PHARMACIA

Pharmacia 70(4): 847–852
DOI 10.3897/pharmacia.70.e111049

Research Article

Molecular docking analysis of ginger (*Zingiber officinale*) on dopamine compare to bupropion as smoking cessation

Rika Mayasari Alamsyah[1], Mieke Hemiawati Satari[2], Sondang Pintauli[3], Shelly Iskandar[2]

1 *Doctoral Study Program, Faculty of Medicine, Universitas Padjajaran, Bandung, West Java, Indonesia*
2 *Lecturer Faculty of Medicine, Universitas Padjajaran, Bandung, West Java, Indonesia*
3 *Lecturer Faculty of Dentistry, Universitas Sumatera Utara, Medan, North Sumatera, Indonesia*

Corresponding author: Rika Alamsyah (rika.mayasari@usu.ac.id)

Received 11 August 2023 ♦ **Accepted** 27 August 2023 ♦ **Published** 20 September 2023

Citation: Alamsyah RM, Satari MH, Pintauli S, Iskandar S (2023) Molecular docking analysis of ginger (*Zingiber officinale*) on dopamine compare to bupropion as smoking cessation. Pharmacia 70(4): 847–852. https://doi.org/10.3897/pharmacia.70.e111049

Abstract

Tobacco use continues to be the leading cause of preventable death worldwide. Smoking is highly addictive because nicotine can stimulate nicotinic acetylcholinergic (nACh) receptors which release dopamine. Smoking cessation can be done with pharmacotherapy such as bupropion or varenicline, but it is associated with side effects. Herbal medicine is a possible easy option for smoking cessation treatment. This study uses ginger as a natural ingredient. Gingerol and shogaol were found to be the active compounds of ginger which are responsible for their pharmacological action and have been identified as TRPV1 agonists. The predictive binding of several forms of gingerol and shogaol to TRPV1 was analyzed using docking analysis in an in silico model. The method used is molecular docking with parameter observations and systematic literature review studies with dopamine as a comparator compound. The results of molecular docking of all herbal compound samples showed that no bioactive compounds had a lower binding energy value than the native ligands. However, all bioactive compounds from ginger show a binding energy value around -8,4 until -7.2 kkal/mol. Based on the molecular docking results, it can be concluded that the ginger herbal compounds have a better interaction potential than the control, although not as good as the native ligands. 12-Shogaol, 8-Shogaol, 12-Gingerol, 10-Shogaol, and 10-Gingerol are thought to target dopamine receptor proteins potentially.

Keywords

Ginger, Dopamin, Molecular Docking, Smoking, *Zingiber officinale*

Introduction

The use of tobacco remains the primary contributor to avoidable mortality on a global scale (GBD 2020). Approximately 1.1 billion individuals engage in tobacco use, with an associated annual mortality rate of 6 million fatalities. Moreover, the inhalation of secondhand smoke is accountable for an extra 600,000 fatalities. If the present trajectory continues, it is projected that the global firearm-related mortality rate would surpass eight fatalities by the year 2030. Furthermore, the implementation of ill-advised measures may exacerbate this issue, resulting in a much higher number of deaths. The addictive nature of tobacco smoking may be attributed to the presence of nicotine (WHO 2022; FDA 2022). The nicotine included in tobacco elicits the activation of nicotinic acetylcholinergic (nACh) receptors, subsequently leading to the release of dopamine. Initially, nicotine

has a direct stimulatory effect on the ventral tegmental area (VTA) dopaminergic neurons, leading to the subsequent release of dopamine inside the nucleus accumbens (NAc). Additionally, the activation of nicotinic acetylcholine receptors (nAChR) situated on the dopaminergic terminals has been shown to enhance the reuptake of dopamine (Di Chiara 1988; Zhang et al. 2009; McGranahan et al. 2011; Faraone et al. 2014; Ashok et al. 2019). Within the human body, dopamine engages in interactions with a specific class of receptors known as dopamine receptors, which are categorized as G-protein coupled receptors (GPCRs) (Pratama 2016; Olasupo et al. 2021).

