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In Silico Repositioning Strategies of Theobromine and Caffeine for Psychiatric and Neurological Disorders

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Abstract: Psychiatric and neurological disorders (PNDs) have correlated diseases and represent a burden on public health. Several drugs are reported to repurpose PNDs therapy. Drugs with antidepressants, anxiolytics, stimulants, antipsychotics, and mood stabilizers are classified for PNDs treatments. Due to the high cost of PNDs therapy and developing novel drugs, this study focused on identifying the theobromine and caffeine for PNDs treatments. Theobromine and caffeine as main compounds of brewed coffee and chocolate were downloaded their 3D structure from the PubChem compound database. Several targetted PNDs proteins involved Adenosine 1 receptor, adenosine 2 receptor, serotonin receptor, GABA receptor, and Acetylcholinesterase were downloaded from protein data bank and predicted their binding cavities by Molegro virtual docker 5. Ligands and proteins were docked and visualized to investigate the inhibition sites. Caffeine and theobromine showed interaction with adenosine 1 receptor and adenosine 2 receptor in adenosine sites, since there were depicting similar structure. Caffeine and theobromine also performed same active sites with serotonin receptor 4 and GABA receptor, indicating a potential activity as serotonin and GABA molecules. Acetylcholinesterase was inhibited by caffeine and theobromine at the catalytic residues. In summary, caffeine and theobromine performed a potential neuroprotection effect for PNDs therapeutics.

Keywords: Brewed coffee, dark chocolate, neurological disorders, psychiatric disorders.

Abbreviations: Gamma aminobutyric acid (GABA); Psychiatric and neurological disorders (PNDs); compound identity (CID); Protein Data Bank (PDB).

Introduction

Psychiatric and Neurological Disorders (PNDs) are essential diseases that concern in the public community. Psychiatric disorders, including anxiety and depression, need more attention and special treatment. Depression and anxiety are common mental illnesses and affect more than 300 million communities worldwide (Auti & Kulkarni, 2019; de Pinho et al., 2021). After the COVID-19 pandemic from the last year of 2019, the COVID-19 patients reported having depression symptoms after 3-6 months of healthcare isolation (de Pinho et al., 2021; Santomauro et al., 2021). Due to the clinical characteristic, depression and anxiety disorder caused psychosocial functions, loss of activity, and decreased quality of life. Depression also caused several neurological disorders, including stroke, parkinson's disease, Huntington's disease, Head injuries, Multiple sclerosis, Cushing's disease, and hypothyroidism. At the same time, anxiety disorders promoted hyperthyroidism, hypoglycemia, pheochromocytoma, Cushing's disease, Porphyra, and cardiovascular disease. According to the clinical affection of psychiatric illness, psychiatric and neurodegenerative disorders were correlated

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to each other. Neurodegenerative disorders were characterized by thinking dysfunctions, loss of ability of general activity engagement, behavior alteration, and loss of memory (de Pinho et al., 2021; Johnston, 2013; Mondal et al., 2018; Remya et al., 2021; Santomauro et al., 2021; Socała et al., 2021). Several therapies have been developed to prevent neurodegenerative disease. Some targeted proteins involved in the serotonin, dopamine, GABA receptors, and other protein-related neural pathways have been focused on drug development. Coffee, tea, cacao are export commodities commonly used as anticonvulsant (Camandola et al., 2019; Kolahdouzan & Hamadeh, 2017).

