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NETWORK PHARMACOLOGY ANALYSIS OF *Cananga odorata* AS A TREATMENT FOR ANXIETY DISORDERS

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Abstract

Anxiety disorder is a psychological disorder associated with the existence of mental disorders and experiencing constant anxiety. In *C. odorata*, part of the flower has the potential as a sedative for the nervous system and for dealing with anxiety. The study aims to analyze the potential compound content in *Cananga odorata* for treating anxiety disorders with *In silico-based* pharmacological network analysis. CO compound data from the KNApSAck database, Absorption, Distribution, Metabolism, and Excretion (ADME) screening using SwissADME, predicted target proteins using Swiss Target Prediction, GeneCards, Venny, String DB pharmacological network analysis, Visualization with Cytoscape version 3.10.0, and Way2drug. The results of the pharmacological tissue analysis of the compound content in *C. odorata* obtained 45 compounds, and 18 known active components meet the criteria of Absorption, Distribution, Metabolism, and Excretion (ADME) that correspond to the drug compounder (Drug Likeness/DL). Based on the pathway that correlates with anxiety disorder therapy are the neurotransmitter systems like serotonin receptors and dopamine receptors. The known therapeutic target proteins are HTR1A, HTR2A, SLC6A4, NR3C1, MAOA, DRD4, HSP90AA1, JUN, ten active compounds associated with *C. odorata* namely Anonaine, (+)-Reticuline, linalool, (-)-Coreximine, Micheline A, (-)-Ushinsunine beta-N-oxide, 4-Terpineol, alpha-Terpeneol, Sampangine, Anaxagoreine. Based on the results of research, *C. odorata* is potentially a treatment for anxiety disorder.

Keywords: *Anxiety Disorder, Cananga odorata, In Silico, Network, Pharmacology*

Background

Indonesia is one of the countries with a source of raw materials from herbal medicinal plants (Jannah, 2018); Yassir *and* Asnah, 2019). Herbal medicines are considered safer and have relatively fewer side effects than modern medicine (Azizah *and* Kurniati, 2020). The Cananga plant with the Latin name *Cananga odorata* (CO), which belongs to the family Annonaceae, is a perennial plant or tree whose flower parts can be used to produce essential oils (Rahma *et al*., 2020; Sundara *et al*., 2022).

CO plants have many advantages, one of which is on the flower side. People use the flower as a ritual material for cultivation and are extracted to take its oil. The essential oil is a sedative to the nervous system, helps to deal with anxiety, tension, and fear, and is an antidepressant for humans. Cultivation of cannabis plants is necessary to support existence in nature (Wulandari *et al.*, 2019). The essential oil of CO contains a compound linalool of the monoterpenes group, one type of aromatherapy that has a balancing effect, anti-anxiety, relaxation, relieves tension stress, fast pulse, rapid breathing, and beneficial for high blood pressure. Cananga aromatherapy (CO) is one kind of non-pharmacological approach to lowering anxiety levels that is easily accessible, safe, and relatively inexpensive.(Fatmasari *et al*., 2023).

According to data from Basic Health Research in Indonesia in 2018, the prevalence of mental disorders (in 2013) has increased from 1.7% to 7%. The cause of a person having a mental illness is stress and anxiety disorder (Sundara *et al.*, 2022). Anxiety disorder is a psychological disorder associated with a mental disorder, causing suffering to experience tremendous and excessive anxiety that is accompanied by specific signs and symptoms (Suhendi *and* Supriadi, 2020). Experiencing constant anxiety can lead to depression and suicide attempts (Ulfianasari *et al*., 2022). Anxiety can be meant to have a feeling of fear of things to come as well as less pleasant because of too many things to think about and also less understood physiologically (Sundara *et al*., 2022).

Anxiety disorder can be experienced from adolescents to the elderly. The physical characteristics of anxiety are sweating hands, heartbeat, trembling, appetite loss, difficulty sleeping, and so on. Cognitive symptoms are anxiety about something, a feeling, for example, a fear of something that will happen in the future, a belief in something scary, a fear of the inability to cope with a problem, think about something, and continue over a long time (Oktapiani *and* Putri, 2018; Sundara *et al*., 2022). Factors influencing anxiety disorder include family history, stressful events, excessive worry, overprotective in unmarried or unemployed women, and poor physical or mental health. The biological factors that trigger anxiety are the neurotransmitters that are present in the human brain. The regulation of the serotonergic system in general anxiety disorder is abnormal. The role of neurotransmitters as triggers of anxiety disorders that are inside the human brain. Another neurotransmitter system that contributes to triggering anxiety is norepinephrine, cholecystokinin glutamate. (Nida, 2014).

In the process of healing anxiety disorder, the disease can be done in several ways, namely with the administration of drugs and specific psychotherapy. For medication is selected depending on the correct diagnosis, the patient can use treatment options such as antidepressants, anti-anxiety, and β-blockers to control some physical symptoms. With proper treatment, people with anxiety disorders can live a more normal life. For anti-anxiety drugs like Benzodiazepines and Buspirone can help alleviate symptoms. The pharmacological treatment of general anxiety disorders is performed with the administration of antidepressants (Selective Serotonin Reuptake Inhibitors (SSRIs), and anti-anxiety (benzodiazepines (BZDs) and non-BZDS (buspirone) (Report, 2023). Patients with anxiety disorder are unable to receive treatment directly. Still, the patient is first seen by factors such as patient motivation, state of the patient, significant cognitive impairment, patient response to previous treatment, as well as the presence of comorbidities and other psychiatric

disorders that may affect, then informed that the patient receives the treatment process in psychological or pharmacological recovery (Vildayanti *et al.*, 2018).

The method used in this study uses silico, which has the advantage of being cheaper and faster to produce results (Makatita *et al.*, 2020). In the branch of bioinformatics, in silico screening involves adding relevant molecular structures to the target protein database. Furthermore, the evaluation results are used to identify structures that have binding and potential physiological activity. Compounds can be evaluated in vitro and in vivo to determine their probability as drug candidates (Shofi, 2022). In previous studies, using Cananga Essential Oil could reduce 5-HT content. The test material was in mice and used quantitative and qualitative analysis using the GC/MS method. However, little information explaining the molecular mechanisms found in CO in the treatment of anxiety disorders was found with the In silico Computer Aided Drug Discovery method. (CADD). This study aims to analyze the potential compound content in CO for treating anxiety disorders with In Silico-based pharmacological network analysis. In the cannabis plant, there are several compounds used: Anonaine, (+)-Reticuline, linalool, (-)-Coreximine, Micheline A, (-)-Ushinsunine beta-N-oxide, 4-Terpineol, alpha-Terpaneol, Sampangine, Anaxagoreine. The results of this study show an overview of the compounds and proteins contained in the CO plant used for the healing process of anxiety disorder disease using the in silico method.

