Original Research Article

Plant steroidal alkaloid binds aromatase catalytic cleft: Sterioselective affinity modulating enzyme function an In Silico study

Athithan Velan

Department of Biochemistry, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India

Received: 08-05-2025 / Revised: 27-05-2025 / Accepted: 20-06-2025

Abstract

Attentive on the impact of ubiquitously present plant molecules on mammalian cell is currently of interest. Specific endocrine deficiency with low testosterone and elevated estrogen causes impaired spermatogenesis. However, inhibition of aromatase enzyme catalytic activity in conversion of testosterone to estrogen is a significant adapting step in logical practice for male infertility therapy. Dietary plant molecules have significant tissue proteins modulatory potential in mammalian. Hence, the present study intends to investigate steroidal alkaloid against aromatase enzyme inhibition potential as drug targets. Molecular docking of tomatidine, tomatidenol and aromatase enzyme protein template was carried out using Auto Dock version 4.0. In Silico molecular docking study yielded binding metrics for tomatidine (-10.15 Kcal/mole) and tomatidenol (-10.01 Kcal/mole) with aromatase enzyme exhibits high docking score, as compared to testosterone (-9.85 Kcal/mole). Dietary plant steroidal alkaloid may potentially inhibit aromatase catalytic activity resulted to improve testosterone level in testicular tissue. In Vitro and In Vivo aromatase enzyme inhibition studies with plant steroidal alkaloid may provide a clear path for the identification and development of novel drug candidates against aromatase enzyme inhibition for male infertility that also provides evidence for the concept of reverse pharmacognosy.

Keywords: Tomatidine, aromatase, spermatogenesis, infertility.

Introduction

Infertility is a multifactorial resulted to failure of pregnancy for 12 months regular unprotected intercourse of couple. Worldwide, 15% of couples are infertile and male factors excuse for 50% cases [1]. Sterioidogenesis and spermatogenesis are a major function was taken places in testicular tissues through which spermatogonia undergo cell division and transform into mature spermatozoa. However, spermatogenesis along with sustaining of healthy sperm subjected to continues supply of testosterone along with Follicular Stimulating Hormone (FSH) stimuli on testicular cells. The hypothalamic-pituitary-gonadal axis regulates the sterioidogenesis and persistence of spermatogenesis via Gonadotropin-Releasing Hormone (GnRH), Luteinizing Hormone (LH) and FSH. Hence, imbalance on GnRH, FSH and LH are interferes sterioidogenesis leads to low level of testosterone affect spermatogenesis and semen quality. Even though the GnRH, FSH and LH are levels are normal, deficiencies in spermatogenesis can be associated with excessive estrogen with low level of testosterone [2]. Although, estrogen have a direct effect on germinal epithelium and feedback inhibition on the hypothalamic-pituitary-gonadal axis leads to demised LH and FSH release resulted to affecting testosterone and sperm production in the testicular tissue [3]. Aromatase enzyme is comes under the cytochrome p450 enzyme family enzyme present in testis, adipose tissues and brain in male. Aromatase enzyme converts testosterone, androstenedione into estrogen. The malfunction of aromatase enzyme lead to increase estradiol level that affecting spermatogenesis resulted to male infertility. Hence, aromatase enzyme inhibitor based therapeutic approach on testosterone dependent infertility and renormalization of testosterone/estradiol level are assumed to be a normal spermatogenesis in testicular tissue [4-5].

