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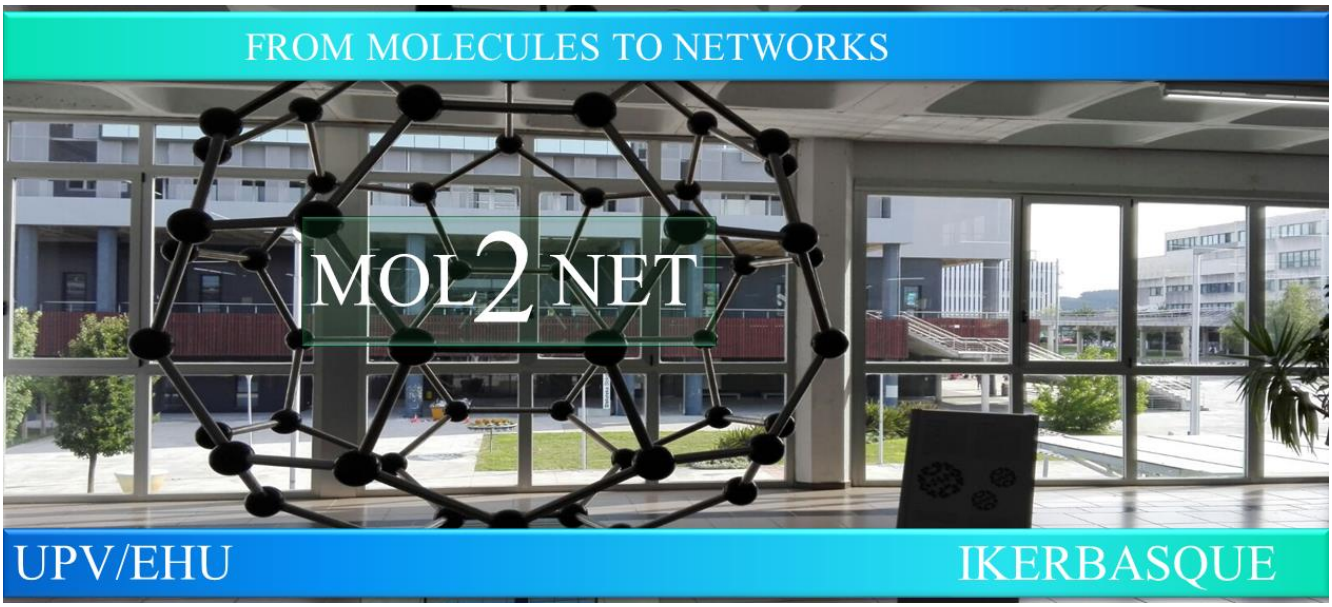

Chemical compounds of tobacco cigarette: A study of the potential for disruption of systemic hormones and interaction with central nervous system enzymes by molecular docking

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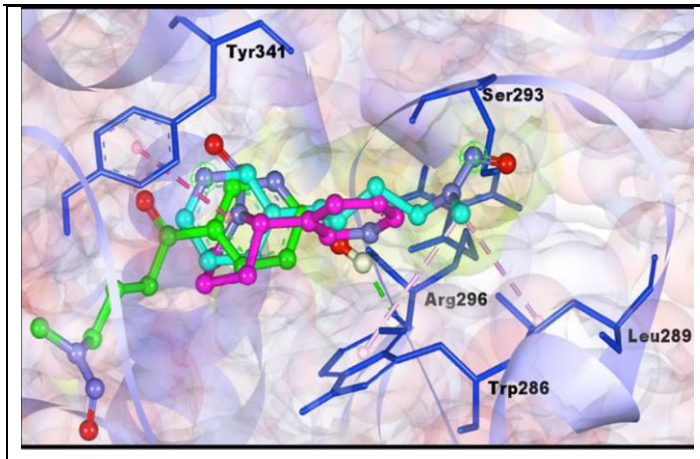
Graphical Abstract	**Abstract**
	Smoking tabacco is a serious disease caused by chemical and emotional dependence on tobacco products, which causes the death of thousands of people each year. The toxic chemicals in tobacco smoke are responsible for many diseases such as cancer, diabetes, heart disease and endocrine problems. As a way to study the interactions of chemical products with proteins of living beings, the molecular docking has been highlighted as a promising tool to help the design of experimental



and clinical studies. In this context, this paper summarizes two works in molecular docking with the objective of elucidating the interaction of different nicotine and its metabolites in the endocrine system and the interaction of nicotine-derived nitrosamines in the central nervous system.