Material and Methods

Methods of Implementation

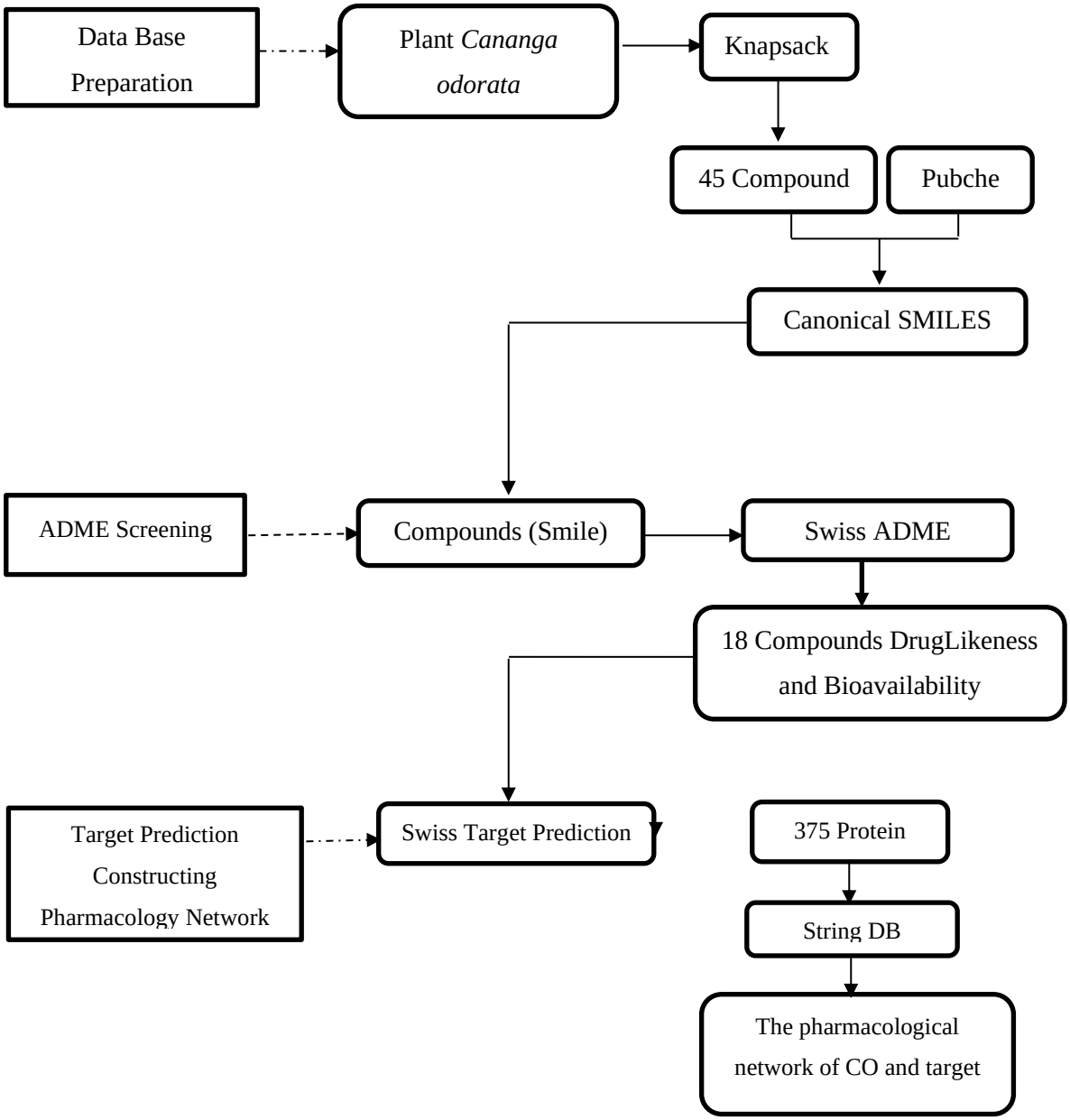


Figure 1. Research Scheme

Materials and Tools

This research uses the In silico method. Through computerized analysis, I use Lenovo brand laptops with specifications using 8192 MB RAM and AMD 3020e processor with Radeon Graphics (2 CPUs), 1.2GHz. The software used in this study is KNApSAcK Family, Pubchem, Swiss ADME, Swiss Target Prediction, GeneCards, Venny diagram, String DB, Cytoscape 3.10.0, and Way2Drug.

Methods

In this study, we used the In-silico analysis method using data already provided by several sites. Data sources used by KNApSAcK Family (http://www.knapsackfamily.com/), PubChem(https://pubchem.ncbi.nlm.nih.gov/), Absorption, Distribution, Metabolism, and Excretion (ADME) screening using Swiss ADME (http/www.swissadme.ch/), predicted target proteins using Swiss Target Prediction (http/www.swisstargetprediction.ch/), GeneCards (https://www.genecards.org/), Venn diagram (https://bioinfogp.cnb.csic.es/tools/venny/), String-DB pharmacological grid analysis (https://string-db.org/), visualization with Cytoscape version 3.10.0, and Way2drug (http//www.way2drugg.com/online/pass).

Phytochemical Data Warehouse and Phytochemical Data Unification

The source of data used to obtain a list of active compounds contained in the CO is the page from the KNApSAcK Family Database (http://www.knapsackfamily.com/). In the KNApSAcK Database, this is used to get the compound from the plant obtained by selecting the inscription "Search Engine" and then selecting the insert "KNApSAcK Keyword Search." After that, enter the scientific name of the plant and select the list inscription. The results are then copied to the Excel worksheet, then in the PubChem database searched one by one Pubchem CID and Canonical SMILES of the metabolite compounds found in the CO plant (https://pubchem.ncbi.nlm.nih.gov/). After searching, the data from the KNApSAcK Family, Pubchem, CID, and Canonical Smiles were 1 in the Excel worksheet.

Prediction of the Absorption, Distribution, Metabolism, and Excretion (ADME) of compounds in CO

Canonical Smile data is inserted into the next stage using the SwissADME database (http://www.swissadme.ch/) for the analysis (Absorption, Distribution, Metabolism, and Extrusion (ADME) of CO. Insert all Canonical smiles data that were previously made one then click on "run," then on the radar analysis of the bioavailability of the active compound. The results of the analysis on the Radar of biological availability at each selected compound do not deviate from finding out the drug similarities of the compounder, then molecular weight, absorption in the intestine (Gastrointestinal (GI) absorption), blood-brain barrier (BBB)) (Daina, Michielin and Zoete, 2017). After that, the result is downloaded to the Excel worksheet.

Prediction of the relationship between CO and cell proteins

After several compounds were selected from Switzerland, ADME continued with analysis to determine the target protein used on the active compound found in the CO. The database used is Swiss Target Prediction (http://www.swisstargetprediction.ch/). To determine the probability values on data ranging from strong, moderate, to weak. Then, search for target proteins from anxiety disorders using GeneCards that efficiently navigate all human biological data related to genes, proteins, cells, biological pathways, and diseases and the relationship between the conditions (Safran *et al.*, 2021). Then, the target proteins associated with the C.odorata compound and the target anxiety disorder proteins were inserted into the Venn diagram to identify anxieties related to the active CO compounds (Noor *et al.*, 2022).

Once the target proteins are known, and the probability values are strong, moderate, and weak, they proceed to be entered into the String DB database (https://string-db.org/) to predict between the proteins and determine the disease to be chosen (Szklarczyk *et al.*, 2021). After that, the part of the disease-related protein in the String DB can be imported into the software Cytoscape version 3.10.0 to visualize the resulting network of the DB string between the protein and the compound associated with the disease. Then, the protein describes the activity related to the selected disease (Doncheva *et al.*, 2019).