Humans are consuming plant based diet in day to day life and deliberately exposed to these plant bio-potential molecules are enter into circulation resulted to modulating cellular and physiological changes in human. Nevertheless, phyto compounds are well known that have significant medicinal value since ancient period. Hence, the searching of dietary based plant biopotencial molecules are ideal alternative and effective therapeutic approach in male infertility. Plant polyphenols, flavonoid and steroidal alkaloid molecules such as gallic acid, cataechins, epigallocatechin-3-gallate, naringenin and myricetin, rutin, kaempferol, qucertin, tomatidine, tomatidenol are ubiquitously

*Correspondence
Dr. Velan Athithan
Department of Biochemistry
JIPMER, Puducherry-605006, India.
ORCID number: 0000-0002-1596-7359.
E-Mail: athi.athithan@gmail.com

present in various vegetables, fruits, green leaf are shown the beneficial effects such as attenuating oxidative damages, improving sperm motility, steroid hormones and their receptors modulating potential and prevent skeletal muscle atrophy [6-10]. The conventional drug discovery approaches are labour-intensive, time-consuming and expensive. An unconventional model of reverse pharmacology can be an innovation in the field of drug discovery. The reverse pharmacology comprises an In Silico analogue manipulative and ligand-enzyme interaction.

These dietary phyto molecules are assumed to inhibit aromatase enzyme. In the present In Silico study, we intend to investigate the aromatase inhibitory effect of specific plant molecules against human aromatase enzyme, placental isoform. In the docking study was performed using testosterone as standard against the phyto molecules.

Materials and Methods

Compound preparation

Chemical structures of molecules, namely, testosterone (CID: 6013), gallic acid (CID:370), myricetin (CID: 5281672), catechin (CID: 9064), quercetin (CID: 5280343), kaempferol (CID: 5280863), naringenin (CID: 439246), quinic acid (CID:6508), epigallocatechin 3-gallate (CID: 65064), tomatidine (CID: 65576), tomatidenol (CID: 12442871) were downloaded from the PubChem database (http://pubchem.ncbi.nlm.nih.gov/) as in .SDF file format (Figure.1). These file were converted into .mol2 format using Open Babel software in the version of 2.4.1. Than optimized by means of ligand preparation script in AutoDock version 4.0. The compound were prepared for docking as detecting root, torsion tree were set and saved in .pdbqt file format [8].

