a range of lower urinary tract symptoms (LUTS) (McVary, 2006); thus, it causes deterioration in the functioning of the urinary system. BPH is a term that refers to a proliferative process of the prostate's cellular parts, an enlarged prostate, or voiding dysfunction caused by prostatic enlargement and bladder outlet blockage and men suffering from BPH may experience severe urination issues, as well as complications, such as recurring renal failure and severe urinary tract infections (Madersbacher *et al*., 2019). An important symptom associated with BPH is the formation of hyperplastic nodules in the transition and periurethral regions of the prostate gland which results in prostate enlargement and, after that, invades the urethra. This process eventually triggers a set of signs, very commonly known as LUTS. The three major kinds of LUTS associated with BPH conditions are storage (this includes urination urgency, urination frequency, nocturia, and urine incontinence), voiding (which provides for reduced flow of urine and a strong sense of incomplete emptying after urination), and post-void dribbling (Das *et al*., 2019).

This condition significantly impacts quality of life and can lead to complications if left untreated. Traditional management strategies as well as the use of Alpha-blockers, 5α-reductase inhibitors and surgical therapy are the preferred drugs/treatment practice for BPH. Due to the fear of sexual dysfunction and the detrimental influence on their quality of life, most patients seek to avoid synthetic drugs and surgery. For this reason, several patients turn to phytotherapy and other alternative therapies (Haddad *et al.,* 2020). Consequently, there is an increasing interest in exploring alternative therapeutic options, particularly those derived from natural sources.

Cnidoscolus aconitifolius, commonly known as the chaya plant, has garnered attention in recent years due to its diverse pharmacological properties. This plant is traditionally used in various cultures for its health benefits, including anti-inflammatory, antioxidant, and antimicrobial activities (Carmona *et al.,* 2014). *Cnidoscolus aconitifolius* (Hospital too far) with its anti-androgenic phytochemicals provides an alternative to synthetic drugs with minimal drawbacks in the prevention, treatment and/or management of BPH (Nwobodo *et al.,* 2024). Leafy green vegetables are a rich source of nutrients, phytochemicals and other health promoting components. *Cnidoscolus aconitifolius* (Chaya plant, tree spinach) can be a prime example of a green leafy vegetable that has strong health promoting connotation (Panghal *et al*., 2021). The minerals contained in Chaya leaf are essential for maintenance of human health and wellness. It helps in osmoregulation, bone health, hemoglobin formation, prevention of prostate cancer, reduction of stroke among others. It provides a wide range of health benefits such as anti-diabetic activity, cardio protective activity, antimicrobials, anti-

inflammatory, hematopoietic property and anticancer properties (Panghal *et al*., 2021).

In recent years, computational methods, particularly in-silico studies, have emerged as powerful tools for drug discovery and understanding molecular interactions (Roth *et al.,* 2017). This study utilizes computational techniques to predict the interaction between bioactive compounds and biological targets, which can provide insights into their potential efficacy and mechanism of action.

This study focusing on the n-hexane leaf fraction of *Cnidoscolus aconitifolius* may offer a novel approach to understanding its potential role in attenuating BPH. By employing molecular docking and other computational tools, it tends to identify key interactions between phytochemicals present in the leaf fraction and targets involved in prostate growth and function. However, this study sets the stage for exploring the potential of n-hexane leaf fraction of *Cnidoscolus aconitifolius* in mitigating BPH through in-silico analysis, which may pave the way for new, natural therapeutic strategies in managing this BPH condition.

Materials and Methods

Collection and extraction of plant materials

The leaves of *Cnidoscolous aconitifolius* were collected by plucking from a garden at Ngozika Housing Estate, Awka, Anambra State, Nigeria and were identified by a taxonomist. The voucher number as deposited in the herbarium of Nnamdi Azikiwe University, Awka is 168 and the sample was kept in the herbarium.

Preparation of Ethanol Leaf Extract of *C. aconitifolus*

The leaves were thoroughly washed, air-dried at room temperature for three weeks to achieve a relatively constant weight and pulverized using an electric grinding machine. One thousand, eight hundred (1800) grams of the ground leaf particles was macerated in 7.2 liters (1:4) of 70% ethanol for 24 hours with intermittent shaking. The ethanol extract was sieved using muslin cloth and filtered using Whatman no 1 (125mm) filter paper. The filtrate was concentrated using a rotary evaporator under vacuum pressure, then further dried using water bath at 40^{o}C and weighed.

Liquid-liquid fractionation of plant extract

Fractionation of the *Cnidoscolus aconitifolius* leaf-extract done at Applied Biochemistry Department Laboratory Nnamdi Azikiwe University, Awka was carried out by sequential extraction with n-hexane, ethyl-acetate and n-butanol, according to the method of Ajali (2004). Briefly, eighty percent (80%) of the concentrated extract was reconstituted in 100ml of water and re-extracted in 300ml of n-hexane. The solution was swirled to ensure even mixture and allowed to stand for 2hrs in a separating funnel setup. Two distinct layers that were formed; water soluble layer (denser) and n-hexane soluble upper layer, were separated. The later was placed in rotary evaporator then into water bath to concentrate whereas the process was repeated with the water soluble layer. This process was repeated for ethyl acetate and n-butanol fractions respectively. At the end, residual ethanol fraction was recovered whereas the remaining part of the ethanol extract together with the fractionally separated extracts were safely kept in a refrigerator for further use. N-hexane fraction of the plant extract was used for this study.