This was followed by the Prediction of Activity Spectra for Substances (PASS) way2drug database (http://www.way2Drug.com/passonline/). Then, it was collected in Excel. Then, there is a probability active (Pa) that describes the biological activity of a potentially active compound,

whereas the probability inactive (Pi) describes the biological activities of potentially inactive compounds (Fakih *et al.*, 2021). The values of Pa and Pi of the compound selected first should be higher than Pi because if the cure for a disease is established, the value of Pa is higher.

Results and Discussion

Identify and predict the bioavailability of the secondary metabolite compound C. odorata

The first step in this study was to obtain a list of active compounds from the CO plant online using a database from the KNApSAck Family. To predict the physicochemistry was done using the Swiss ADME database that included logP(iLOGP) ≤ 5, molecular weight ≤ 500 g/mol, number of hydrogen bond acceptors ≤10, and number of Hydrogen bond donors ≤5 (Naufa *et al.*, 2022). To analyze a substance into a drug can be done by predicting the bioavailability radar using the Brain Or Intestinal EstimateD permeation method (BOILED) Egg. This method serves to classify the absorption of a compound. In it, it shows a white area for the ability of the mixture to absorb in the intestinal tract and a yellow zone for penetration of blood–brain barrier (BBB). The list of names of 18 compounds of *C. odorata* that are predicted to meet the ADME criteria **(Table 1).** The results obtained formed in the form of a table that contains eight columns **(Table 2).**

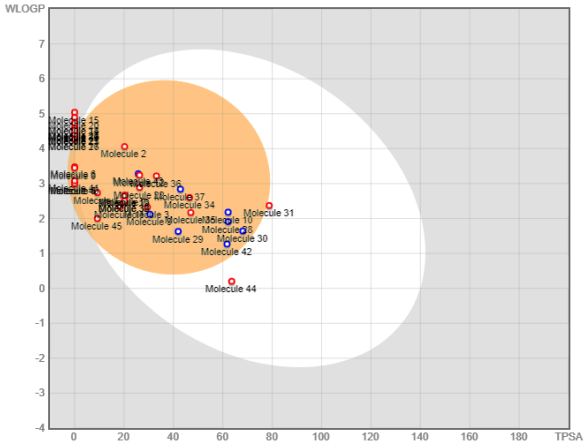


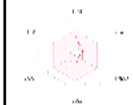
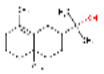
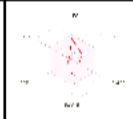
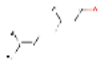
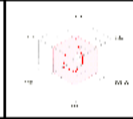
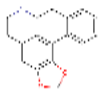
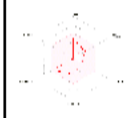
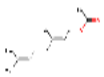
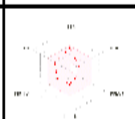
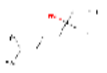
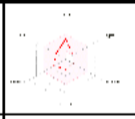
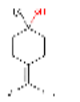
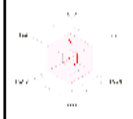
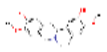
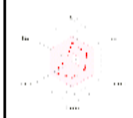
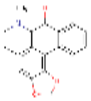
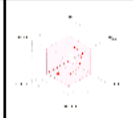
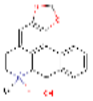
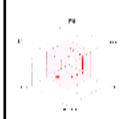
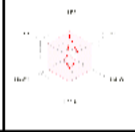
Figure 2. The analysis results predicted the bioavailability of the active compound of *C. odorata* using the BOILED-Egg method.

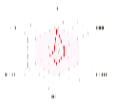
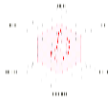
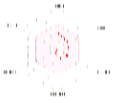
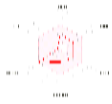
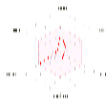
Table 1. Results 18 C. odorata compounds from the predicted KNApSAck Family database meet the ADME criteria.

No.	Compound Name	Compound Code
1.	1,8-Cineole	Mol 1
2.	gamma-Eudesmol	Mol 2
3.	beta-Nerol	Mol 3
4.	Anonaine	Mol 4
5.	(+)-Reticuline	Mol 5
6.	Geranyl acetate	Mol 6
7.	linalool	Mol 7
8.	gamma-Terpineol	Mol 8
9.	(-)-Coreximine	Mol 9
10.	Micheline A	Mol 10
11.	(-)-Ushinsunine beta-N-oxide	Mol 11
12.	4-Terpineol	Mol 12

13.	alpha-Terpineol	Mol 13
14.	Cananodine	Mol 14
15.	Sampangine	Mol 15
16.	beta-Terpineol	Mol 16
17.	Anaxagoreine	Mol 17
18.	4-Methylanisole	Mol 18

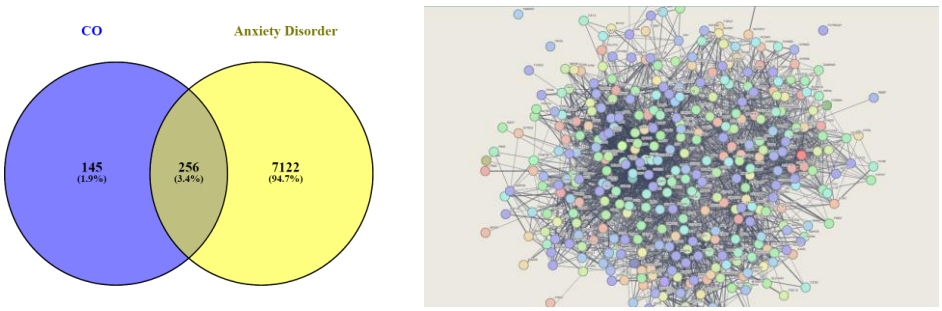
Table 2. Results of Absorption, Distribution, Metabolism, and Excretion analysis (ADME). The first column to know the name of the compound, the second column to understand the chemical shape of the composition, the third and seventh columns to see the drug similarities of a molecule, the fourth column should not exceed the value of 0.55, then ineffective, the fifth column must not exceed 500, then not effective, the sixth Column to find the penetration of cerebral blood cloths, the eighth Column for finding intestinal absorption.

Molecule	Compound structure	Bioavailability Radar	Bioavailability Score	MW	BBB permeant	Lipinski	GI absorption
1,8-Cineole			0,55	154,25 g/mol	Yes	0	High
gamma-Eudesmol			0,55	222,37 g/mol	Yes	0	High
beta-Nerol			0,55	154,25 g/mol	Yes	0	High
Aromadendrene			0,55	205,34 g/mol	Yes	0	High
(+)-Reticuline			0,55	329,39 g/mol	Yes	0	High
Geranyl acetate			0,55	196,29 g/mol	Yes	0	High
Linalool			0,55	154,25 g/mol	Yes	0	High
gamma-Terpineol			0,55	154,25 g/mol	Yes	0	High
(-)-Corynoline			0,55	327,37 g/mol	Yes	0	High
Micheline A			0,55	295,33 g/mol	Yes	0	High
(-)-Usambarine beta-N-oxide			0,55	311,33 g/mol	Yes	0	High
4-Terpineol			0,55	154,25 g/mol	Yes	0	High

alpha-Terpineol			0,55	154,25 g/mol	Yes	0	High
Camanodine			0,55	277,75 g/mol	Yes	0	High
Sanpangine			0,55	288,76 g/mol	Yes	0	High
beta-Terpineol			0,55	154,25 g/mol	Yes	0	High
Anxagonine			0,55	287,72 g/mol	Yes	0	High
d-Methylunicole			0,55	122,16 g/mol	Yes	0	High

Target protein prediction results

It was then conducted to analyze target proteins that could interact with active compounds using the Swiss Target Prediction database. From the 18 compounds obtained, it was predicted that the target protein would interact with as many as 375 proteins as the CO compound. Out of the 375 proteins with a probability value of more than 0, had good protein activity. Further analysis of proteins associated with anxiety disorders using the GeneCards database resulted in 7122 proteins. Next, a Venn diagram was created to predict plants related to anxiety disorder disease associated with the active compound CO (Noor *et al.*, 2022). Protein prediction intersection results related to the active compound CO with an anxiety disorder from 375 to 256 proteins. (**Figure 3**).