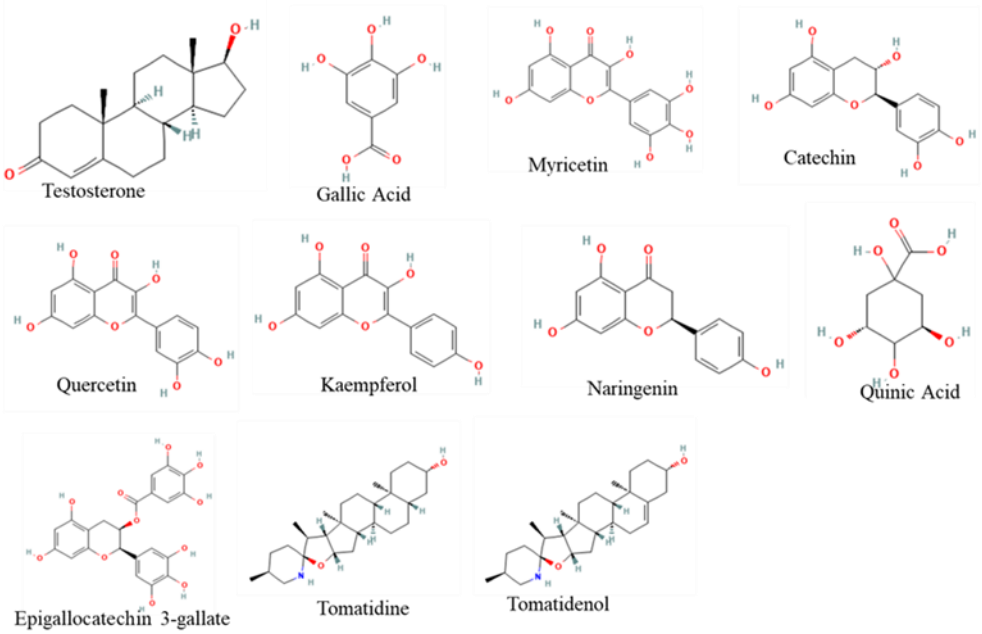


Figure 1. Shows 2D structure of plant molecules

Protein preparation and grid box generation

3D structures of aromatase enzyme isoform (PDB ID: 5JKV) were retrieved from protein databank (http://www.rcsb.org). AutoDock tools (http://autodock.scripps.edu/resources/adt) used protein template preparation for molecular docking (Figure.2). The script procedures are water molecules removal, polar hydrogen atoms addition, assignment of Kollman charges and conversion of the protein files in .pdbqt format for molecular docking. 3D structures of proteins and chemical structures of ligand were complexed together to form a grid. Therefore, the centroid of the molecule in complex structures was chosen to generate grid points are X = 60, Y = 60 and Z = 60 axis set for docking. The grid file was generated using "grid generation panel" in AutoDock software ver. 4.0. [11].

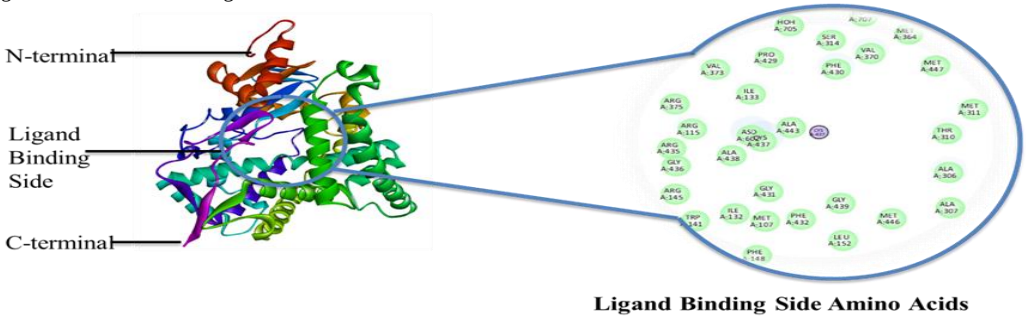
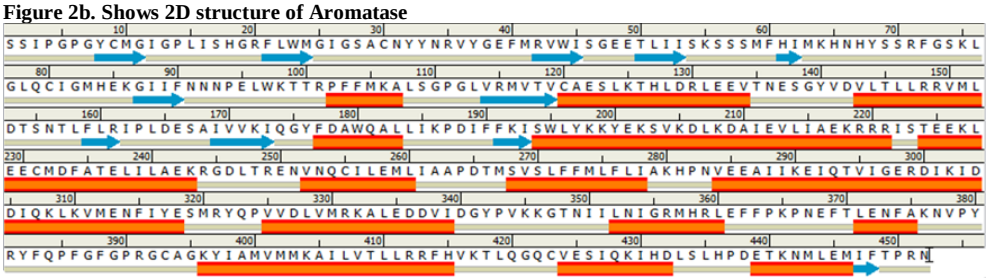


Figure 2a. Shows structure of Aromatase and Ligand binding side amino acids

Figure 2b. Shows 2D structure of Aromatase



Molecular docking and Evaluation of binding energy

Protein-ligand docking performed using AutoDock4 tool. For each ligand 100 docking runs with default parameters were performed by treating ligand as flexible and protein as rigid. The results were visualized using BIOVIA Discovery Studio 2024. The docking conformational clusters at lowest binding energy were considered to be an inhibitor and further analysis carried out. The AutoDock ver. 4.0 was used to calculate the total binding energy of plant compounds against Aromatase enzyme. A numerous docked conformations obtained and these one with a lowest total binding energy in ligand binding cavity of Aromatase enzyme were selected as possible binding conformation. Interactions of plant compounds and Aromatase enzyme amino acid residues on the ligand binding cavity were analyzed using BIOVIA Discovery Studio 2024 [12-13].