Coffee contains several bioactive compounds, including alkaloid, aromatic, flavonoids, and phenolic compounds. Metabolite profiles of coffee were affected by environmental factors and the coffee process after harvesting (Putri et al., 2019). The secondary metabolite of coffee has been reported as an antioxidant, anti-aging, anti-inflammatory, and anti-obesity (Meng et al, 2013; Bare et al., 2019; Bare et al., 2019; Camandola et al., 2019). Cacao uses for producing chocolates. Dark chocolate also contains two-main bioactive compounds, involved caffeine and theobromine (Camandola et al., 2019; Motamayor et al., 2013). Caffeine and theobromine were reported to have a potential activity for neurodegenerative prevention. Caffeine improved clinical outcomes in the cerebral spinal post-traumatic injury. Theobromine in chocolate has the ability a relaxant agent, stimulant, and analgesic, according to *in vitro* and *in vivo* studies (Bare et al., 2020; Cheung et al., 2012; de Pinho et al., 2021; Kolahdouzan & Hamadeh, 2017; Liu et al., 2020; Socała et al., 2021; Wasim et al., 2020). However, the action mechanism of caffeine and theobromine for psychiatric and neurological disorders showed limited information. Therefore, this study presented the potential therapeutic agents for psychiatric and neurological disorders through *in silico* approach.

Materials and Methods

Ligands structure retrieval

Caffeine and theobromine were identified in coffee and dark chocolate with high concentrations. Both of caffeine and theobromine structures were collected from PubChem compound database, integrated with National Center for Biotechnology Information (NCBI). The caffeine and theobromine compound ID were CID 2519 (https://pubchem.ncbi.nlm.nih.gov/compound/2519) and CID 5429 (https://pubchem.ncbi.nlm.nih.gov/compound/5429).

Pharmacokinetics prediction

The pKCSM online web server predicted the pharmacokinetics properties of caffeine and theobromine. Pharmacokinetics characteristics included absorption, distribution, metabolism, excretion, and toxicity (Pires et al., 2015).

Proteins structures acquiring

Targeted protein of this study was Serotonin receptor 4 (PDB ID 5v54), GABA receptor (UNIPROT ID AF-P80404), Adenosine 1 receptor (PDB ID 5N2S), Adenosine 2 receptor (PDB ID 3EML), and Acetylcholineesterase (PDB ID 4EY6) (Cheng et al., 2017; Jaakola et al., 2008; Liu et al., 2020; Rath et al., 2021). All targeted proteins were downloaded their 3D structure from Protein Data Bank and UNIPROT databases. Binding cavities of targeted protein were predicted by Molegro Virtual Docker ver.5 with parameter van der Waals surface maximum five (Bitencourt-Ferreira & de Azevedo, 2019). The specific grid of proteins also was identified, involved Serotonin receptor 4 performed specific grid X 1.59; Y -0,65; Z 28.39; radius 13. The X -4.69; Y -6.50; dan Z -12.47, radius 15 for GABA receptor, X 103.413; Y 131.85; Z 50.264 radius 12 for Adenosine 1 receptor, X -9.06; Y -9.76; Z 54.82 radius 10 for Adenosine 2 receptor, and X -4.5; Y -48.74; Z -16.0 radius 10 for Acetylcholineesterase.

Docking study

Docking study was carried out by Molegro virtual docker version 5. Molegro virtual Dockes version

five is a robust software for docking with performing binding site prediction, specific grid docking, performing repetition for qualifying the docking results (Bitencourt-Ferreira & de Azevedo, 2019). Ligands and protein were redocked in specific grid of proteins with several parameters, including MolDock Grid resolution 0.30 A, RMSD<2, binding pose <5, and 10 repetitions.

Data analysis

Ligand – protein interaction models were superimposed and converted to the pdb format by PyMol. Ligands – proteins complexes were analyzed by Discovery Studio version 21.1.1. The binding energy was described as an average of the summary among MolDock score, Moldock Grid Score and Rerank score.

Results and Discussion

Pharmacokinetics properties of caffeine and theobromine

The ADMET properties of caffeine and theobromine were presented in Table 1. Caffeine and theobromine showed similar structure with purine – based structure. Almost the ADMET properties performed similar each other, including the water solubility, intestinal absorption, metabolism profiles, renal OCT substrate, hERG 1/II inhibitor, hepatotoxicity, Skin Sensitisation, *T. pyriformis* toxicity, and Minnow toxicity.