(A) (B)

Figure 3. (A) Venny diagram (https://bioinfogp.cnb.csic.es/tools/venny/) the number of proteins involved in the anxiety disorder with keywords entered in the gene card database (https://www.genecards.org/) "anxiety disorder" in a yellow circle. Target proteins interacting with CO were obtained from analysis using Swissstargetprediction (http://www.swisstargetprediction.ch/) in a blue circle. Both old yellow irises contain

256 target proteins that interact with the content of the CO compound. (B) Network of 256 target CO proteins related to DB string software (https://string-db.org/).

Result String DB pharmacological grid analysis

The Pharmacology Network further analyzes binding strength and biological processes to create a pharmacological network between target proteins that interact with selected active CO compounds using the String DB database (Szklarczyk *et al.*, 2021). Of the 375 proteins associated with anxiety disorder, eight proteins are linked to the CO compound **(Figure 4)**. The pathways that correlate with anxiety disorder therapy are neurotransmitter systems such as the serotonergic synapse and the dopaminergic synapse.

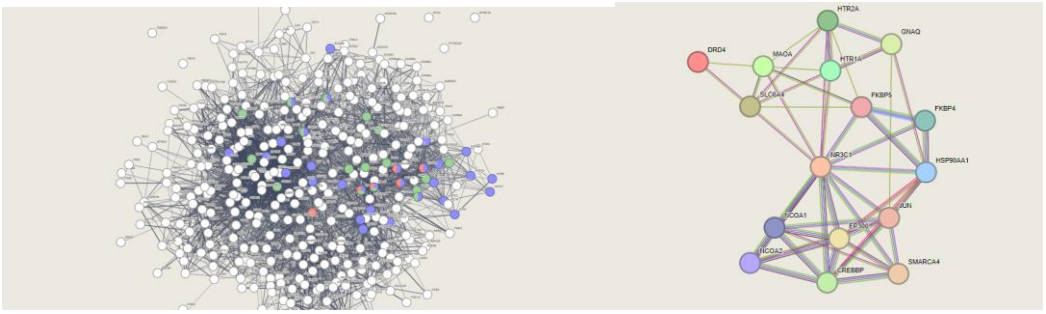


Figure 4. Results of the pharmacological network and signaling path associated with the protein. The serotonergic synapse signaling path marked a blue circle, and the dopaminergic synapse signaling path marked a green process using String DB.

Table 3. Protein-related compounds are predicted to treat anxiety disorder.

Compound	Target Proteins
Anonaine	MAOA, HTR1A, SLC6A4, HTR2A, DRD4
(+)-Reticuline	MAOA, HTR1A, SLC6A4, HTR2A, DRD4, JUN
4-Terpineol	NR3C1, SLC6A4
alpha-Terpineol	NR3C1, SLC6A4
Linalool	NR3C1
(-)-Coreximine	MAOA, SLC6A4, HTR1A, HTR2A, DRD4, HSP90AA1
Micheline A	HTR1A, SLC6A4, HTR2A, DRD4
(-)-Ushinsunine beta-N-oxide	HTR1A, SLC6A4, HTR2A, DRD4
Sampangine	HTR1A, SLC6A4, HTR2A, DRD4
Anaxagoreine	HTR1A, SLC6A4, HTR2A, DRD4

Of the eight proteins associated with the CO compounds, HTR1A, HTR2A, SLC6A4, NR3C1, MAOA, DRD4, HSP90AA1, and JUN **(Table 3)**. The results of this study are seen from the results of a pharmacological network using String DB to predict the signaling pathways associated with anxiety disorder, namely Serotonergic synapse and Dopaminergic Synapse. The serotonin receptor that is bound to this study is HTR1A. The autoreceptor in the prasinaps neuron, when stimulated, can inhibit the release of 5-HT from the presinaps neuron to the synapse. 5-HT1A receptor activation increases potassium flow and inhibits cyclical adenylate activity (Vildayanti *et al*., 2018). Some mental disorders, such as anxiety, depression, alcohol dependence, drug abuse, and aggressive and impulsive behavior, are associated with abnormalities in monoamine oxidase levels (Qiu *et al.*, 2021).

On the Biological Process diagram, the Molecular Function and Cellular Component are obtained from the DB String Network **(Figure 5)**. The results of the disease selection found in String DB obtained eight proteins associated with ten compounds, then using Cytoscape software that works to visualize the resulting network of String DB between the protein and the compound related to the disease. The results of the KEGG pathway are visualized in the Cytoscape to predict eight proteins and two signaling paths that can be used to treat anxiety disorder **(Figure 6)**. The results obtained in **(Figure 7)** use the Way2drug database to analyze biological activity based on high Probability Active (Pa) values so that it can be predicted as anxiety disorder therapy of the active compound CO.