Results

The aromatase enzyme binding interaction with dietary plant molecules were studied by In Silico molecular docking. Based on molecular docking simulations energies obtained, aromatase enzyme exhibited highest binding affinity towards tomatidine and tomatidenol exhibiting -10.15 and -10.01 Kcal/mole respectively, compared to testosterone that presented binding affinity -9.85 Kcal/mole with aromatase enzyme (Table. 1 and Figure. 3). Also, the gallic acid, myricetin, catechin, quercetin, kaempferol, naringenin, quinic acid, epigallocatechin 3-gallate, exhibited binding affinity, -5.32, -6.47, -6.64, -6.69, -6.87, -7.12, -7.29, -8.79 Kcal/mole respectively (Table. 1).

Table.1. Plant molecules and aromatase enzyme interaction

Aromatase (5JKV)	G-Score kcal/mol	Van der waals	Hydrogen bond	Alkyl/π-Alkyl	π-sigma
Testosterone (CID: 6013)	-9.85	PHE134, PHE221, ILE305, ASP309, THR310, ILE133, LEU372, VAL373, LEU477, SER478.	ARG 115, ALA 306, MET 374.	TRP224, VAL370	-
Gallic Acid (CID:370)	-5.32	PHE134,CYS437,GLY439	ARG115, ILE132, ILE133, TRP141, ARG145, ARG435, ALA438.	ILE133, ALA438	-
Myricetin (CID: 5281672)	-6.47	TRP141, TRP224, THR310, ILE372, VAL373, MET374,ARG435, IEU477	ARG115, CYS437, ALA438	ILE133, PHE134, ALA438	ILE133, PHE134
Catechin (CID: 9064)	-6.64	ILE133, PHE134, PHE221, TRP224, ILE305, ALA307, ASP309, LEU372, VAL373.	ARG115, ALA306, MET374, LEU477.	VAL370, MET374, IEU477	THR310
Quercetin (CID: 5280343)	-6.69	PHE134, PHE221, TRP224, ILE305, ALA307, ASP309, LEU372, VAL373, SER478.	ARG115, ALA306,MET374, ILU477	VAL370, MET374	THR310, VAL370
Kaempferol (CID: 5280863)	-6.87	ARG115, PHE134, PHE221, TRP224, ILE305, THR310, VAL369, LEU372, VAL373, SER478	ALA306, ASP309, MET374, ILE477	ILE133,VAL370, MET374, ILE477	-
Naringenin (CID: 439246)	-7.12	ALA306, ALA307, THR310, SER314, PHE317, SER363, PRO368, ASP371, ILE398.	SER314, MET364, GLN367, VAL369, VAL370.	MET311, ALA443, MET364	CYS437
Quinic Acid (CID:6508)	-7.29	PHE221, TRP224, VAL373	ARG115,VAL370,LEU372, ARG478	PHE134, MET374	-
Epigallocatechin 3-gallate (CID: 65064)	-8.79	ILE133, PHE134, IEU153, PHE221, TRP224, ALA307, ASP309, THR310,	ARG115, ALA306, IEU372,MET374, ILE477	VAL373, ALA306, VAL370, LYS437	ARG115. MET374

		ASP371, ALA438,GLY439,SER478			
Tomatidine (CID: 65576)	-10.15	ARG115, ILE134, PHE148, MET160, THR198, THR310, MET311, ILE372, MET374, GLY436, ALA438, GLY439	SER199	ILE133, LEU152, PHE203, MET303, ALA306, ALA307, VAL370, VAL373, CYS437, ILE443	-
Tomatidenol (CID: 12442871)	-10.01	ARG115, ILE134, PHE143, MET160, THR198, THR310, MET311,ILU372, GLY439, ILE443	SER199	ILE133, ILE152, PHE203, MET303, ALA306, ALA307, VAL370, VAL373, CYS437, ALA438.	-