Keywords: Tobacco smoking; Docking molecular; Cigarette smoke carcinogens; endocrine disruption; central nervous system

Introduction

Tobacco smoking is a serious global epidemic disease that causes chemical, psychological, and behavioral dependence and is one of the greatest threats to public health, causing impoverishment and death. It is estimated to be responsible for the death of more than 8 million people per year, of which 1.2 million are passive smokers (1). In Brazil 443 people die a day because of smoking, 161,853 deaths annually causing a loss of R$125,148 billion in the health system and the economy(2). This disease is brought by the use of products derived from the plant *Nicotiana tabacum* of the solanaceae family, whose leaves are smoked mainly in the form of cigarettes.

The nicotine majority alkaloid constituent about 98% of chemicals in tobacco, works as a neuro-regulator which can disturb the central nervous system (CNS) resulting in the alteration of biochemical and physiological functions(3), In the liver about 80-90% of nicotine is transformed into cotinine, a stable metabolite with a relatively long half-life (4) although they are found in smaller quantities in tobacco, cotinine and nornicotine are formed endogenously in the liver as metabolites of nicotine (5) and the remainder is metabolised to trans-3′-hydroxycotinine (33–40%) and secondary metabolites, This being the main metabolite found in the urine of smokers, other secondary metabolites in nicotine are 5′-hydroxycotinine cotinine glucuronide, trans-3'-hydroxycotinine glucuronide, trans-3′-hydroxycotinine , etc (5,6).

Furthermore, Cigarette smoke (CS) contains more than 7000 toxic chemicals and at least 69 of them may be carcinogenic (CSC), which contributes to the development of several types of carcinomas (4,6)(7) as heart disease, diabetes, cancer, emphysema, epigenetic problems, endocrine problems, and many other disorders(8), Among the chemical compounds present in cigarette smoke, nitrosamines are distinguished as carcinogens (9).

Computational methods have been increasingly used to predict the molecular interactions and binding position of ligands with their target protein molecules, for the design of new inhibitors or/ and as an aid to the design of experimental and clinical trials. (10,11).

This work describes two papers that conducted as molecular docking studies with constituent chemicals from cigarette smoke, Rehan et al (2022)(4) investigating the interference of nicotine metabolites on hormone against the three endocrine transport proteins and Jamal and Alharbi (2021)(7) investigating the effect of carcinogenic nitrosamines on enzymes in the central nervous system (CNS), testing their hypothesis that nitrosamines can alter normal enzyme function and ultimately result in serious disease.

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Materials and Methods

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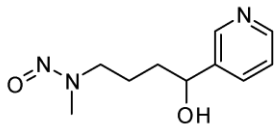
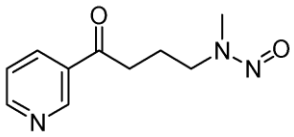
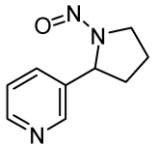
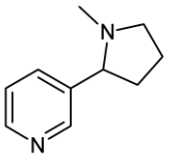
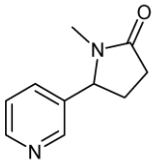
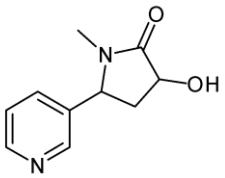
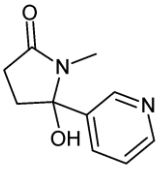
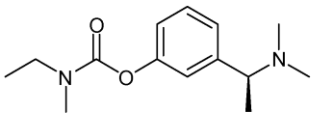
.Table 1: list of chemicals, target and standard used in the studies