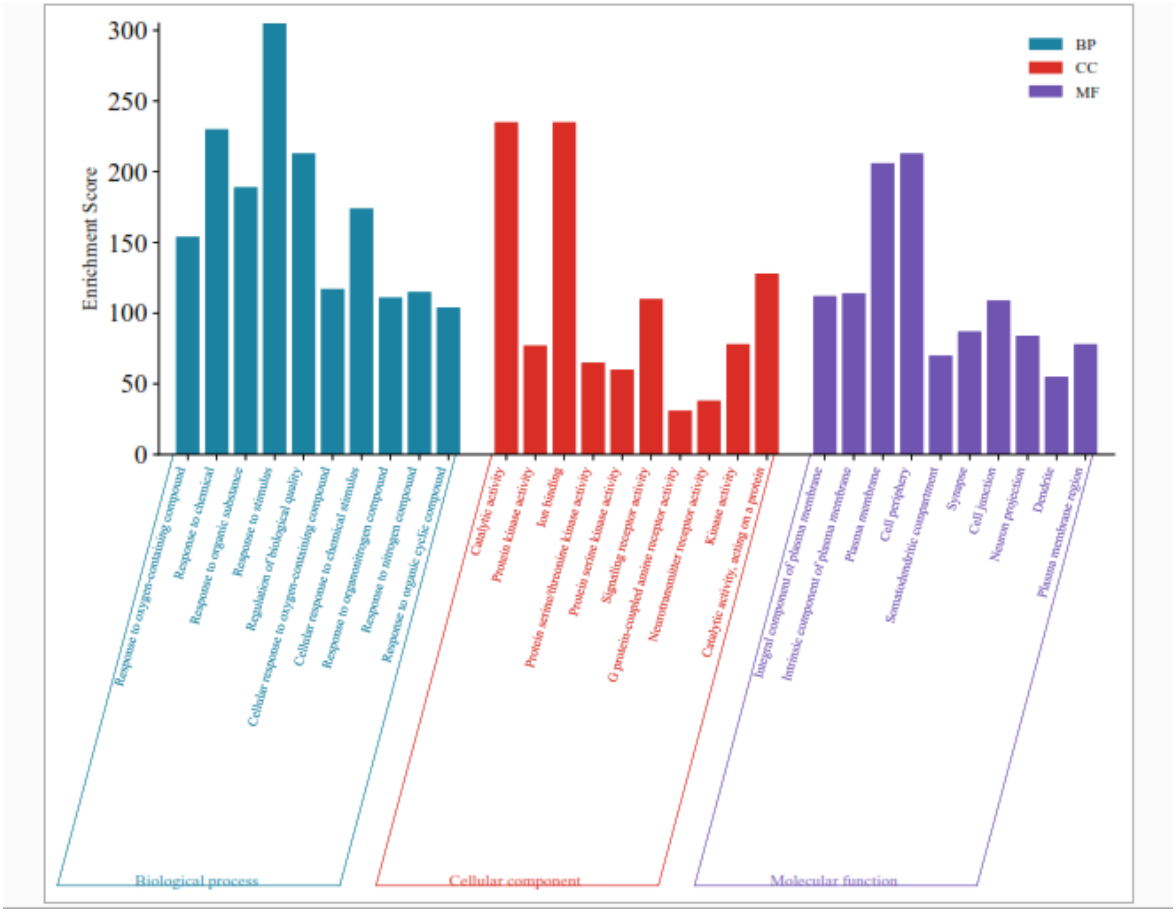


Figure 5. Column Diagram Biological Process (PP), Molecular Function (MF), Cellular Component (CC)

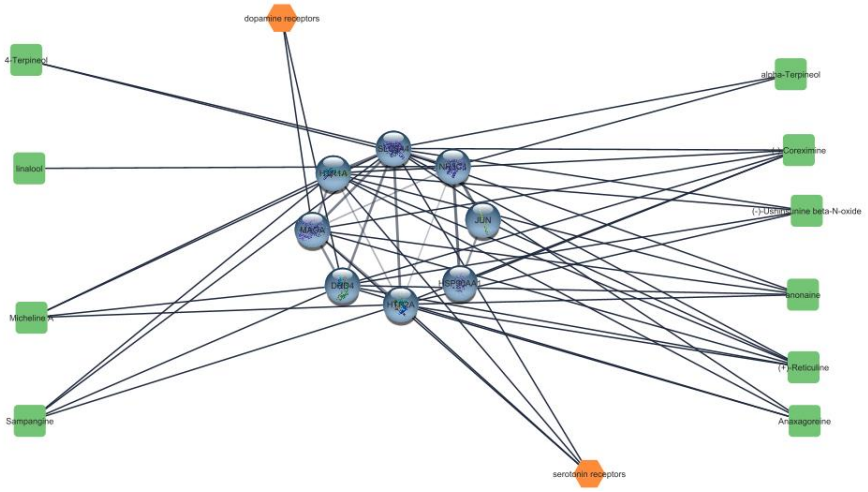
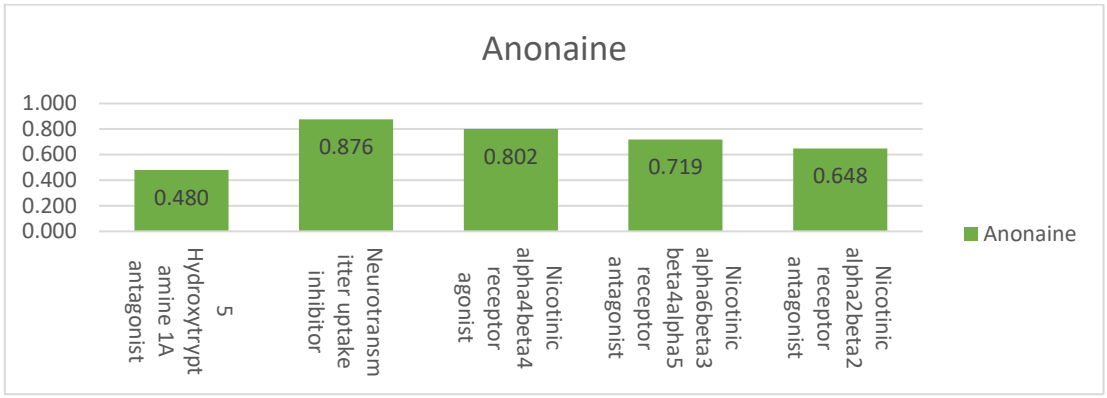
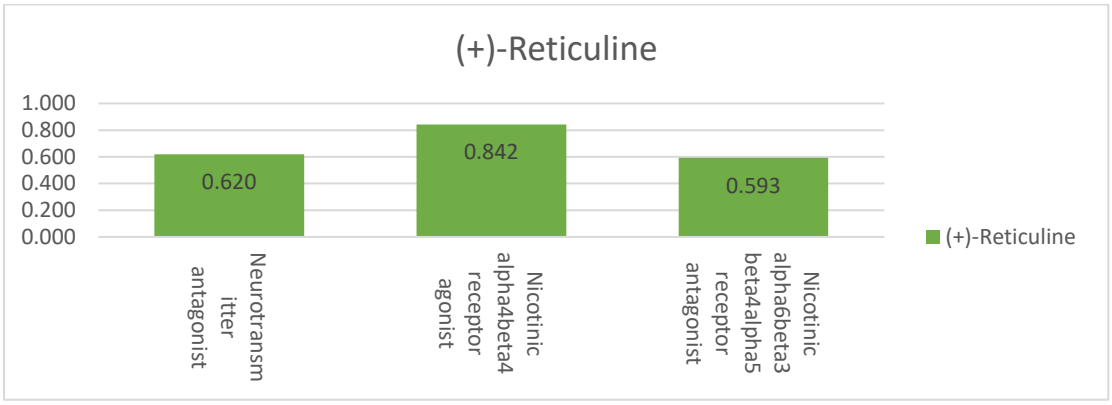
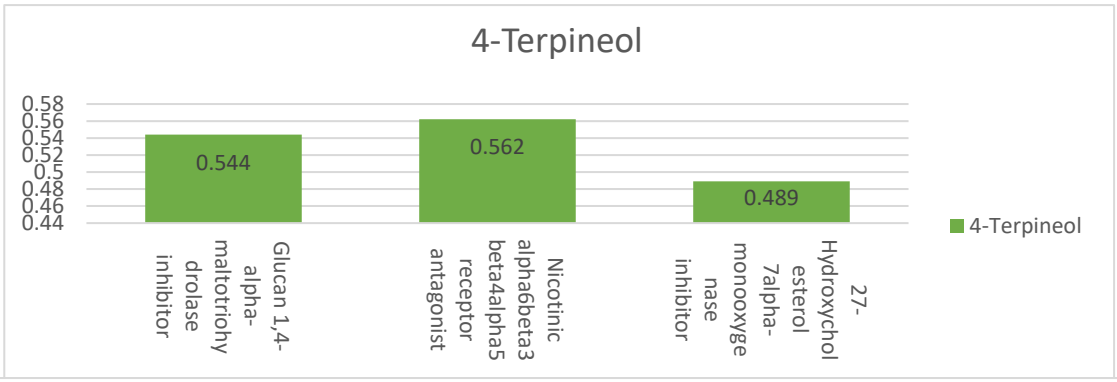
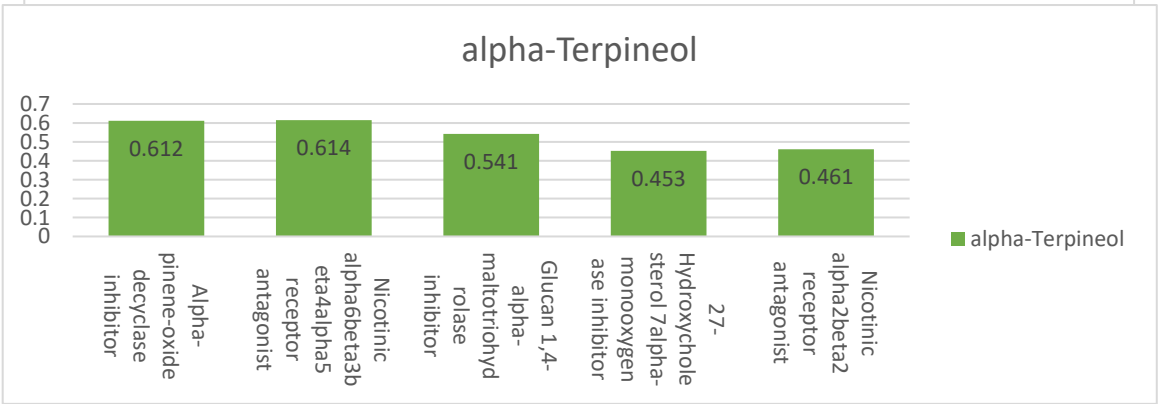