In aromatase enzyme and tomatidine, tomatidenol interaction, tomatidine interaction, SER199 amino acid residues form hydrogen bonds, while ARG115, ILE134, PHE148, MET160, THR198, THR310, MET311, ILE372, MET374, GLY436, ALA438, GLY439 residues form Van der waals interaction and ILE133, LEU152, PHE203, MET303, ALA306, ALA307, VAL370, VAL373, CYS437, ILE443 residues via Alkyl/π-Alkyl interaction (Table 1 and Figure. 4). Similarly, tomatidenol interact with SER199 amino acid residues form hydrogen bonds, although ARG115, ILE134, PHE143, MET160, THR198, THR310, MET311, ILU372, GLY439, ILE443 residues form Van der waals interaction, similarly ILE133, ILE152, PHE203, MET303, ALA306, ALA307, VAL370, VAL373, CYS437, ALA438 residues form Alkyl/π-Alkyl interaction (table 1). testosterone, on the other hand, interacts with aromatase amino acid residues ARG 115, ALA 306, MET 374 via hydrogen bond, while Van der waals interactions are observed with PHE134, PHE221, ILE305, ASP309, THR310, ILE133, LEU372, VAL373, LEU477, SER478 amino acid residues and TRP224, VAL370 residues form Alkyl/π-Alkyl with lowest binding affinity (-9.85 Kcal/mole) as compared to the three plant molecules (Table 1 and Figure. 5).