Smoking cessation can be done with pharmacotherapy such as nicotine replacement therapy, bupropion or varenicline. However, these drugs are associated with side effects such as nausea, dry mouth, and sedation (Jiloha 2014; Howes et al. 2020; Mendelson 2022). Herbal medicine is a possible option for smoking cessation treatment that is easily accessible, less expensive and has fewer side effects. This study uses ginger as a natural ingredient to be formulated with medicine. Zingiber officinale or also known as ginger, is widely used as a food or beverage ingredient and is also used as a herbal medicine. Ginger is known for its unique and significant therapeutic effects such as anticancer, antioxidant, anticoagulant, cardiovascular effects, antimicrobial, antiemetic, antipyretic, anti-inflammatory and chemoprotective potential. Gingerol and shogaol were found to be ginger's active compounds responsible for their pharmacological action. Of the eight ginger elements, shogaol and ginger enone-A showed the highest dock scores with strong and active site residue interactions so they could be the most appropriate choice (Nag and Banerjee 2021). Gingerol and shogaol are the most suitable compounds for ginger use and are structurally similar to capsaicin and have been identified as TRPV1 agonists. Predictive binding of several forms of gingerol and shogaol to TRPV1 was analyzed using docking analysis in an in silico model (Fajrin et al. 2020; Crichton et al. 2023). Each ginger homologous group contains unbranched alkyl chains with lengths and masses ranging between 300 and 500 Da. For example, gingerol homologs include 4-, 6-, 8-, 10-, and 12-gingerol and shogaol homologues include 4-, 6-, 8-, 10-, and 12-shogaol (Peng et al. 2023). The method used is molecular docking with observation parameters and systematic literature review studies with dopamine as a comparison compound (Pratama 2016; Syahputra 2020; Harahap 2021).

Materials and methods

Molecular docking

This study employs a computer approach known as a technical technique. The in silico approach is an appropriate methodology for evaluating the structure of the medicine that has been acquired. The molecular docking procedure involves the placement of DUD and DUD-E molecules into the ligand binding site of the target protein, which is carried out using PLANTS1.2. The docking process follows the standard parameters for optimal results. Consequently, the first docking score was calculated using the ChemPLP algorithm, which integrates PLP (Piecewise Linear Potential) with GOLD Chemscore. The binding center for docking is determined by using the coordinates of the ligand's center inside the target protein structure. A frequently used value for the bond site radius in docking is 10, which is considered rather big. The radius of the glucocorticoid receptor (GR; 9) was somewhat decreased in accordance with the dimensions of the ligand binding site. For the purpose of NIB rescoring, a total of ten docking solutions are generated for each chemical. The objective is to provide an alternative docking solution for the purpose of rescoring.The R-NiB method largely depends on the use of early docking success software to create several docking poses during the rescoring phase. It should be noted that no coordinate optimization or further sampling was conducted in this process. The use of the CROP score in this research has an inherent impact on the outcomes of the R-Ni analysis. Consensus scoring enhances the integration of the original ChemPLP docking score with the R-NiB score. All potential permutations in which CROP-based and ShaEP-based scores were allocated distinct weights were examined at intervals of 5%. The discussion focused on the consensus scoring configuration that yielded the greatest initial enrichment. The scores assigned to each anchoring conformer by the PLANTS and ShaEP algorithms were subjected to normalization, resulting in a transformation to a standardized scale ranging from 1 to 0. These normalized values were then merged to provide a consensus score. The calculation of the enrichment factor involves determining the valid positive rate when either 1% or 5% of the feed molecule has been detected (EFn%DEC). This measure is used to ensure the reliability of future comparisons with other samples. The equation for calculating the enrichment factor is shown below.BThe calculation of the enrichment factor involves the use of a positive rate, namely either 1% or 5% (EFn%DEC). Please refer to the equation provided below.