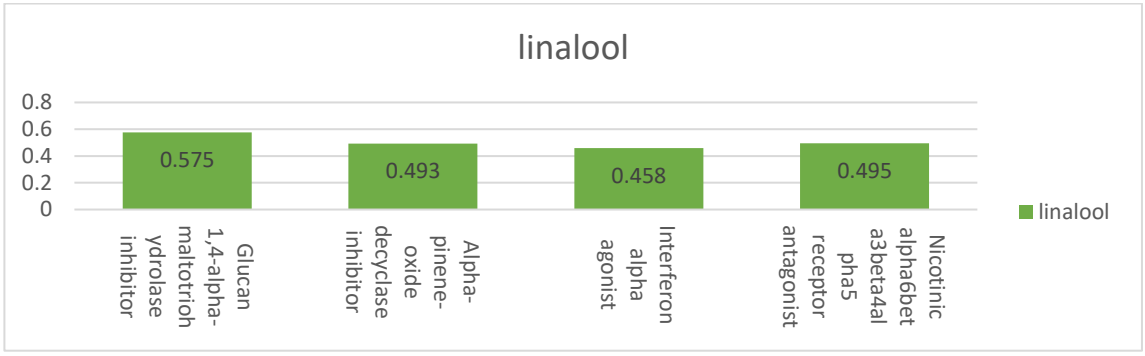
Figure 6. A network of interactions between 10 active compounds in CO (Green) and anxiety disorder target proteins (Young Blue). CO contains ten active substances that are known to interact with eight target proteins from 2 signal pathways (orange) in anxiety disorders.