Caffeine and theobromine interacted with adenosine 1 receptor and adenosine 2 receptor

Caffeine and theobromine promoted interaction with adenosine 1 receptor and adenosine 2 receptor in the same active sites (Figure 1). The similar active sites both of caffeine and theobromine in adenosine 1 receptor were ILE1174, PHE1276, TYR1117, ASN1175, and ILE1379. Interestingly, some of the residues bound to caffeine and theobromine in the different atoms. ILE137 showed van der Waals in caffeine, while ILE1379 bound to aromatic ring of theobromine with hydrophobic interaction. PHE1276 interacted with the N atom of caffeine, while theobromine showed interaction in the N and H atom. Caffeine and theobromine bound to adenosine 2 receptor in same binding sites, involved ALA59, VAL84, ILE274, PHE168, ILE66, PHE62, and ILE80. The interaction type among caffeine and theobromine in adenosine 1/2 receptor was van der Waals, hydrogen bonds, and hydrophobic interactions. Both caffeine and theobromine revealed interaction in the membrane surface site of adenosine 2 receptor and the adenosine site of adenosine 1 receptor.

Table 1. Pharmacokinetics properties of caffeine and theobromine

Pharmakokinetics parameters		Caffeine	Theobromine	Pharmakokinetics parameters		Caffeine	Theobromine
Absorption	Water Solubility (log mol/L)	-2.023	-2.175	Distribution	VDss (log L/kg)	-0.595	-0.154
	Caco2 permeability (log Papp in 10-6 cm/s)	1.115	0.517		Fraction unbound (Fu)	0.651	0.729
	Intestinal absorption (% absorbed)	99.272	98.3		BBB Permeability (log BB)	-0.268	-0.379
	Skin permeability (log Kp)	-3.376	-2.758		CNS permeability (log PS)	-2.977	-3.081
	P-glycoprotein substrate	No	Yes	Toxicity	AMES Toxicity	No	Yes
	P-glycoprotein I/II inhibitor	No	No		Max tolerated dose (log mg/kg/day)	0.001	0.042
Metabolis	CYP3A4	No	No		hERG I inhibitor	No	No

Pharmakokinetics parameters		Caffeine	Theobromine	Pharmakokinetics parameters		Caffeine	Theobromine
m	substrate						
	CYP1A2 inhibitor	No	No		hERG II inhibitor	No	No
	CYP2C19 inhibitor	No	No		Oral Rat Acut Toxicity (LD50) (mol/kg)	2.802	2.385
	CYP2C9 inhibitor	No	No		Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	0.701	0.972
	CYP2D6 inhibitor	No	No		Hepatotoxicity	Yes	Yes
	CYP3A4 inhibitor	No	No		Skin Sensitisation	No	No
Excretion	Total clearance (log ml/min/kg)	0.193	0.336		*T. pyriformis toxicity (log ug/L)*	0.285	0.285
	Renal OCT2 substrate	No	No		Minnow toxicity (log mM)	2.34	2.844