Figure 3. Shows Aromatase and Testosterone interaction

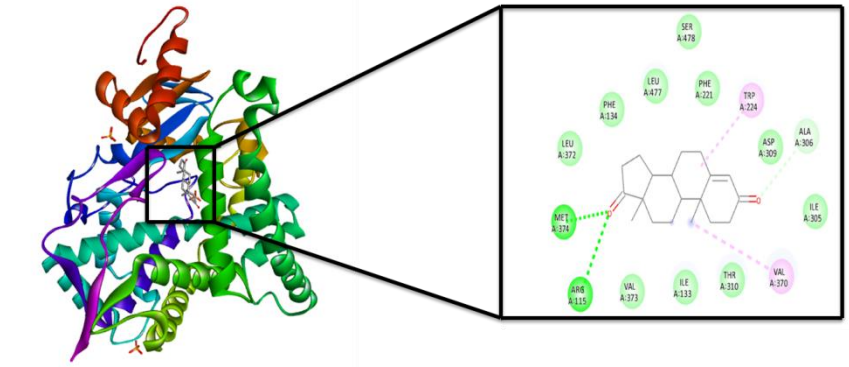


Figure 4. Shows Aromatase and Tomatidine interaction

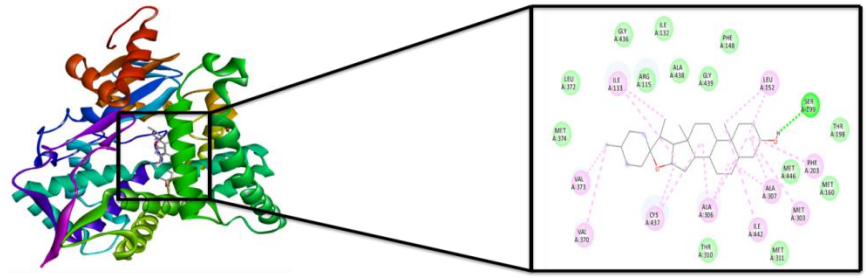


Figure 5. Shows Aromatase and Tomatidenol interaction

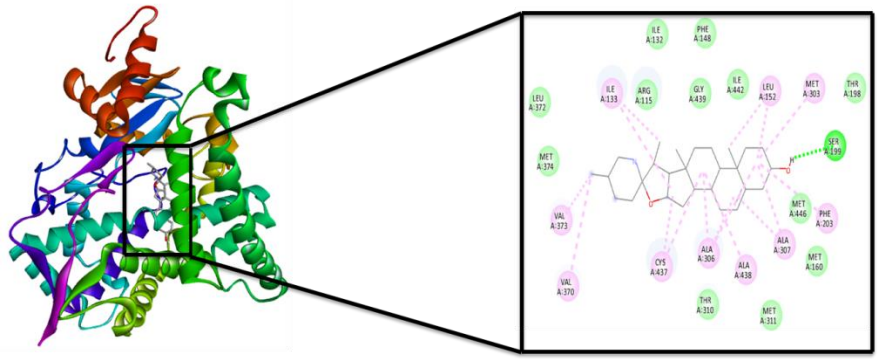
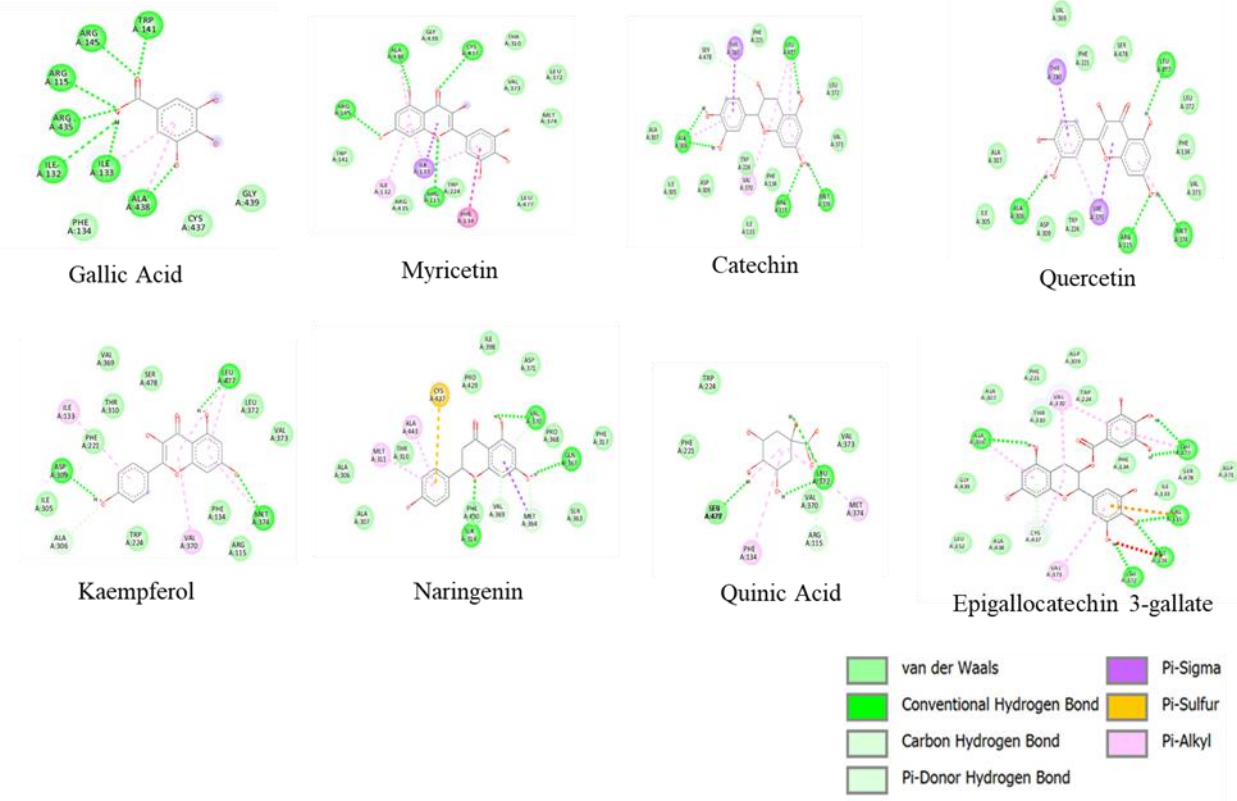