Characterization of extracts

Gas Chromatography–Mass Spectrometry (GC-MS) analysis

This was carried according to method of Odo *et al.* (2017). The analysis was done at Central Research Laboratory, Ilorin,

Kwara State. The n-hexane fraction of *C. aconitifolius* fraction was analyzed using GC-MS analyser. Helium (99.999 %) was used as the carrier gas at a flow rate of 1 ml per min in split mode. The spilt ratio and ionization voltage were 110:1(v/v) and 70eV respectively. Two (2µl) microlitre of the extracts was injected into the GC column for analysis. The GC (Agilent 7890N) and MS (5975B MSD) were equipped with DB-5ms capillary column (30m x 0.25mm; film thickness 0.25µm). The initial temperature was set at 40^{o}C which was increased to 150^{o}C at the rate of 10^{o}C per min. The temperature was again increased to 230^{o}C at the rate of 5^{o}C per min. The process was continued till the temperature reached 280^{o}C at the rate of 20^{o}C per min which was held for 8 minutes. The injector port temperature was kept constant at 280^{o}C and detector temperature was 250^{o}C. To identify the unknown components present in the n-hexane, their individual mass spectral peak value were compared with the database of National Institute of Science and Technology, 2014. The phytochemicals were identified after comparing the unknown peak value and chromatogram from GC-MS against the known chromatogram peak value from the NIST Library database. Subsequently, the details about their molecular weight, retention time and percentage content were also obtained.

Molecular docking analysis

The chemical compounds (ligands) that were obtained from the results of GCMS analysis of the n-hexane fraction were subjected to molecular docking with anti-benign prostate hyperplasia protein target. The molecular target that was investigated was the 5a-reductase. The 3D Structure of the molecule was obtained from protein databank (www.rcsb.org). The existing ligands and water molecules were removed and hydrogen molecules were added. The SDF (structure-data file) structure of the compound and standard ligand such as finasteride was obtained from the PubChem database. Both the 5a-reductase enzymes and the ligands were prepared using Chimera version 1.14. The ligands were docked to the protein target and the binding affinities were determined using Autodock Vina from PyRX (Trott, O. and Olson, 2010). Molecular interactions between proteins and ligands were viewed using molecular docking tools; Chimera version 1.14 and discovery studio version 2020 according to method employed by Iwaloye *et al.* (2020).