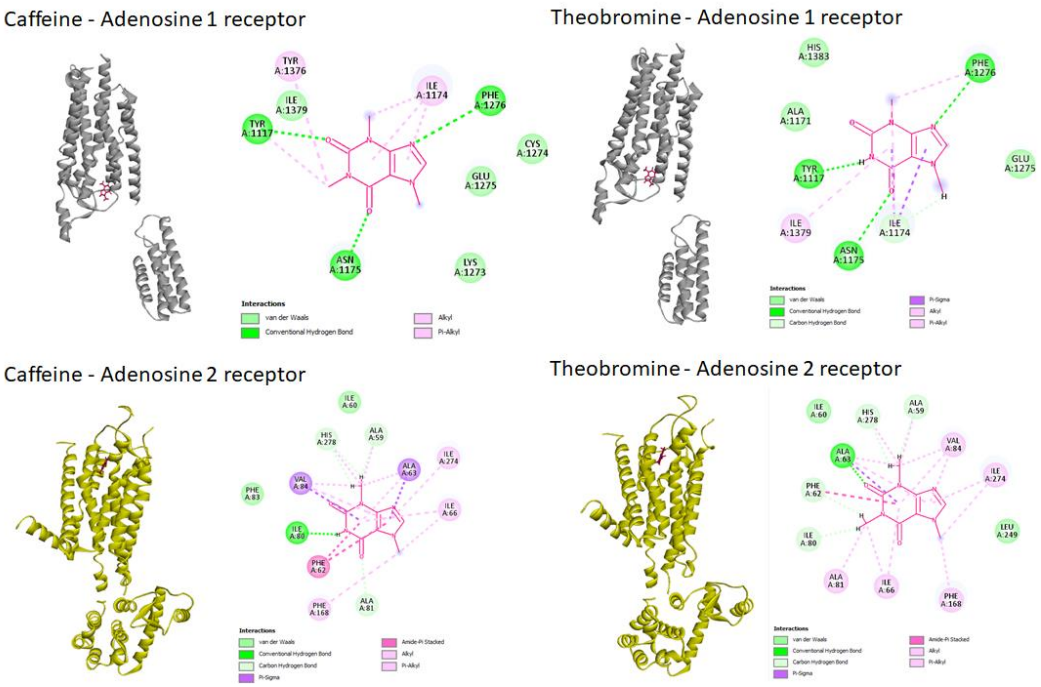

Figure 1. Binding pose of theobromine and caffeine toward adenosine 1/2 receptors.

Caffeine and theobromine interacted with GABA receptor and serotonin receptor 4

Caffein demonstrated several active sites both on GABA and serotonin receptors with higher van der Waals residues than theobromine (Figure 2). In GABA receptor, caffeine and theobromine have similar binding sites, including ASN168, VAL328, PHE217, SER165, and HIS218. Hydrogen bond interaction was exposed at GLN329 and ASN168 of caffeine – GABA receptor complex, also performed in LYS357, SER165, HIS218, and ASN168 of theobromine – GABA receptor complex. interestingly, VAL328 of GABE receptor bound to caffeine and theobromine with hydrophobic interaction.

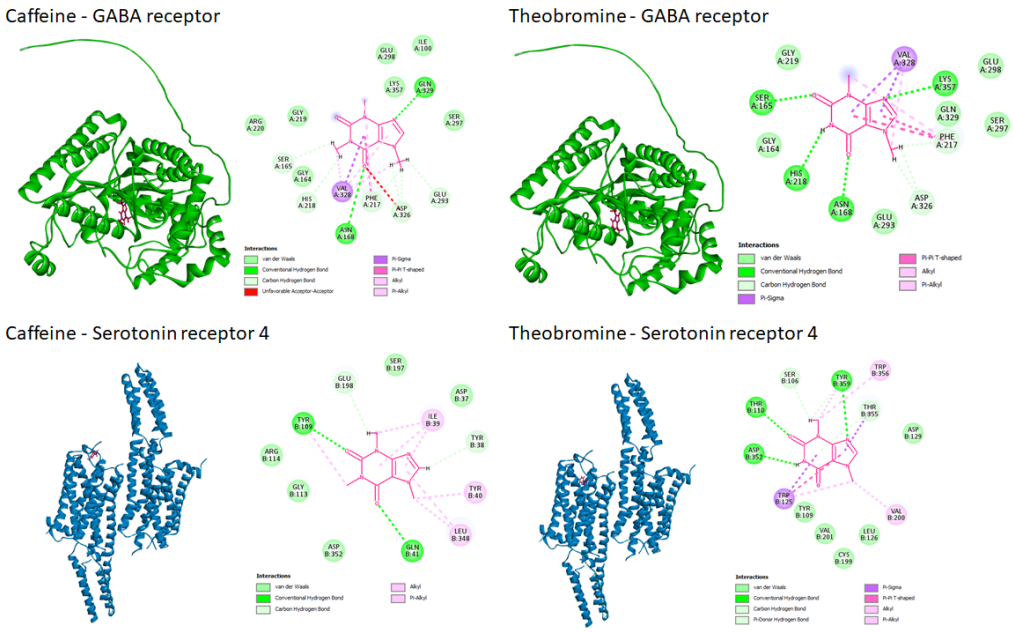

Figure 2. The 3D and 2D models of the interaction among theobromine and caffeine with serotonin and GABA receptors.