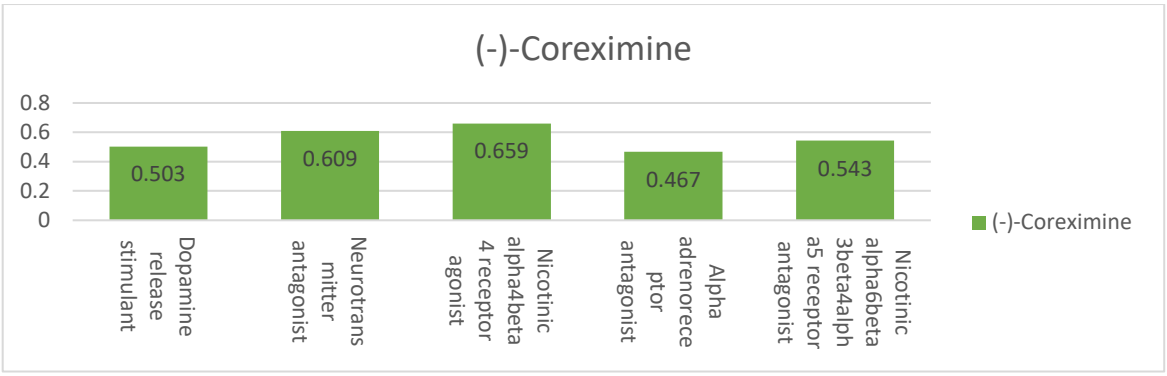


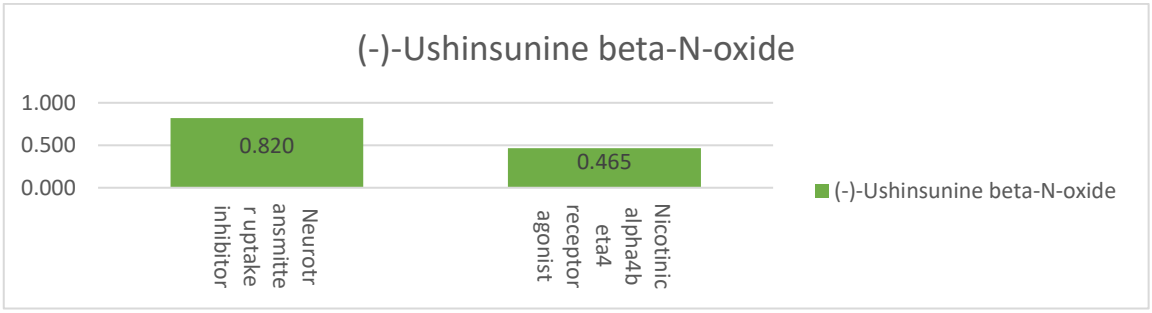


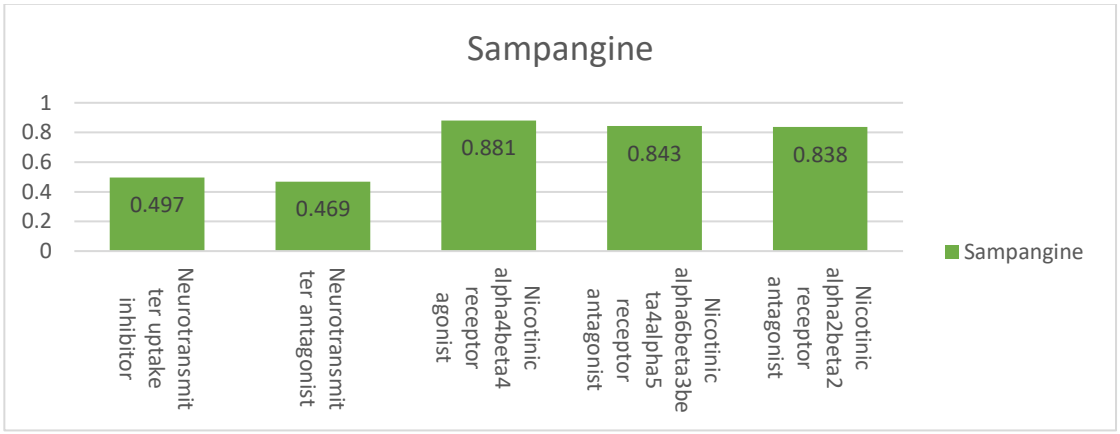


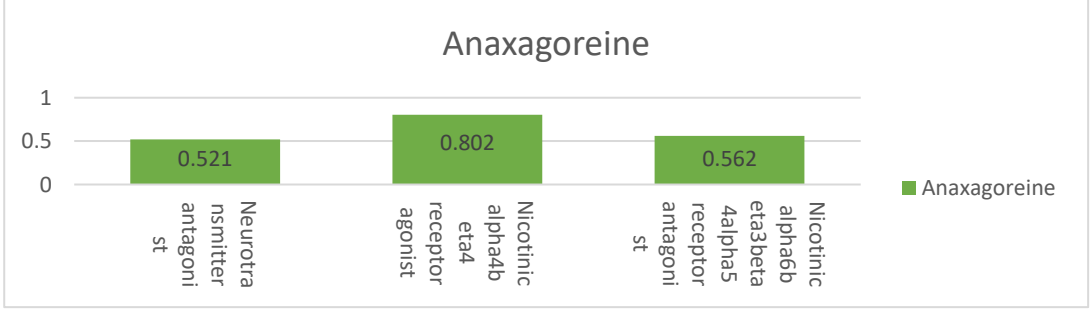



linalool
0.8
0.6
0.4
0.2
0
0.575
0.493
0.458
0.495
Glucan 1,4-alpha-maltotriohydrolase inhibitor
Alpha-pinene-oxide decyclase inhibitor
Interferon alpha agonist
Nicotinic alpha6beta3beta4alpha5 receptor antagonist
linalool


(-)-Coreximine
0.8
0.6
0.4
0.2
0
0.503
0.609
0.659
0.467
0.543
Dopamine release stimulant
Neurotransmitter antagonist
Nicotinic alpha4beta4 receptor agonist
Alpha adrenoreceptor antagonist
Nicotinic alpha6beta3beta4alpha5 receptor antagonist
(-)-Coreximine


(-)-Ushinsunine beta-N-oxide
1.000
0.500
0.000
0.820
0.465
Neurotransmitter uptake inhibitor
Nicotinic alpha4beta4 receptor agonist
(-)-Ushinsunine beta-N-oxide


Sampangine
1
0.8
0.6
0.4
0.2
0
0.497
0.469
0.881
0.843
0.838
Neurotransmitter uptake inhibitor
Neurotransmitter antagonist
Nicotinic alpha4beta4 receptor agonist
Nicotinic alpha6beta3beta4alpha5 receptor antagonist
Nicotinic alpha2beta2 receptor antagonist
Sampangine


Anaxagoreine
1
0.5
0
0.521
0.802
0.562
Neurotransmitter antagonist
Nicotinic alpha4beta4 receptor agonist
Nicotinic alpha6beta3beta4alpha5 receptor antagonist
Anaxagoreine

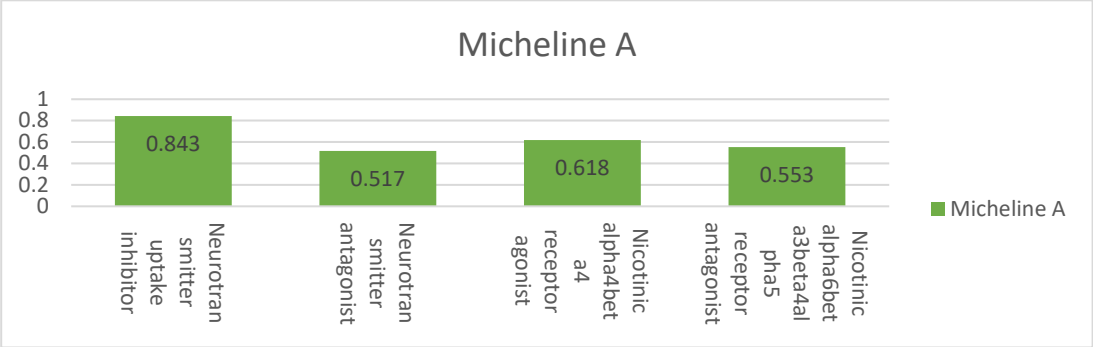


Figure 7. Predict the percentage value of biological activity (Pa) associated with anxiety disorder to compounds contained in CO extract using Way2Drug PASS Online Database analysis.

Anti-anxiety mechanism CO Active Compound

The results of the eight target proteins were NR3C1, MAOA, HTR1A, HTR2A, SLC6A4, DRD4, HSP90AA1, and JUN. Search results, analysis, as well as those selected from the active compound *Cananga odorata*, are Anonaine, (+)-Reticuline, 4-Terpineol, alpha-Terpineol, linalool, (-)-Coreximine, Micheline A, (-)-Ushinsunine beta-N-oxide, Sampangine, Anaxagoreine. The results of the search, analysis, and selection of the active compounds CO are Anonaine, (+)-Reticuline, 4-Terpineol, alpha-Terpineol, linalool, (-)-Coreximine, Micheline A, (-)-Ushinsunine beta-N-oxide, Sampangine, Anaxagoreine (Tan *et al.*, 2015). The proteins in the String-DB database related to the Kyoto Encyclopedia of Gene and Genome (KEGG) pathway contain Serotonergic and Dopaminergic synapses.

HTR1A (5 hydroxytryptamine (serotonin) receptor 1A): The primary serotonin inhibitor receptor (5-HT) is found in the brain in two different populations, the autoreseptor and the heteroreseptor. Autoreceptors are expressed on the serotonin neurons in the raphe nuclei and provide a feedback loop of regulation by inhibiting the rate of serotonin cell combustion. Hetero-receptors are extensively expressed in the brain, including the cortex, amygdala, and hippocampus, on the non-serotonine neurons (Piszczek *et al.*, 2015). HTR2A (5-hydroxytryptamine (serotonin) receptor 2A): Engaged in anxiety disorder and its current treatment using a Selective Serotonin Reuptake Compound Inhibitor (SSRI) causes side effects, shows low effectiveness, and requires daily doses (Rohn *et al.*, 2023). Psilocybin emerged as a potential therapy for several neuropsychiatric conditions, including depression, anxiety, substance abuse, and headaches (Kim *et al.*, 2020). SLC6A4 (Sodium Dependent Serotonin Transporter) is a serotonin transporter gene. It could encode the serotonin transporter (5-HTT) that ends the action of serotonin through the reuptake of neurotransmitters from the synaptic space to the presynaptic neuron. SSRIs and SNRIs are first-line pharmacotherapies for treating severe depression, anxiety disorders, and other mental conditions.

MAOA (Monoamine oxidase type A) Could be linked to emotional stability and neuroticism. Neurotransmitter metabolism is the center of several functional circuits of the brain that are associated with stress regulation and is one of the factors involved in biological sensitivity to stress (Bousman *et al.*, 2023; Liu *et al.*, 2021; Syed and Nemeroff, 2017). DRD4 is functionally linked to the dopamine system's signal transmission, regulating executive functions such as control and inhibition of attention and action. The dopamine receptor gene D4 (DRD4) is mainly emphasized in the dopaminergic system, and research finds the gene Catechol-O-methyltransferase (COMT) is necessary in responding to treatment; Akay *et al.*, 2018).