$$EF_{n\%DEC} = \frac{Ligs_{n\%DEC}}{Ligs_{all}} X100\%$$

Molecular dynamic simulation

The molecular dynamics (MD) simulation was conducted using the gmx_MMPBSA Version=v1.5.6 software, which is based on MMPBSA.py v.16.0 (Valdés-Tresanco et al. 2021). A total of 500 frames were evaluated at a temperature of 310.15 Kelvin. The interpretation of the molecular dynamics (MD) results was visually presented via the use of several graphical representations. Specifically, a graph depicting the root mean square deviation (RMSD) was employed to illustrate the structural deviations of the

protein backbone. Additionally, the root mean square fluctuation (RMSF) was plotted on the C-alpha atoms to demonstrate the local flexibility of the protein. Furthermore, the solvent-accessible surface area (SASA) of the protein was shown using the qtGrace program.

Results and discussion

Molecular docking

Dopamine receptors

Redocking was carried out beforehand between each protein and its native ligand from PDB, namely 6CM4 (8NU/Risperidone), 5WIU (AQD/Nemonapride), and 4M48 (21B/Nortriptyline). RMSD redocking results are better below 2 Å to validate that the methods and grid boxes used are appropriate or valid (Trott and Olson 2010). RMSD of native ligands from redocking results were 2.112 Å, 0.553 Å and 0.859 Å, respectively. We have tried the RMSD redocking for 6CM4 until optimal, but the best is still above 2 Å. The results of molecular docking of all samples of herbal compounds show that no bioactive compounds have lower energy binding values than native ligands. However, all bioactive compounds derived from ginger show a binding energy value of less than -7 ± 0.5 kcal/mol, as shown in Table 1. In addition, the Top 5 of the 13 derivative compounds were selected (based on the average binding affinity/BA ranking), which were continued for further analysis together with positive controls and native ligands, namely 12-Shogaol, 12-Gingerol, 10-Gingerol, 10-Shogaol and 8-Shogaol.

Fig. 1, shows the results of the 3D visualization of the respective complexes of the dopamine receptor protein with compound and control ligands. The binding position and each ligand are the same as the control because the grid box has been adjusted to the control redocking, which produces an RMSD below 2 Å (Trott and Olson 2010). Based on the molecular docking results, it can be concluded that the herbal compound ginger has a better interaction potential than the control, although not as good as the native ligand. 12-Shogaol, 12-Gingerol, 10-Gingerol, 10-Shogaol and 8-Shogaol are predicted to target dopamine receptor proteins potentially.

Results of the molecular mechanics poisson-boltzmann surface area (MMPBSA) *D2* Dopamine Receptors

The mmPBSA results from the molecular dynamics simulations between D2 Dopamine Receptors and 12- Shogaol and Bupoprion in Table 2 show that the free energy value of Bupropion is more negative. The free energy value between D2 Dopamine receptors and Bupropion is -13.68 kcal/mol. Based on free energy calculations with mmPBSA, Bupropion interacts better with D2 Dopamine Receptors. The results are consistent with the molecular dynamics simulation results.

Results of Molecular Dynamics (MD) simulation D2 dopamine receptor with some test compounds

Root Mean Square Deviation (RMSD)

RMSD measures the average deviation of a protein structure from its original conformation at a given time and is an essential indicator for evaluating the structural stability of a protein. Molecular Dynamics Simulation has been carried out for 50,000 ps to see the stability of the D2 Dopamine Receptor when it interacts with the test compounds, namely 12-Shogaol and Bupropion. MD results indicate the Native protein (D2 Dopamine Receptor) has RMSD at around 0.5 nm. Meanwhile, the D2 Dopamine Receptor experienced a slight increase in the RMSD value when interacting with the test compounds 12-Shagaol and Bupropion, namely 0.7 and 0.8 nm (Fig. 2). Even though there was an increase in the RMSD value, the increase was not too significant. The RMSD D2 Dopamine Receptor graph and the interactions with 12-Shogaol and Bupropion have the same RMSD value at 40 ns.