The 3D models of caffeine and theobromine with serotonin receptor illustrated that bound in different binding sites (Figure 2). Active sites residues of caffeine – serotonin receptor 4 were TYR109 and GLN41 with hydrogen bonds, ILE39, TYR40, LEU348, and TYR109 with hydrophobic interactions. While, theobromine depicted five hydrogen bonds, including THR110, TYR359, THR355, SER106, and ASP352. TRP125, TRP356, and VAL200 showed hydrophobic interaction with serotonin receptor 4.

Caffeine and theobromine interacted with Acetylcholinesterase

Caffeine inhibited Acetylcholinesterase in several residues, involved HIS405, LEU536, TRP532, CYS409, PRO410, GLN413, and PRO537 (Figure 3). Theobromine, a chocolate bioactive compound, promoted binding site residues, HIS405, TRP532, PRO410, and ASN233. HIS405, PRO410, and TRP532 revealed the same active sites, both caffeine and theobromine. HIS405 of Acetylcholinesterase bound to O and C atom of caffeine with hydrogen and π – alkyl, while HIS405 only interacted with C atom of theobromine with a hydrogen bond. PRO410 residue also bound to pentacyclic ring and C atom with π – alkyl interaction, and in theobromine, PRO410 bound to benzene ring with π – alkyl interaction. TRP532 interacted with C and H atoms of caffeine and theobromine.

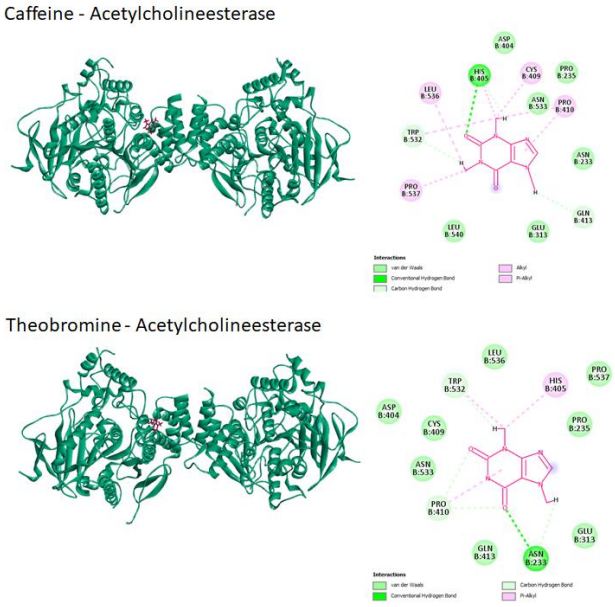

Figure 3. The binding pose of theobromine and caffeine with Acetylcholinesterase

The binding energy among of caffeine and theobromine was described at Figure 4. Theobromine showed lower binding energy than caffeine in all of ligands – protein complexes. Lower binding energy in ligands – protein complexes might be affected by some factors including type of interactions, compound

structures, protein structures and ligand – protein complex structure. Lower binding energy suggested tight interaction between ligand and protein target.

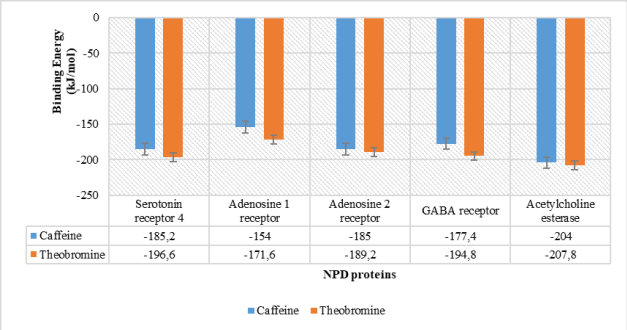

Figure 4. The binding energy of among of theobromine and caffeine with serotonin receptor 4, adenosine 1/2 receptors, GABA receptor, and Acetylcholinesterase proteins

