The Pharma Innovation Journal 2021; 10(1): 770-772

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2021; 10(1): 770-772
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www.thepharmajournal.com
Received: 10-11-2020
Accepted: 16-12-2020

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A computational approach to use the FPP capped ZnO nanoparticle as an ameliorative drug in testicular toxicity

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Abstract
Pectins are complex polysaccharides of the plant cell wall and generally recognized as safe as food ingredient and used as an adsorbent, antibacterial and antitumour substance. Similarly, Nanoparticles of ZnO proven to be antioxidants in earlier studies. Testicular toxicity is the major complication of cancer chemotherapy and it affects the spermatogenesis and steroidogenesis pathway. Testosterone is a major hormone involved in male fertility. A new *in silico* approach was carried out using a combination of Fractionated pectin powder (FPP) capped nZnO with the enzymes involved in the testosterone synthesis pathway. The docking scores were analysed and the best ligand-target interactions were identified. Hence present study projects the positive role of FPP capped nZnO with the steroidogenic enzymes.

Keywords: Docking score, ligand, target

Introduction
The necessary prerequisite for the maintenance of spermatogenesis in the adult testis is the major male sex hormone testosterone. Testosterone is synthesized from the Leydig cells from the cholesterol with the help of four important enzymes *viz*., cholesterol side-chain cleavage enzyme, 17α hydroxylase, 3β Hydroxysteriod Dehydrogenase (HSD), and 17β Hydroxysteriod Dehydrogenase [1]. The testicular steroidogenesis is mainly controlled by two rate-limiting enzymes 3β HSD and 17β HSD. Any alteration in the activities of these enzymes directly reflects changes in testosterone production [2]. Decreased activities of 3β HSD and 17β HSD was earlier reported in Adriamycin [3] and Cisplatin-induced testicular toxicities [4].

The deficiency of testosterone affects the differentiation of pachytene spermatocytes and spermatids Testosterone withdrawal leads to increased germ cell apoptosis highlighting its role as a cell survival factor, protecting the germ cells from apoptotic death. Testosterone is the only hormone that sustains complete spermatid differentiation though FSH may stimulate early events in spermatogenesis, including spermatogonial proliferation and meiosis [5, 6].

Zinc is an essential, natural mineral that acts as an antioxidant and a cofactor for more than 80 enzymes involved in DNA transcription and protein synthesis necessary for germ cell development [7]. Nanoparticles of ZnO had significantly improved the antioxidant status, sperm count, and testosterone levels in chemotherapy-induced testicular toxicity [8]. Similarly, Pectins are also reported to have a protective effect against experimentally induced testicular toxicity [9, 10]. Hence, the present study is designed to identify the interaction between Fractionated pectin powder (FPP) capped nZnO with enzymes involved in the testosterone synthesis pathway.

Materials and Methods
In silico studies were performed to identify the interaction between the targets and the ligands. In the present study, the targets were identified as $P450_{scc}$ - cholesterol side-chain cleavage enzyme, $P450_{17\alpha}$ -17α hydroxylase, 3β HSD - 3β hydroxysteriod dehydrogenase and 17β HSD - 17β hydroxysteriod dehydrogenase involved in the testosterone synthesis pathway and the ligand was FPP capped nZnO.

(a) Target preparation
FASTA format of the required target proteins was downloaded from the NCBI database. 3D structures of the proteins were modelled using online software. Using 3D Refine online software, the prepared model was refined and finally, the structure was validated using what-if server and Ram page online software.

(b) Ligand preparation

FPP (Pectin) 3D structure was downloaded from Pubchem online database and nZnO 3D structure was modelled using Schrodinger software and it was capped with FPP.

(c) Molecular docking

The molecular interaction between target and ligand was executed by Accelrys Discovery Studio. Initially, the target protein was uploaded to the software. Water molecules and attached ligands were removed. Energy minimization was done by applying CHARMm (Chemistry at Harvard Molecular mechanics) force field and binding sockets were predicted. Similarly, the ligand was uploaded in the software and clean geometry was done. Finally, using the Ligand fit protocol, docking was done. The docking score and ligand binding energy were analyzed.