Root Mean Square Fluctuation (RMSF)

We also analyzed the flexibility of the D2 Dopamine Receptor and its interactions with the test compounds (Fig. 2). The root mean square fluctuation (RMSF) refers to the measure of the average displacement of individual amino acid residues within a protein in relation to the average conformation. There is a positive correlation between the magnitude of residual fluctuation and the level of flexibility shown by the residue when subjected to pressure treatment (Huang et al. 2021). The RMSF D2 Dopamine Receptor value when interacting with 12-Shogaol and Bupropion compounds is slightly smaller when compared to the RMSF D2 Dopamine Receptor without the ligand.

Solvent-Accessible Surface Area (SASA)

SASA analysis calculates the protein surface area that solvents can access. Increasing SASA values can show relative expansion (Krebs and De Mesquita 2016). In the D2 Dopamine Receptor without ligand compounds, the SASA value is 231.06 nm2. Meanwhile, the SASA D2 Dopamine Receptor value, when interacting with the test compounds 12-Shogaol and Bupropion, experienced a slight change, namely 232.92 nm2 and 230.30 nm2, respectively (Fig. 3).

Conclusion

In conclusion, 12-Shogaol and 12-Gingerol can be potential as an alternative of smoking cessation drug or can be used as a primary platform for developing new smoking cessation drugs. In research, 12 shogaol and 12 gingerol also affect dopamine. Molecular Dynamic (MD) simulations show that bupropion has a more stable bond than 12-shogaol, but ginger has a stronger bond. Therefore, we suggest conducting further research to see which

Table 1. Binding affinity (BA) between dopamine receptor target proteins and compound ligands and controls.

Ligan	6CM4		5WIU		4M48		Mean Ranking
	Ranking	Binding affinity (Kkal/mol)	Ranking	BA (Kkal/mol)	Ranking	BA (Kkal/mol)	
Dopamine	16	-6.6	16	-6.1	16	-6.1	16.00
Bupropion	5	-7.8	15	-7	9	-7.4	9.67
Nemonapride	-	-	1	-9.3	-	-	1.00
Risperidone	1	-11.6	-	-	-	-	1.00
Nortriptyline	-	-	-	-	1	-10.1	1.00
12-Shogaol	2	-8	4	-8.3	4	-7.6	3.33
12-Gingerol	4	-7.9	5	-8.3	10	-7.3	6.33
10-Shogaol	7	-7.7	2	-8.4	2	-8	3.67
10-Gingerol	3	-7.9	7	-8.2	12	-7.2	7.33
8-Shogaol	9	-7.6	3	-8.3	6	-7.5	6.00