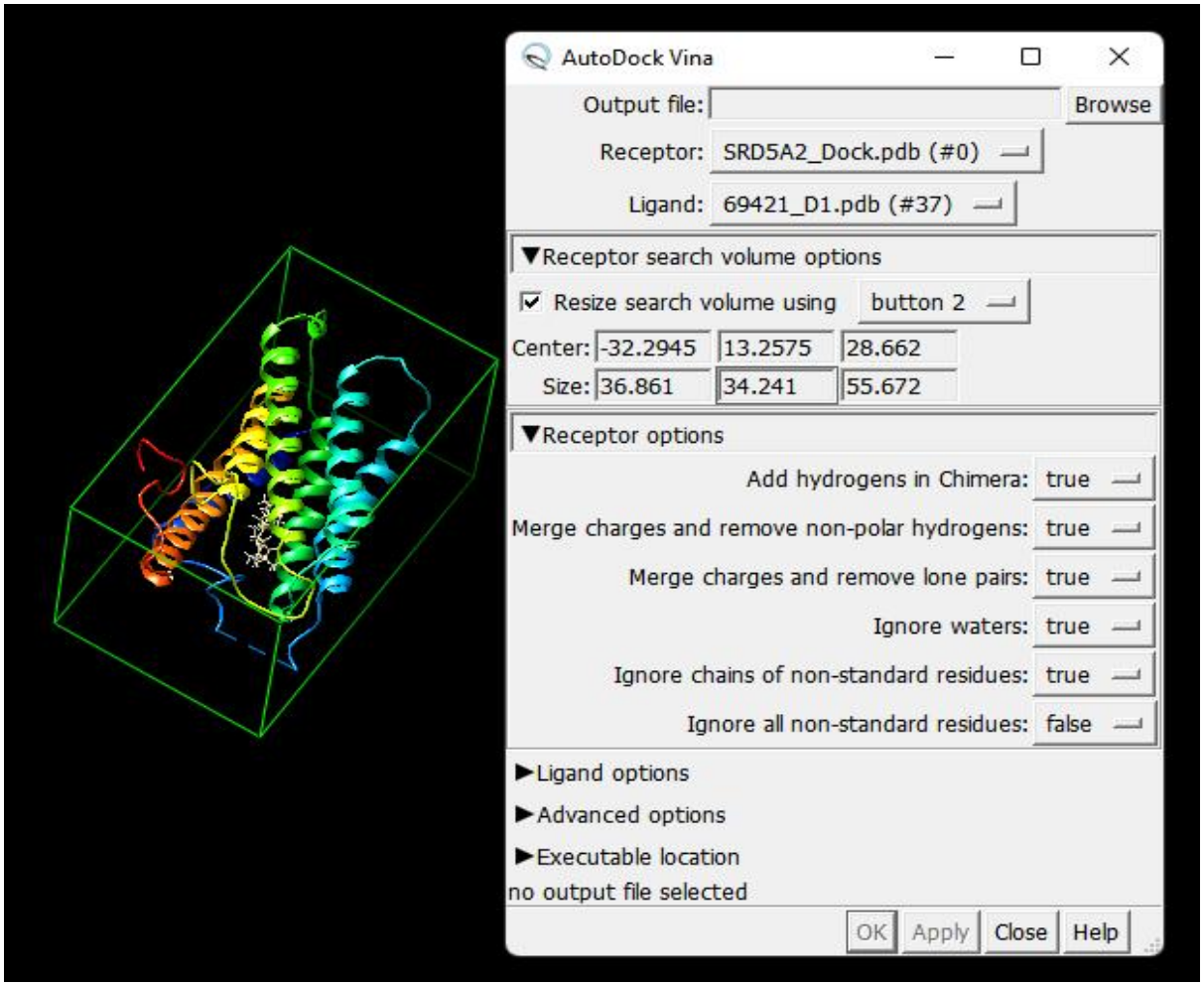


Plate 1: AutoDock Vina Grid Box setting for 5-alpha reductase

Results

The findings of GC-MS assay identified the phytochemical composition of the n-hexane fraction extracted from *Cnidoscolus aconitifolus*. The resulting data, showcasing identified phyto components, is presented in Figure and Table 1 below;

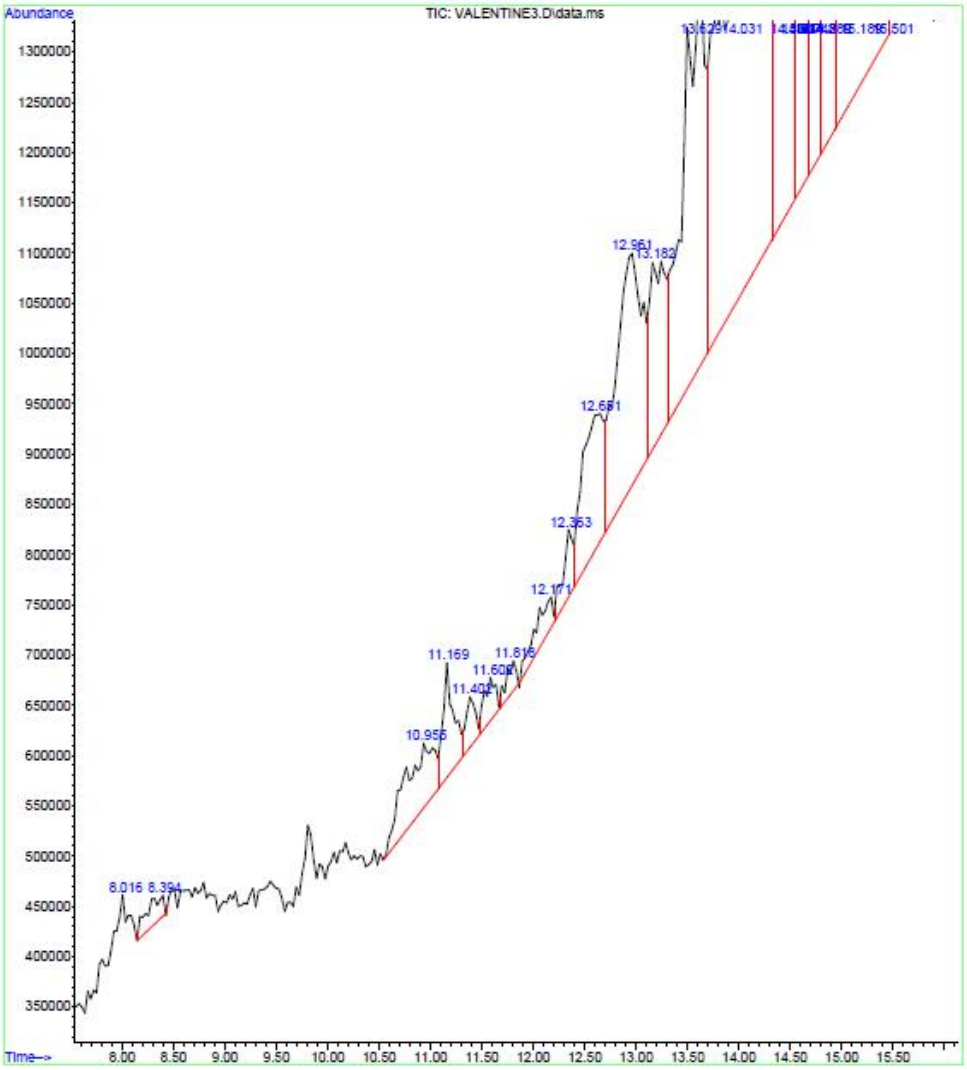


Table 1: GC-MS Phyto-Components Identified in N-Hexane Fraction of *Cnidoscolus aconitifolus*