Discussion

Adenosine normally bound to their receptor, which were adenosine 1 receptor and adenosine 2 receptor. In presynaptic terminal, the interaction between adenosine and adenosine 1 receptor, inhibited calcium pump to open and transport calcium for further neurological mechanism. Besides that, the adenosine also prevented transferring glutamate and ATP from presynaptic terminal. Unreleased ATP from presynaptic cells caused low energy for cells metabolism. Adenosine 2 receptor also found in denditric region, blood vessels and astrocyte. Binding adenosine to adenosine 2 receptor in denditric region promoted kalium, in blood vessel the adenosine – adenosine 2 receptor caused vasodilatation. Furthermore, adenosine also transported to astrocyte and converted to AMP to produce ATP. The adenosin 1/2 receptor inhibition with caffeine and theobromine revealed adenosine substitution (Cheng et al., 2017; Jaakola et al., 2008; Yuan et al., 2015).

The current study found that caffeine and theobromine interacted with serotonin receptor 4 in sertotonin active sites, also with GABA receptor in GABA binding sites. A previous study reported that (2S, 4R)-(−)-trans-4-phenyl-N,N-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine was competitive agonist for serotonin receptor 4 (Sakhuja *et al.*,, 2015). Lohning et al., (2016) reported that the allosteric site of serotonin receptor were N56, D138, Y140, N184, and R219. Gingerol and shogaol, ginger bioactive compound were reported interacting with serotonin receptor 4 in serotonin binding sites. Interestingly, in the present study, caffeine and theobromine also showed interaction in siliar binding sites of gingerol and shogaol. Sari and Krisnamurti, (2021) reported that 1-dehydrogingerdione, a volatile ginger compound inhibited GABA aminotransferase for neural disease therapy. Serotonin and GABA were released from serotonin neuron and GABAergic neurons. Released serotonin enters to presynaptic cell through serotonin receptor, the interaction of serotonin with its receptor inhibited Potasium pump activity. While, GABA molecules from GABAergic neurons naturally bound to the GABA receptor and induced Cl- ion entering the cell and inhibited the secretion of K+ ion, also prevented the acquiring of Ca2+ ion. Johnston, (2013) reviewed several drugs promoted anticonvulsant agents, including flumazenil, bicuculline, picrotoxin/picrotoxinin, gabazine, suramin, sepranolone, salicylidene salicylhydrazide (SCS), bilobalide, RU5135, and 4-(3-biphenyl-5-(4-piperidyl)-3-isoxazole (3-biphenyl-4-PIOL). Besides that, Johnston, (2013) also reported bioactive compounds of *Ginkgo biloba* inhibited GABA synthesis by reducing released L-Glutamate.

In the post synaptic cell, Acetylcholinesterase expressed highly and hydrolyzed acetylcholine to acetate and choline. Then, choline was transformed to synaptic cell. The present study, caffeine and theobromine inhibited Acetylcholinesterase in catalytic sites of Acetylcholinesterase and might be prevented neurodegenerative disorders (Cheung et al., 2012). Several studies reported that Acetylcholinesterase agonists to protect neurodegenerative. Cardamom oil, demethylcurcumin, circumdatin D, anchovy peptides, tacrine, and chlorogenic acid ameliorated the cholinergic system through Acetylcholinesterase inhibition and promoted neuroprotection (Kwon et al., 2010; Mondal et al., 2018; Auti & Kulkarni, 2019; Agarwal et al., 2020;

Liu et al., 2020; Zhang et al., 2020; Remya et al., 2021; Socała et al., 2021).

Conclusions

Caffeine and theobromine inhibited some protein-related neural disorders, including adenosine 1/2 receptors, serotonin receptor 4, GABA receptor, and Acetylcholinesterase. Caffeine and theobromine revealed as potential substitutive compounds for serotonin, adenosine, and GABA. Caffeine and theobromine also inhibited Acetylcholinesterase in catalytic sites, switching off Acetylcholinesterase activity. *In vitro*, *in vivo*, and clinical studies are required for further investigations.

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Conflict of Interest: The authors declare that there are no conflicts of interest concerning the publication of this article.

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