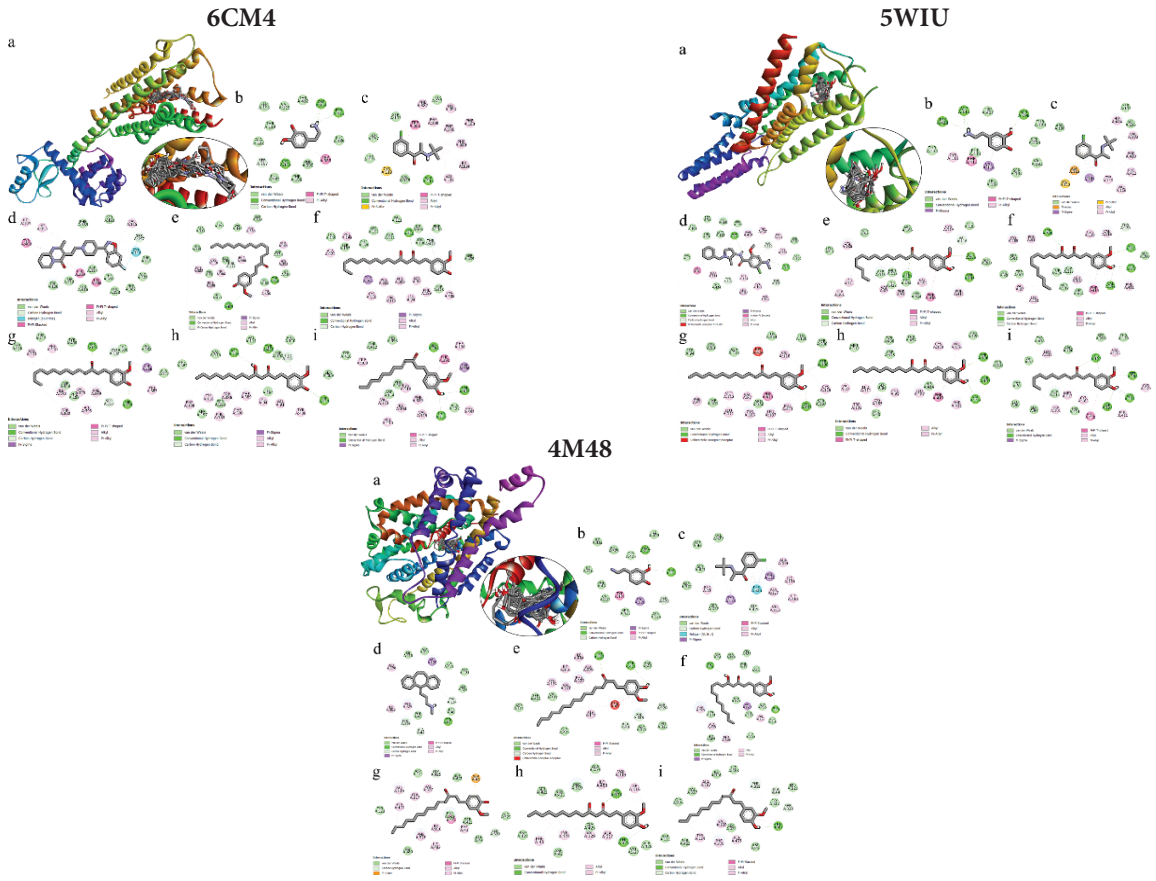

Figure 1. Docking result visualization, a) Ligand bond position, b) Dopamine, c) Bupropion, d) Nemonapride/NL, e) 12-Shogaol, f) 12-Gingerol, g) 10-Shogaol, h) 10-Gingerol, and i) 8-Shogaol.

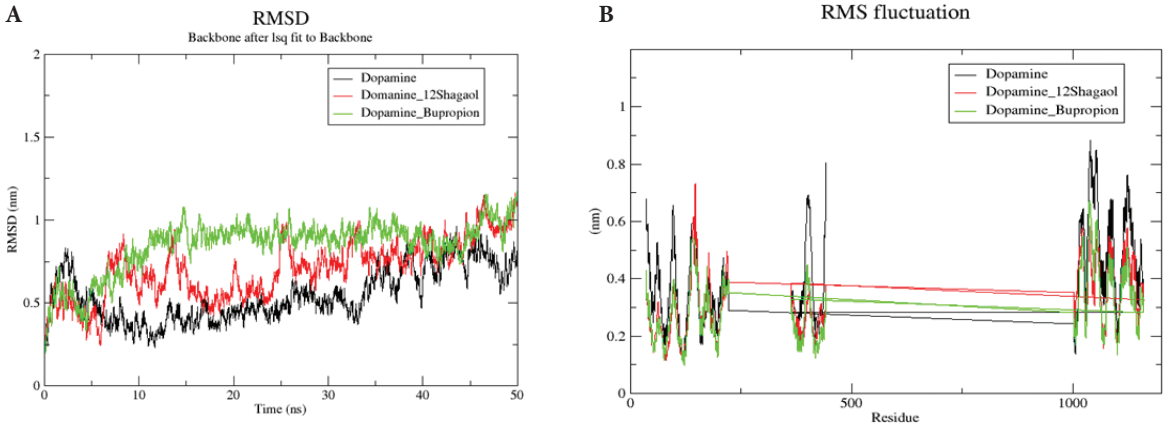

Figure 2. Root Mean Square Deviation (**A**), Root Mean Square Fluctuation (**B**) D2 Dopamine Receptor when interacting with the test compounds 12-Shogaol and Bupropion.