Peak No	RT (min)	Name of compound	Peak area (%)	PubChem CID	Molecular Formula	Molecular weight (g/mol)	Model	Binding Affinity (kcal/mol)
STD	-	Finasteride	-	57363	$C_{23}H_{36}N_2O_2$	372.5	1	-11.2
1	8.016	5-Vinyl-pyrazole	0.463	565051	$C_5H_6N_2$	94.11	1	-4.5
2	8.394	3-Phenoxypropionic acid	0.550	81596	$C_9H_{10}O_3$	166.17	3	-6.0
3	10.955	2,4,5-Trichlorophenyl	2.457	543695	$C_9H_5Cl_3O_2$	251.5	1	-6.4

		propenoate						
4	11.169	1H-Pyrazole-1-acetamide,4-iodo-N-(phenylmethyl)-	1.574	1510934	$C_{12}H_{12}IN_3O$	341.15	2	-7.3
5	11.402	2-Decanynoic acid	0.596	324381	$C_{10}H_{16}O_2$	168.23	1	-5.3
6	11.602	Chloroacetic acid, 3-tridecyl ester	0.618	536408	$C_{15}H_{29}ClO_2$	276.84	1	-5.9
7	11.818	Ethyl 9-hexadecenoate	0.374	5364759	$C_{18}H_{34}O_2$	282.5	1	-6.1
8	12.171	cis-11-Hexadecenal	0.810	5364495	$C_{16}H_{30}O$	238.41	1	-5.9
9	12.363	Cyclooctacosane	0.766	520451	$C_{28}H_{56}$	392.7	5	-7.6
10	12.651	Oxacycloheptadecan-2-one	3.791	7984	$C_{16}H_{30}O_2$	254.41	1	-7.5
11	12.961	9-Octadecenoic acid (Z)-	7.994	445639	$C_{18}H_{34}O_2$	282.5	1	-6.2
12	13.182	Cyclopropaneoctanal, 2-octyl-	3.757	550143	$C_{19}H_{36}O$	280.5	1	-6.4
13	13.629	Tetradecanal	11.394	31291	$C_{14}H_{28}O$	212.37	1	-5.5
14	14.031	cis-9-Hexadecenoic acid	25.099	445638	$C_{16}H_{30}O_2$	254.41	1	-6.4
15	14.506	Oleic Acid	7.276	445639	$C_{18}H_{34}O_2$	282.5	1	-6.2
16	14.614	1-Octadecene	3.731	8217	$C_{18}H_{36}$	252.5	1	-5.6
17	14.742	9-Octadecene, (E)-	3.169	5364599	$C_{18}H_{36}$	252.5	1	-6.0
18	14.889	9-Octadecenoic acid (Z)-,	3.681	5283468	$C_{21}H_{40}O_4$	356.5	1	-6.7
19	15.189	2- Chloropropionic acid, hexadecyl ester	17.485	11734	$C_3H_5ClO_2$	108.52	-	-
20	15.501	cis-7,cis-11-Hexadecadien-1-yl acetate	4.413	5363265	$C_{18}H_{32}O_2$	280.4	1	-6.3

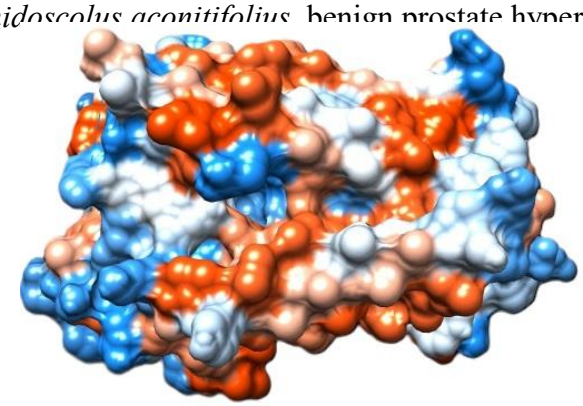


Figure 1(a): Hydrophobicity view of Free Docked 5-Alpha Reductase

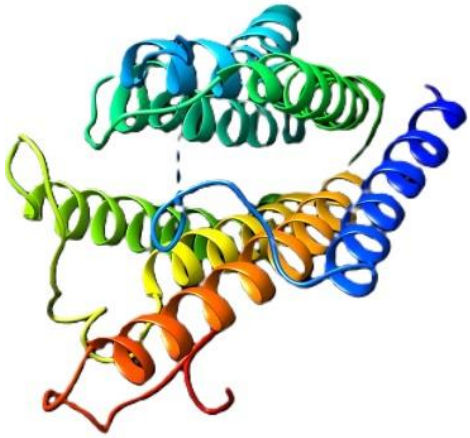


Figure 1(b): 3D Representation of Free Docked 5-Alpha Reductase



Figure 1(c): 3D Representation of 5-Alpha Reductase docked with ligands of n-hexane fraction