Figure 6. Shows Aromatase ligand binding cavity amino acids and phytomolecules interaction



In aromatase enzyme and epigallocatechin 3-gallate, quinic acid, naringenin, kaempferol, quercetin, catechin, myricetin and gallic acid interaction. The epigallocatechin 3-gallate interacted with ARG115, ALA306, IEU372,MET374, ILE477 residues via hydrogen bond, ILE133, PHE134, IEU153, PHE221, TRP224, ALA307, ASP309, THR310, ASP371, ALA438,GLY439,SER478 residues via Van der waals interactions and VAL373, ALA306, VAL370, LYS437 residues via Alkyl/π-Alkyl interaction and ARG115, MET374 residues form π-sigma interaction. Similarly, quinic acid interacted with ARG115, VAL370, LEU372, ARG478 residues via hydrogen bond, PHE221, TRP224, VAL373 residues via Van der waals interactions and PHE134, MET374 residues via Alkyl/π-Alkyl interaction. Naringenin interacted with SER314, MET364, GLN367, VAL369, VAL370 residues via hydrogen bond, ALA306, ALA307, THR310, SER314, PHE317, SER363, PRO368, ASP371, ILE398 residues via Van der waals interactions and MET311, ALA443, MET364 residues via Alkyl/π-Alkyl interaction and CYS437 residues form π-sigma interaction. Kaempferol interacted with ALA306, ASP309, MET374, ILE477 residues via hydrogen bond, ARG115, PHE134, PHE221, TRP224, ILE305, THR310, VAL369, LEU372, VAL373, SER478 residues via Van der waals interactions and ILE133, VAL370, MET374, ILE477 residues via Alkyl/π-Alkyl interaction. Quercetin interacted with ARG115, ALA306,MET374, ILU477 residues via hydrogen bond, PHE134, PHE221, TRP224, ILE305, ALA307, ASP309, LEU372, VAL373, SER478 residues via Van der waals interactions and VAL370, MET374residues via Alkyl/π-Alkyl interaction and THR310, VAL370 residues form π-sigma interaction. Catechin interacted with ARG115, ALA306, MET374, LEU477 residues via hydrogen bond, ILE133, PHE134, PHE221, TRP224, ILE305, ALA307, ASP309, LEU372, VAL373 residues via Van der waals interactions and VAL370, MET374, IEU477 residues via Alkyl/π-Alkyl interaction and THR310 residue form π-sigma interaction. Myricetin interacted with ARG115, CYS437, ALA438 residues via hydrogen bond, TRP141, TRP224, THR310, ILE372, VAL373, MET374,ARG435, IEU477 residues via Van

der waals interactions and ILE133, PHE134, ALA438 residues via Alkyl/π-Alkyl interaction and ILE133, PHE134 residues form π-sigma interaction. Gallic Acid interacted with ARG115, ILE132, ILE133, TRP141, ARG145, ARG435, ALA438 residues via hydrogen bond, PHE134, CYS437, GLY439 residues via Van der waals interactions and ILE133, ALA438 residues via Alkyl/π-Alkyl interaction with lowest binding affinity as compared to testosterone (Table. 1 and Figure.6).

Discussion

Male infertility is a multifactorial and remains a significant worldwide health issue. Recent studies disclose that specific endocrine abnormality in men with impaired sperm production have elevated level of estrogen resulted to low testosterone/estrogen radio. Pavlovich et al. reported that infertile men blood the testosterone/estrogen radio of 6.9, whereas normal spermatogenesis men blood testosterone/estrogen radio of 14.5 and proposed that the testosterone/estrogen radio 10 as a lower limit cut-off of normal spermatogenesis men [14]. Current logical practice are focusing the aromatase inhibitor to men with impaired spermatogenesis are associated with low testosterone level and testosterone/estrogen radio abnormality are targeting on aromatase enzyme to reducing the estrogen level with using testolactone, anastrazole and letrozole to restore testosterone level in infertile male [15].