Results and Discussion

FPP capped nZnO showed good interaction with $P450_{scc}$ and 3β HSD. It interacted with different amino acids of target proteins and their distance listed in Table 1.

Table 1: It interacted with different amino acids of target proteins and their distance listed

Target (binding site)	Interaction site	Dock score	-PMF	Interacting amino acid	No. of Hydrogen bond- Distance Å
$P450_{scc}$ (5)	2	50.238	89.58	Isoleucine	1- 2.689
				Glutamine	2- 2.190, 2.988
				Phenylalanine	No hydrogen bond
$P450_{17\alpha}$ (17)	2	14.081	26.41	Arginine	2- 1.807,2.532
				Proline	1- 2.466,
				Phenylalanine	1-2.718
3β HSD (21)	2	50.18	29.63	Theronine	3-2.088,2.698,2.088
				Arginine	1- 2.780
				Aspargine	3-1.948,1.887,2.780
17β HSD (24)	7	7.383	40.69	Aspargine	1-2.865
				Glycine	1- 2.454
				Lysine	1-2.122
				Serine	2-2.071, 2.236

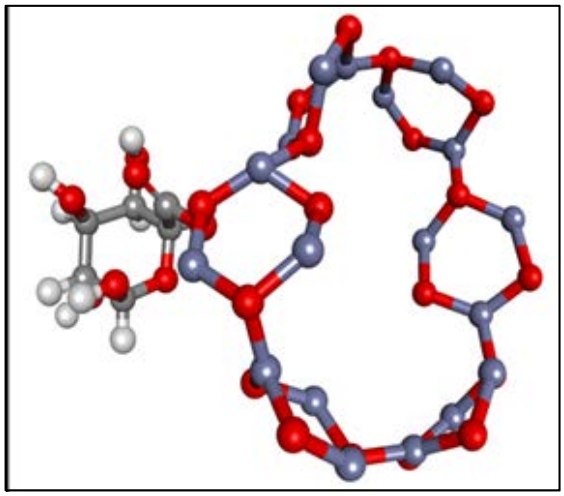

Fig 1: 3D structure of FPP capped nZnO

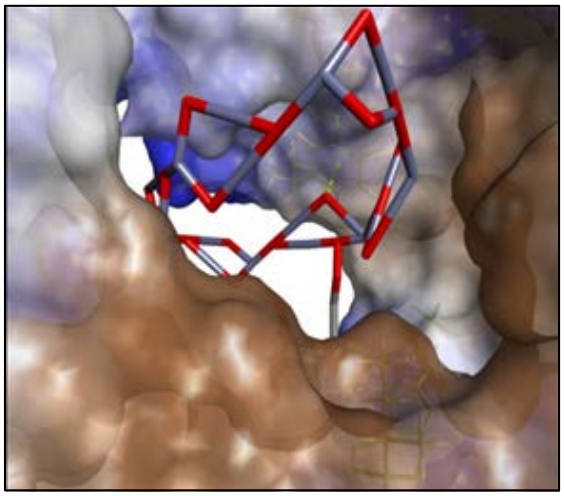

Fig 3: Interaction with hydrophobic domain of target

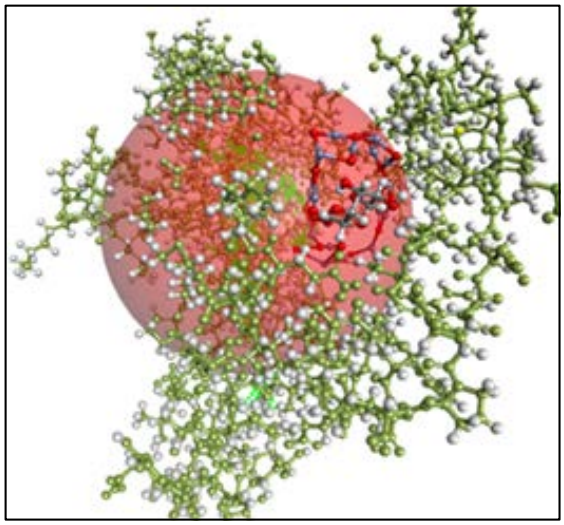

Fig 2: Interaction of ligand &Target

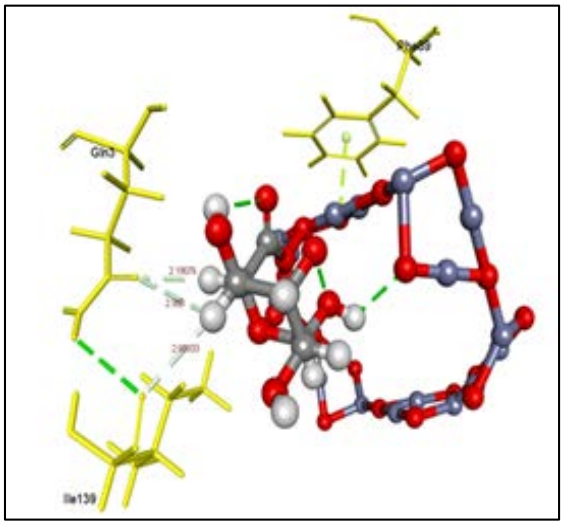

Fig 4: Interaction with $P450_{scc}$