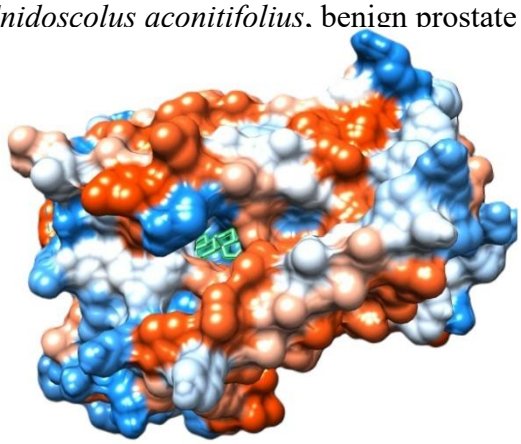


Figure 2(a): Hydrophobicity view of 5-Alpha Reductase interaction with Finasteride (a standard BPH drug)

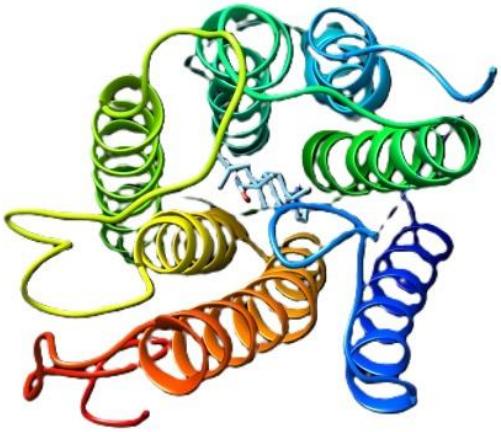


Figure 2(b): 3D Representation of 5-Alpha Reductase interaction with Finasteride

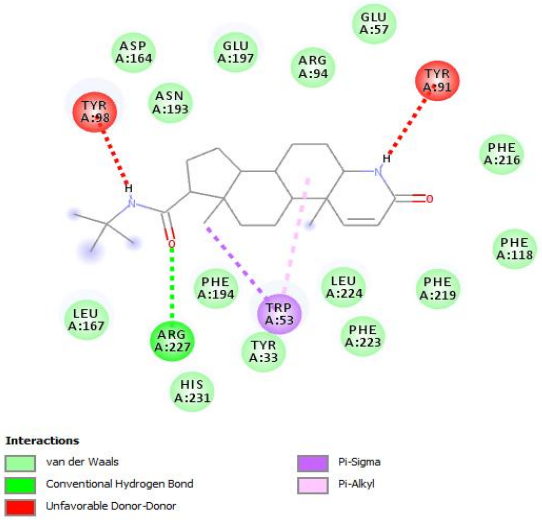


Figure 2(c): 2D representation of 5-Alpha Reductase interaction with Finasteride

Figures 2a and 2b showed how Finasteride (a standard BPH drug) binds to the binding pocket of the enzyme 5a-reductase. Figure 2c demonstrated the interaction between the amino acids present at the binding pocket of 5a-reductase and finasteride molecule.

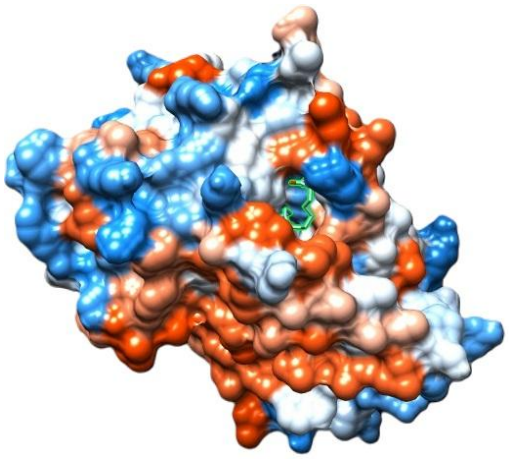


Figure 3(a): Hydrophobicity view of 5-Alpha Reductase interaction with 9-Octadecenoic acid (one of components of the n-hexane fraction)

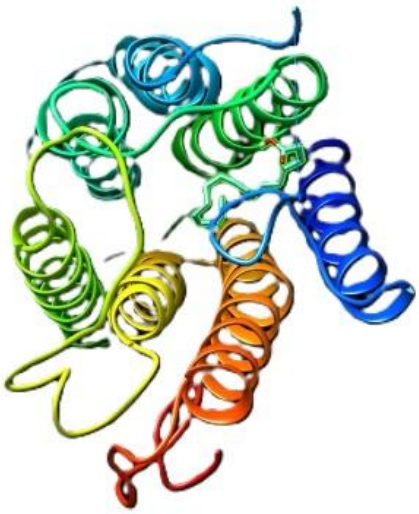


Figure 3(b): 3D Representation of 5-Alpha Reductase interaction with 9-Octadecenoic acid