	Jamal and Alharbi (2021)	Rehan *et al* (2022)
Ligand structure	(4(methylnitrosam ino)-1-(3pyridyl)-1butanol) **(NNAL)**  CN(CCCC(C1=CN=CC=C1)O)N=O 4(methylnitrosam ino)-1-(3pyridyl)-1butanone **(NNK)**  CN(CCCC(=O)C1=CN=CC=C1)N=O N'nitrosonornicotine **(NNN)**  C1CC(N(C1)N=O)C2=CN=CC=C2	Nicotine **(NIC)**  CN1CCCC1C2=CC=CN=C2 Cotine **(COT)**  CN1C(C2=CC=CN=C2)CCC1=O Trans-3'- hydroxycotinine **(T3H)**  CN1C(C2=CC=CN=C2)CC(O)C1=O 5'- hydroxycotinine **(5HC)**  OC(CC1)(C2=CC=CN=C2)N(C)C1=O
Target	● Human Acetylcholinesterase (AChE) enzymes (PDB ID: 3LII); ● Human Butyrylcholinesterase (BuChE) enzyme (PDB ID: 1P0M)	● Circulatory hormone carrier proteins (SHBG) [PDB ID: 1D2S] ● Corticosteroid-binding globulin (CBG) [PDB ID: 2VDY] ● Thyroxine-binding globulin (TBG) [PDB ID: 2VDY]
Ligand standard	Rivastigmine **(RIVA)**  CCN(C)C(=O)OC1=CC=CC(=C1)[C@H](C)N(C)C	● Dihydrotestosterone ● Cortisol ● Thyroxine

The structural information (and their respective SMILES) of the target ligands and proteins (respective PBD ID) involved in the studies is listed in Table 1.

- Binder treatment

Jamal and Alharbi (2021) transformed the two-dimensional (2D) files of the ligands NNAL, NNK, NNN and RIVA using the CORINA online platform (https://www.mn-am. com/online_demos/corina_demo) (Molecular Networks GmbH and Altamira, LLC), then the 3D structures were subjected to CHARMm force field assignment followed by the energy minimization protocol algorithm available in BIOVIA Discovery Studio Visualizer 2020 (BIOVIA 2020).
Rehan et al (2022) et al, used the pubchem SDF files and converted them to mol2 format using Obabel v. 2.4.1, initial preparations of the ligand and protein structures were made using chimera v. 1.15, or the docking search space in each target protein, the large area within the 10 Å vicinity of its bound native ligand was considered.

- Treatament of 3D structure

Both papers chose proteins from the Protein Data Bank (PDB; https://www.rcsb.org/) with high resolution. However, the authors used different strategies to prepare the PDB file and highlighted different reasons for choosing PDB.
Jamal et al. highlighted the experimental data for obtaining the 3D structure of the proteins used in their work, in treating the PDB file they removed the HETATM molecules and water and inimized the energy by applying the CHARMm force field, added the hydrogens using the en atoms were added to the 3D structures of enzymes using BIOVIA Discovery Studio Visualizer 2020.
Rehan et al (2022) et al, emphasized the choice of proteins for being in complex with their native ligands: cortisol for CBG, thyroxine for TBG and dihydrotestosterone for SHBG, being critical for locating the exact ligand binding site importat for docking.