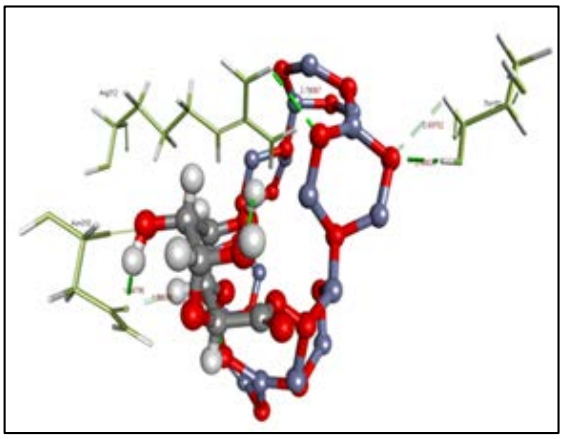

Fig 5: Interaction with 3β HSD

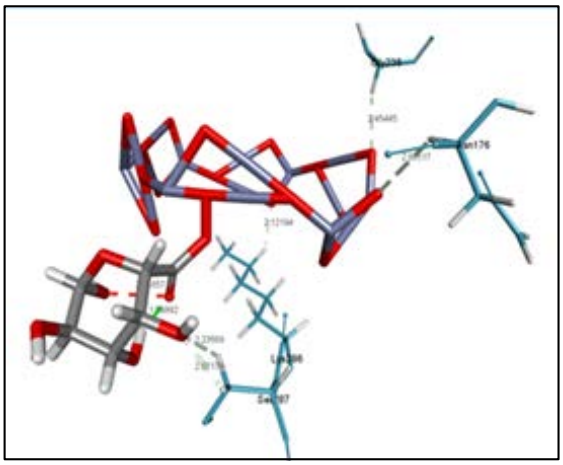

Fig 6: Interaction with 17β HSD

FPP capped nZnO showed good interaction with $P450_{scc}$ and 3β HSD and also showed high docking scores among the four targets involved in the synthesis of testosterone. Highly interacting ligands with negative energy are required to get the desired function.

The type of bond between the ligand and the target, the number of bonds, and their distance are important for docking studies. In the present study, the interaction between the hydrogen bonds contributes to the strong interaction between the ligand and target. A number of bonds more than 1 and a distance below 3 Å are required for good interaction.

Conclusion

The Nano composite FPP capped nZnO showed good docking scores with $P450_{scc}$ and 3β HSD enzymes involved in the testosterone synthesis pathway. Hence, the present study might be helpful in the design and development of novel drugs for treating testicular toxic conditions. Further *in-vitro* and *in vivo* studies are needed to elucidate the concrete mechanisms.

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