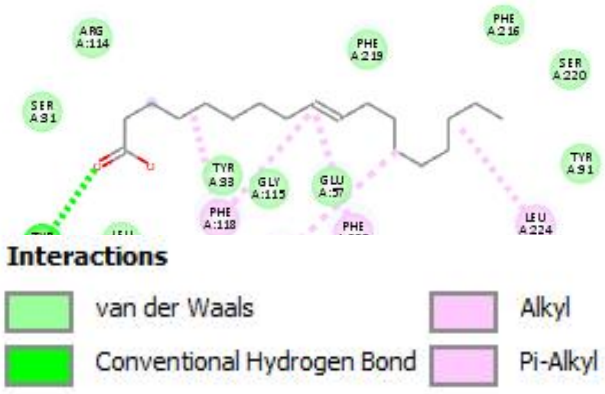


Figure 3(c): 2D representation of 5-Alpha Reductase interaction with 9-Octadecenoic acid

These diagrams Figures 3a and 3b showed the binding of 9-Octadecenoic acid at the binding pocket of the enzyme 5a-reductase. Figure 3c demonstrated the interaction between the amino acids present at the binding pocket of 5a-reductase and 9-Octadecenoic acid molecule.

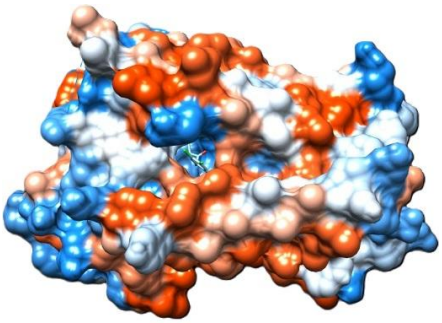


Figure 4(a): Hydrophobicity view of 5-Alpha Reductase interaction with 2,4,5-Trichlorophenyl propenoate (one of components of the n-hexane fraction)

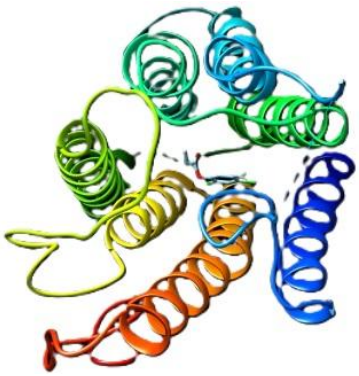


Figure 4(b): 3D Representation of 5-Alpha Reductase interaction with 2,4,5-Trichlorophenyl propenoate

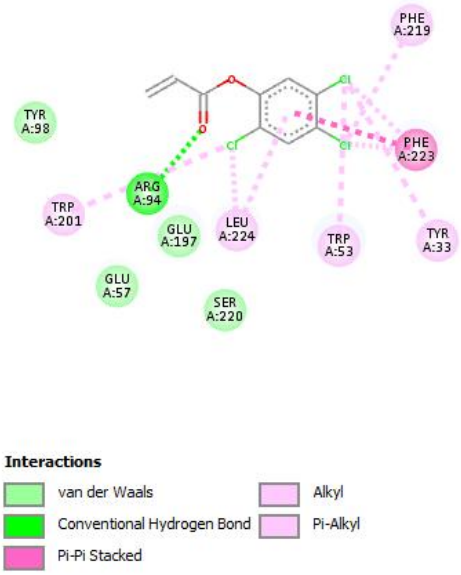


Figure 4(c): 2D representation of 5-Alpha Reductase interaction with 2,4,5-Trichlorophenyl propenoate

These diagrams Figures 4a and 4b showed the binding of 2,4,5-Trichlorophenyl propenoate at the binding pocket of the enzyme 5a-reductase. [illegible] demonstrated the interaction between the amino acids present at the binding pocket of 5a-reductase and 2,4,5-Trichlorophenyl [illegible] molecule.

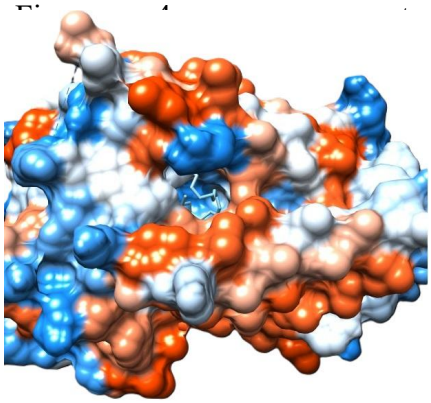


Figure 5(a): Hydrophobicity view of 5-Alpha Reductase interaction with cis-9-Hexadecenoic acid (one of components of the n-hexane fraction)

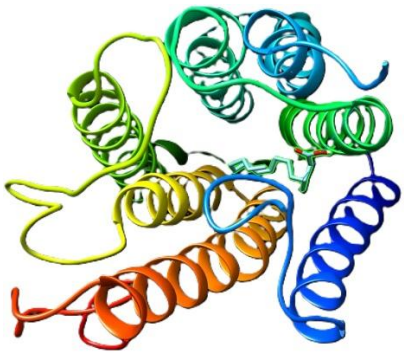


Figure 5(b): 3D Representation of 5-Alpha Reductase interaction with cis-9-Hexadecenoic acid