- Docking molecular

For molecular docking Jamal and Alharbi (2021) used the AutoDock Version 4.2 suite program in order to find the binding energy (ΔG) and inhibition constant (Ki) of NNN, NNK and NNAL including RIVA as standard with selected biomolecules and enzymes AChE and BuChE. At the end of the parameter settings a total of 50 docking simulation runs were defined for LGA (Morris et al. 2008). The best extracted CSC enzyme conformations and ΔG, Ki values were analyzed from the generated output files. 3D and 2D plots of the CSC-enzyme complex were generated by BIOVIA Discovery Studio molecular visualization software, 2020 (BIOVIA 2020). As an additive study of the complexes obtained from docking studies was done using MDS analysis and Molecular Mechanics/Poisson-Boltzmann Surface Area Analysis (MM-PBSA). MDS is a technique by which we can analyze the conformational space between the ligand and protein interaction (Leach 2007), providing the trajectories of the molecules depending on Newton's equations of motion for the ligand-protein complex system. The MM-PBSA method was used to calculate the binding free energy of the best interaction complexes NNAL+ AChE complex, NNK+AChE complex and NNK+BuChE complex. The calculation also evaluates the extensive ligand-protein interaction analysis. Both methods were obtained using the GROningen MAchine for Chemical Simulation (GROMACS) tool version 2018.1.
Rehal et al (2022), initially performed an auto docking analysis using Dock v. 6.9, to ensure the quality of the molecular docking and confirm the reliability of the results obtained. With the three selected transport proteins they snapped the native ligands bound to their respective proteins (thyroxine with TBG, cortisol with CBG, and dihydrotestosterone with SHBG). The deviation of the docked pose relative to the original pose of the native ligand has been calculated as the root mean square deviation (RMSD) using Pymol v. 2.3.0, the protein-ligand interactions and illustrations of graphs were obtained using Ligplot+ v. 1.4.5.

In addition, to obtain the binding energy and the dissociation constant were predicted for the ligand-protein complexes using another independent software, Xscore v. 1.2.11. In order to verify that the alkaloids were anchored to the same binding site as the native ligands the common binding poses and interaction for the residues of the alkaloid compound and the native ligand were compared.

Results and Discussion

According to Jamal and Alharbi (2021), the interaction of CSC with the CNS enzymes AChE and BuChE. The ΔG obtained ranged from -7.32 to -8.57 kcal/mol during the interaction of CSC with AChE, while the ΔG ranged from -6.98 to -8.08 kcal/mol with BuChE. Furthermore, the MDS analysis of the enzyme molecules clearly showed that a significant interaction occurred based on the observed data from the deviation and fluctuation plots in the system due to the presence of NNK and NNAL. Furthermore, the MM-PBSA results showed a good binding ΔG -87.381 (+/-13.119) and -66.335 (+/-18.185) kJ/mol during the interaction of NNK with AChE and BuChE.

Rehal et al (2022), found that self-docking analyses of the native ligands to their respective carrier proteins demonstrated the quality of the docking and the reliability of the results. The docking results demonstrate that the four nicotine metabolites interacted with each of the transport proteins and bound profoundly to their binding pockets. Nicotine and its metabolites formed unbound contacts and/or hydrogen bonds with amino acid residues of the carrier proteins. For SHBG, Met-139 and Phe-67 were the most significant amino acid residues for binding the ligand to nicotine, showing the maximum number of interactions and the maximum ΔASA, and for CBG, Asn-264 and Trp-371 were the most important amino acid residues.

For TBG, Leu-269, Ser-23, Arg-381, Asn-273 and Lys- were the most relevant amino acid residues for the binding to nicotine ligand. Overall, most of the amino acid residues of the transport proteins interacting with the nicotine ligands showed a similarity to the residues interacting with the native ligands of the carrier protein. In conjunction, amino acid interactions, the binding energies dissociation constants and Dock scores suggest that nicotine and its three metabolites competed with the native (endogenous) ligands (hormones) in binding to their transport proteins.

Conclusions

Jamal and Alharbi (2021) suggest that CSCs are capable of altering the normal functioning of the CNS and may lead to the onset of a tumor, other related diseases and neurodegenerative diseases. These results could be useful for the evaluation of the effect of environmental carcinogens on biological systems, including the CNS. Better detection of CNS changes due to CSCs may be elaborated. The research community can take advantage of current studies, including computational analysis, to design in vitro and in vivo biological experiments for future investigations and prospects.

Rehan et al (2022) conclude that nicotine and its three metabolites have the potential to interfere with the binding of native endogenous ligands SHBG (testosterone, estradiol), CBG (cortisol, progesterone) and TBG (thyroxine, triiodothyronine) and result in the disbalance of their transport and homeostasis in the blood circulation.

In conclusion, the molecular docking studies described contribute to a better understanding of the actions of tobacco cigarette chemicals in the human body, and are a tool that can guide future clinical trials and wet-way experiments.

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