However, humans are exposed the dietary molecules such as polyphenols, flavonoids and steroidal alkaloids are assimilated into circulatory system resulted to modulating metabolic and cell signalling processes in the various tissues resulted to cellular and physiological changes was observed in mammalians. Searching the dietary based estrogen lowering bio-potential molecules are urgently needed to treat infertile male remained as a commendable decision with the more effective and unacceptable side effects for long time consumption in oral formulation are ideal treatment option.

Present study under taken various plant molecules such as polyphenols, flavonoids and steroidal alkaloids compounds gallic acid, cataechins, epigallocatechin-3-gallate, naringenin (polyphenol), myricetin, kaempferol, qucertin (flavonoids) and tomatidine, tomatidenol (steroidal alkaloid). These molecules ubiquitously present in herbs, onions, tomatoes, broccoli, fruits and tea leaves thus shown various beneficial health effects in human, such as anti-oxidant, anti-inflammatory, anti-tumor, anti-diabetic, anti-obesity, anti-atherosclerotic, anti-myocardial ischemia, anti-allergenic, anti-microbial, anti-viral, cytoprotective, vasoproductive, and nuroprotective effects [16-17].

However, present molecular docking study, 10 compounds are investigated as aromatase enzyme inhibitor namely gallic acid, cataechins, epigallocatechin-3-gallate, naringenin, myricetin, kaempferol, qucertin and tomatidine and tomatidenol. Among these phyto compounds investigated the tomatidine and tomatidenol (-10.15 and -10.01 Kcal/mole) exhibiting high binding affinity towards the ligand binding side of aromatase enzyme compared to testosterone (-9.85 Kcal/mole), Hani et al. also performed similar study earlier with plant molecules and found potential aromatase enzyme inhibition effects was reported [17-19].Similarly, the naringenin, quercetin, and myricetin (-7.12, -6.69, -6.47 Kcal/mole) showed almost equal binding affinity towards aromatase enzyme substrate binding cavity, compared to testosterone. The amino acid residues ALA306 interact Van der waals interaction with naringenin, but in testosterone the amino acid ALA306 form H-bond, THR310 amino acid residues in the ligand binding side forms Van der waals interaction with both naringenin as well as testosterone and the amino acid CYS437 form π-sulfur bond with naringenin, thus can be offer high binding affinity in the molecules compared with testosterone. The ligand binding cavity amino acid residues ARG115, ALA306, MET374 form H-bonds, PHE134, PHE221, TRP224, ILE305, ALA307, ASP309, LEU372 residues forms Van der waals interaction with quercetin and testosterone are indicative of positive results of sterioselective inhibition of aromatase by quercetin [20]. Enzyme catalytic side amino acids ARG115 form H-band, VAL373, LEU477 form Van der waals interactions are similar in both myricetin and testosterone, also the myricetin form π-sigma interaction with ILE133, PHE134 amino acid residues indicative of aromatase catalytic reaction modulating capacity of myricetin [21-25]. However, present study reporting aromatase enzyme inhibition potential of phyto compounds. Hence, the dietary phyto molecules serve an effective therapeutic agent in male infertile subject.

Conclusions

The present In Silico molecular docking study suggests that tomatidine and tomatidenol the dietary plant molecules exhibiting high binding affinity towards the ligand binding side of aromatase enzyme. Daily consumption of tomatidine and tomatidenol will be beneficial to restore testosterone level in testicular tissue in infertile male. Outcome of our In Silico molecular docking results may be the basis for In Vivo and In Vitro studies of tomatidine and tomatidenol against aromatase enzyme, at the same time, establishing the concept of reverse pharmacology.

Acknowledgement

The author acknowledges the Department of Biochemistry and Molecular Biology, Pondicherry University, Puducherry for provided facilities to carry out in this work.

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