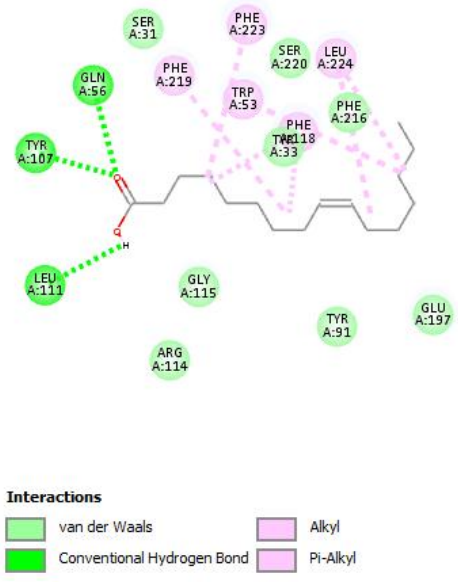


Figure 5(c): 2D representation of 5-Alpha Reductase interaction with cis-9-Hexadecenoic acid

These diagrams Figures 5a an ed the interaction between the the binding of 2,4,5-Tri s present at the binding pocket propenoate at the binding p ctase and cis-9-Hexadecenoic enzyme 5a-reductase. ıle.

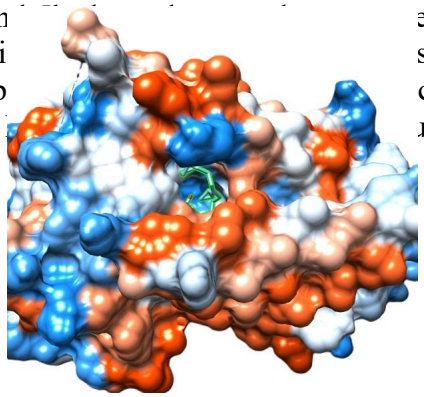


Figure 6(a): Hydrophobicity view of 5-Alpha Reductase interaction with Cyclopropaneoctanal, 2-octyl (one of components of the n-hexane fraction)

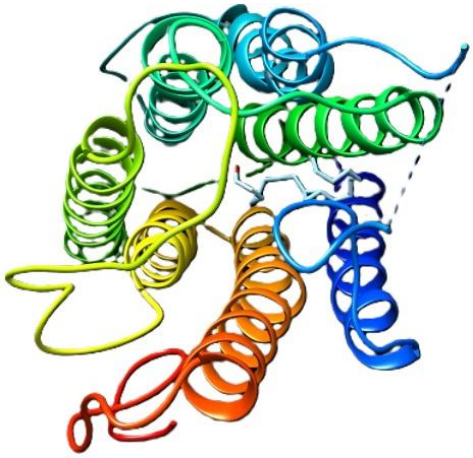


Figure 6(b): 3D Representation of 5-Alpha Reductase interaction with Cyclopropaneoctanal,2-octyl

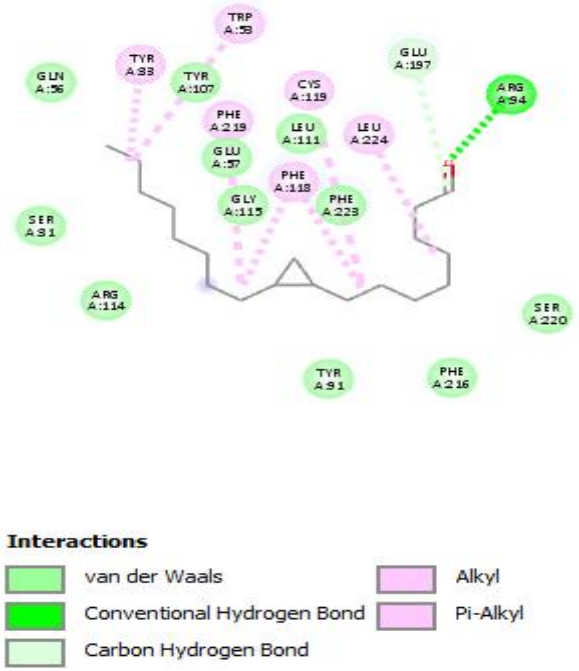


Figure 6(c): 2D representation of 5-Alpha Reductase interaction with Cyclopropaneoctanal,2-octyl

These diagrams Figures 6a and 6b showed the binding of Cyclopropaneoctanal,2-octyl at the binding pocket of the enzyme 5a-reductase. Figure 6c demonstrated the interaction between the amino acids present at the binding pocket of Cyclopropaneoctanal,2-octyl molecule.

Discussion

The in-silico study on the n-hexane leaf fraction of *Cnidoscolus aconitifolius* highlights its potential in mitigating benign prostatic hyperplasia (BPH). In-silico studies are invaluable for elucidating the molecular mechanisms through which bioactive compounds exert their effects. For the n-hexane leaf fraction of *Cnidoscolus aconitifolius*, molecular docking simulations revealed promising interactions with key targets implicated in prostate enlargement, such as androgen receptors (AR) and 5-alpha reductase (5-AR) (Liu *et al.,* 2020). The binding affinity of the phytochemicals in the leaf fraction to these targets suggests a potential for modulating androgen-driven pathways that are central to BPH pathogenesis (McVary, 2006). N-hexane as a solvent, often extracts compounds with significant biological activity, which might contribute to the observed effects (Rang *et al.,* 2016).