Table 2. Results of mmPBSA D2 Dopamine Receptor calculations with 12-Shogaol and Bupoprion.

Energy Component	Average (kcal/mol)	
	6 cm4_12Shogaol	Bupropion
ΔBOND	0	0
ΔANGLE	0	0
ΔDIHED	0	0
ΔVDWAALS	-48.64	-35.85
ΔEEL	-9.16	-17.96
Δ1-4 VDW	0	0
Δ1-4 EEL	0	0
ΔEPB	35.5	22.6
ΔENPOLAR	-37.23	-26.79
ΔEDISPER	61	44.31
ΔGGAS	-57.79	-53.81
ΔGSOLV	59.26	40.13
ΔTOTAL	**1.47**	**-13.68**

Molecular Dynamic content of other ginger components is more stable.

Conflict of interest

The authors declare no conflict of interest in conducting this study.

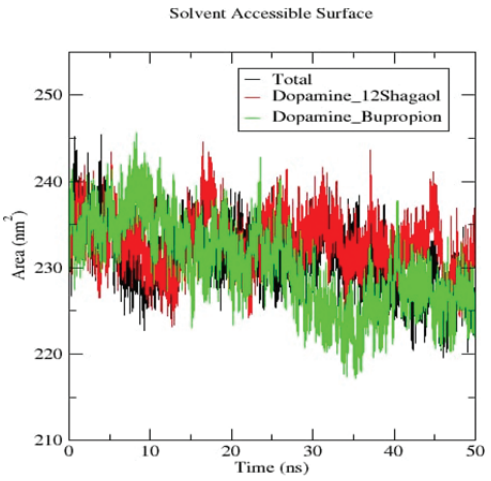

Figure 3. Solvent-Accessible Surface Area (SASA) D2 Dopamine Receptor when interacting with test compounds Shogaol and Bupropion.

Acknowledgments

The authors are grateful to Indonesian Endowment Fund for Education/Lembaga Pengelola Dana Pendidikan (LPDP) from the Ministry of Finance Republic Indonesia for funding this research.

References

Ashok AH, Mizuno Y, Howes OD (2019) Tobacco smoking and dopaminergic function in humans: A meta-analysis of molecular imaging studies. Psychopharmacology 236: 1119–1129. https://doi.org/10.1007/s00213-019-05196-1

Crichton M, Marshall S, Marx W, Isenring E, Lohning A (2023) Therapeutic health effects of ginger (*Zingiber officinale*): Updated narrative review exploring the mechanisms of action. Nutrition Reviews 81(9): nuac115. https://doi.org/10.1093/nutrit/nuac115

Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proceedings of the National Academy of Sciences of the United States of America 85: 5274–5278. https://doi.org/10.1073/pnas.85.14.5274

Fajrin FA, Nugroho AE, Nurrochmad A, Susilowati R (2020) Ginger extract and its compound, 6-shogaol, attenuates painful diabetic neuropathy in mice via reducing TRPV1 and NMDAR2B expressions in the spinal cord. Journal of Ethnopharmacology 249: 112396. https://doi.org/10.1016/j.jep.2019.112396

Faraone SV, Spencer TJ, Madras BK, Zhang-James Y, Biederman J (2014) Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter functioning: A meta-analysis. Molecular Psychiatry 19: 880–889. https://doi.org/10.1038/mp.2013.126

FDA [Food and Drug AS] (2022) Food and Drug. https://www.fda.gov/tobacco-products/health-effects-tobacco-use/nicotine-why-tobacco-products-are-addictive [06/29/2022]

GBD (2020) Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Global Health Metrics 396(10258): P1223–1249. [October 17, 2020, Open AccessPublished:October 17, 2020] https://doi.org/10.1016/S0140-6736(20)30752-2

Harahap U, Purnomo H, Satria D (2021) In-silico analysis Of 1, 3-BIS (p-Hydroxyphenyl) urea as anti-inflammatory through inhibition of COX-1 and TNF-α. Rasayan Chemical Journal 14(3): 1489–1492. https://doi.org/10.31788/RJC.2021.1436163