Phytochemical constituents are responsible for most medicinal activities attributed to medicinal plant species (Chukwu *et al*, 2020). The analysis of these phytochemicals is paramount as World Health Organization (WHO) has specified the need to determine the composition of biologically active substances considered for nutritional and medicinal purposes (WHO, 2012).

The preliminary phytochemical analysis carried out on n-hexane fraction of the extract of *C. aconitifolius* leaves showed the presence of some bioactive compounds, their retention time and peak percentage in the plant as presented in (Table 1).

Results of the GC-MS analysis of *C. aconitifolius* leaf extract showed 20 compounds. Some of the compounds are 9-Octadecanoic acid with the best percentage peak of 7.994% and retention time of 12.961; 2,4,5-Trichlorophenylpropanote was detected with percentage peak of 2.457% and a retention time of 10.955 was detected; cis-9-Hexadecenoic acid with percentage peak of 25.099% and retention time of 14.031 was detected while as Cyclopropaneoctanal, 2-octyl with percentage peak of 3.791% and retention time 12.651 was found.

The phyto-components were docked with the enzyme 5-alpha reductase in order to ascertain the possible binding poses and to correctly predict their various binding affinities to 5-alpha reductase. The results of the docking show the interaction between the ligands (Phyto-components) and 5-alpha reductase.

For the standard ligand Finasteride, the van der waals bond, conventional hydrogen bond, unfavorable donor-donor bond, Pi-sigma bond and Pi-alkyl bond were present, interacting with amino acids at different positions within the enzyme as seen in Figure 2c. This is similar to the binding of some of the components of the n-hexane fraction such as 9-octadecanoic

acid, as seen in figure 3, in which the van der waal bond, conventional hydrogen bond, alkyl bond and Pi-alkyl bond are present, interacting with amino acids at different positions within the enzyme. For example, there is an alkyl bond binding the amino acid leucine at position 224 to the carbon; whereas for 2,4,5-Trichlorophenylpropanote, the van der waal bonds, conventional hydrogen bond, Pi-pi stacked bond, alkyl bond, Pi-alkyl bond is present, interacting with amino acids at different positions within the enzyme.

The findings from this research shows that the presence of 9-octadecenoic acid (z) in the plant indicates that the plant may possess some biological activity such as anti-inflammatory, anti-alopecic, 5-α reductase inhibitory activity, lubricant, antitumor, immune-stimulant, diuretic, antiandrogenic, antibacterial, antifungal, and lipoxygenase inhibitor activities just as reported by Chukwu *et al*, (2020). The most effective and efficient compound is the 9-Octadecanoic acid in comparism with the standard finesteride because of its binding affinity. 9-Octadecanoic acid possess the biological activity important for the inhibition of 5a-reductase.

Thus, the effectiveness of the n-hexane leaf fraction can be attributed to the specific phytochemicals it contains. Compounds such as flavonoids, saponins, and phenolic acids are known for their anti-inflammatory and antioxidant properties, which can influence prostate health (Carmona *et al.,* 2014). These compounds may mitigate oxidative stress and inflammation, common contributors to BPH development (Haddad *et al.,* 2020). The in-silico data suggest that these phytochemicals could potentially inhibit the enzymatic activities or receptor interactions that drive prostate cell proliferation.

The results of this study support the potential of *Cnidoscolus aconitifolius* as a natural therapeutic agent for BPH. Traditional use of this plant in various cultures aligns with these findings, suggesting a historical basis for its efficacy (Carmona *et al.,* 2014). The *in-silico* approach complements traditional knowledge by providing a mechanistic framework for understanding how the plant's bioactive compounds may exert their effects. This integration of traditional and computational methods can guide future experimental studies and clinical trials.

While the *in-silico* study provides valuable insights, it has limitations. Computational models rely on available structural data and prediction algorithms, which may not fully capture the complexity of biological systems (Roth *et al.,* 2017). The accuracy of these models depends on the quality of the input data and assumptions made during simulations. Furthermore, the bioavailability and pharmacokinetics of the n-hexane leaf fraction have not been addressed, which are critical factors in determining its therapeutic efficacy *in vivo*. Future research should focus on validating these computational predictions through *in-vitro* and *in-vivo* experiments. This includes assessing the actual biological activity of the n-hexane leaf fraction in BPH models and determining its safety profile and efficacy in clinical settings. Additionally, exploring the isolation and characterization of specific phytochemicals responsible for the observed effects could provide more targeted therapeutic options.

Conclusion

The in-silico study provides promising evidence that n-hexane leaf fraction of *Cnidoscolus aconitifolius* may attenuate BPH through interactions with key molecular targets. While the findings support the potential of this natural

product, further empirical validation is essential to confirm its therapeutic benefits. This study underscores the value of integrating computational approaches with traditional knowledge to explore novel treatments for common health conditions like BPH.

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