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N (2020) Antidepressants for smoking cessation. Cochrane Database of Systematic Reviews 2020(4): 1–252. https://doi.org/10.1002/14651858.CD000031.pub5

Huang Y, Zhang X, Suo H (2021) Interaction between β-lactoglobulin and EGCG under high-pressure by molecular dynamics simulation. PLoS ONE 16(12): e0255866. https://doi.org/10.1371/journal.pone.0255866

Jiloha RC (2014) Pharmacotherapy of smoking cessation. Indian Journal of Psychiatry 56(1): 87. https://doi.org/10.4103/0019-5545.124726

Krebs BB, De Mesquita JF (2016) Amyotrophic lateral sclerosis type 20-In Silico analysis and molecular dynamics simulation of hnRNPA1. PLoS ONE 11(7): e0158939. https://doi.org/10.1371/journal.pone.0158939

McGranahan TM, Patzlaff NE, Grady SR, Heinemann SF, Booker TK (2011) alpha4beta2 nicotinic acetylcholine receptors on dopaminergic neurons mediate nicotine reward and anxiety relief. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 31: 10891–10902. https://doi.org/10.1523/JNEUROSCI.0937-11.2011

Mendelsohn C (2022) Optimal use of smoking cessation pharmacotherapy. Australian Prescriber 45(1): 10. https://doi.org/10.18773/austprescr.2022.001

Nag A, Banerjee R (2021) Network pharmacological evaluation for identifying novel drug-like molecules from ginger (*Zingiber officinale* Rosc.) against multiple disease targets, a computational biotechnology

approach. Network Modeling and Analysis in Health Informatics and Bioinformatics 10(1): 55. https://doi.org/10.1007/s13721-021-00330-6

Olasupo SB, Uzairu A, Shallangwa GA, Uba S (2021) Unveiling novel inhibitors of dopamine transporter via *in silico* drug design, molecular docking, and bioavailability predictions as potential antischizophrenic agents. Future Journal of Pharmaceutical Sciences 7: 1–10. https://doi.org/10.1186/s43094-021-00198-3

Peng Y, Zeng Y, Zheng T, Xie X, Wu J, Fu L, et al. (2023) Effects of Tiaopi Xiezhuo decoction on constipation and gut dysbiosis in patients with peritoneal dialysis. Pharmaceutical Biology 61(1): 531–540.

Pratama MRF (2016 [July]) Studi *In Silico* Afinitas Katinon dan Metabolitnya terhadap Reseptor Dopamin D 1 dan D 2 (In Silico study affinities of cathinone and metabolites towards dopamine D 1 and D 2 Receptors). In proceedings of the National seminar treatment of drug abuse.

Syahputra RA, Harahap U, Dalimunthe A, Nasution P, Haro G, Widodo DH, Satria D (2020) *In-silico* toxicity prediction of bioactive compounds of *Vernonia amygdalina* Delile. And digoxin. Rasayan Journal of Chemistry 13(02): 1220–1224. https://doi.org/10.31788/RJC.2020.1325638

Trott O, Olson AJ (2010) AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry 31(2): 455–461. https://doi.org/10.1002/jcc.21334

Valdés-Tresanco MS, Valdés-Tresanco ME, Valiente PA, Moreno E (2021) gmx_MMPBSA: A new tool to perform end-state free energy calculations with GROMACS. Journal of Chemical Theory and Computation 17(10): 6281–6291. https://doi.org/10.1021/acs.jctc.1c00645

WHO [World Health Organization] (2022) Tobacco. https://www.who.int/news-room/fact-sheets/detail/tobacco [Acces January 2023]

Zhang L, Doyon WM, Clark JJ, Phillips PE, Dani JA (2009) Controls of tonic and phasic dopamine transmission in the dorsal and ventral striatum. Molecular Pharmacology 76: 396–404. https://doi.org/10.1124/mol.109.056317