NR3C1(glucocorticoid receptor): The axis of the hypothalamus-pituitary-adrenal gland (HPA Axis) controls the release and regulation of stress hormones and is closely linked to stress associated with physical and mental illness. When faced with physiological or psychological stress, the hypothalamus will release the Corticotropin-Releasing Hormone (CRH) and

vasopressin to stimulate the pituitary gland to release the adrenocorticotrophic hormone (ACTH), which will then reach the adrenal glands through the systemic circulation to promote the release of glucocorticoids. (GC). GC, known as cortisol, is the primary stress hormone that works on many tissues and organs, including the brain, to bring the human body into certain stress conditions to cope effectively. Then, the brain undergoes a negative inhibition for the release of CRH in the hypothalamus and ACTH in the pituitary gland by binding glucocorticoid receptors (GR) and mineralocorticoid receptors to avoid overstimulation of the HPA axis, which then causes dysfunction. When GR is synthesized by the expression of the glucocorticoid receptor gene (NR3C1), it has an essential effect on the maintenance and regulation of the normal function of the HPA axis. NR3C1 can be recognized as an important candidate gene for anxiety disorder (ZHOU *et al.*, 2017).

Conclusion

Based on the results of this study using an In Silico-based pharmacological network analysis from the KNApSAcK database, there are 45 compounds, known 18 active compound meets the criteria of Absorption, Distribution, Metabolism, and Excretion (ADME) corresponding to the drug compounder (Drug Likeness/DL), eight target proteins associated with ten active Compounds that have potential with CO namely Anonaine, (+)-Reticuline, linalool, (-)-Coreximine, Micheline A, (-)-Ushinsunine beta-N-oxide, 4-Terpineol, alpha-Terpeneol, Sampangine, Anaxagoreine. In this study, it could be helpful to carry out advanced research using in vitro and in vivo trials to give more accurate results on CO plants as anxiety disorder therapy.

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References

Akay, A. P. *et al.* (2018) 'Allele frequencies of dopamine D4 receptor gene (DRD4) and Catechol-O-methyltransferase (COMT) Val158Met polymorphism are associated with methylphenidate response in adolescents with attention deficit/hyperactivity disorder: A case control preliminary stu', *Psychiatry and Clinical Psychopharmacology*, 28(2), p. 177-184. doi: 10.1080/24750573.2017.1418134.

Azizah, A. N. *and* Kurniati, C. H. (2020) 'Obat Herbal Meredakan Batuk Pilek', 2(3), p. 259–269.

Bousman, C. A. *et al.* (2023) 'Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants', *Clinical Pharmacology and Therapeutics*, 114(1), p. 51-68. doi: 10.1002/cpt.2903.

Daina, A., Michielin, O. *and* Zoete, V. (2017) 'SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules', *Scientific Reports*, 7. doi: 10.1038/srep42717.

Doncheva, N. T. *et al.* (2019) 'Cytoscape StringApp: Network Analysis and Visualization of Proteomics Data', *Journal of Proteome Research*, 18(2), p. 623-632. doi: 10.1021/acs.jproteome.8b00702.

Fakih, T. M., Ramadhan, D. S. F. *and* Darusman, F. (2021) 'In Silico Activity Identification of Cyclo Peptide Alkaloids from Zizyphus Spina-Christi Species Against Sars-Cov-2 Main Protease', *Jurnal Biodjati*, 6(1), p. 71-81. doi: 10.15575/biodjati.v6i1.10603.

Fatmasari, F. H., Mukti, R. A. *and* Nuraini, I. (2023) 'Uji Ketahanan pH Minyak Atsiri dari Kulit Buah Jeruk dan Bunga Kenanga sebagai Bahan Pengganti Aromaterapi pada Mata Kuliah Perawatan Badan', *Journal on Education*, 5(3), p. 6353-6358. doi: 10.31004/joe.v5i3.1419.

Jannah, S. H. (2018) 'Kawasan Hutan Olat Cabe Desa Batu Bangka Program Studi Pendidikan Biologi , FPMIPA , IKIP Mataram , Indonesia Bioscientist : Jurnal Ilmiah Biologi', *Jurnal Ilmiah Biologi*, 6(2), p. 145-172.

Kim, K. *et al.* (2020) 'Structure of a Hallucinogen-Activated Gq-Coupled 5-HT2A Serotonin Receptor', *Cell*, 182(6), p. 1574-1588. doi: 10.1016/j.cell.2020.08.024.

Liu, X. *et al.* (2021) 'Mechanism of pharmacological effect of Angelica essential oil on anxiety based on network pharmacology and molecular docking', *Tropical Journal of Pharmaceutical Research*, 20(4), p. 789-796. doi: 10.4314/tjpr.v20i4.19.

Makatita, F. A., Wardhani, R. *and* Nuraini (2020) 'Riset in silico dalam pengembangan sains di bidang pendidikan, studi kasus: analisis potensi cendana sebagai agen anti-aging', *Jurnal ABDI*, 2(1), p. 59-67.

Naufa, F., Mutiah, R. *and* Indrawijaya, Y. Y. A. (2022) 'Studi in silico potensi senyawa katekin teh hijau (Camellia sinensis) sebagai antivirus SARS CoV-2 terhadap spike glycoprotein (6LZG) dan main protease (5R7Y)', *J.Food Pharm.Sci*, 10(1), p. 584-596.

Nida, F. L. K. (2014) 'Zikir Sebagai Psikoterapi Dalam Gangguan Kecemasan Bagi Lansia', *Jurnal Bimbingan Konseling Islam*, 5(1), p. 133-150.

Noor, F. *et al.* (2022) 'Network Pharmacology Approach for Medicinal Plants: Review and Assessment', *Pharmaceuticals*, 1-33. doi: 10.3390/ph15050572.

Oktapiani, N. *and* Putri, A. (2018) 'Rasional Emotif Terapi Gangguan Kecemasan Sosial dengan Menggunakan Pendekatan', *Fokus*, 1(6), p. 227-232.

Piszczek, L. *et al.* (2015) 'Modulation of anxiety by cortical serotonin 1A receptors', *Frontiers in Behavioral Neuroscience*, 9, p. 1-10. doi: 10.3389/fnbeh.2015.00048.

Qiu, M. *et al.* (2021) 'mRNA Levels of MAOA and 5-HT2A Receptor in Patients With Pathological Internet Use: Correlations With Comorbid Symptoms', *Frontiers in Psychiatry*, 12, p. 1-8. doi: 10.3389/fpsyt.2021.667699.

Rahma, P. A. Y. *et al.* (2020) 'Analisis Kualitatif Kandungan Bunga Kenanga (Cananga odorata) Secara Fitokimia dengan Menggunakan Pelarut Etanol', *Journal of Research and Education Chemistry*, 2(1), p. 43. doi: 10.25299/jrec.2020.vol2(1).4783.

Report, C. (2023) 'Case Report Psychodynamic Overview of Generalized Anxiety', 7(1). doi: 10.33086/mhsj.v7i1.3558.

Rohn, T. T. *et al.* (2023) ' Genetic Modulation of the HTR2A Gene Reduces Anxiety-Related Behavior in Mice', *PNAS Nexus*, 2(6), p. 1-13. doi: 10.1093/pnasnexus/pgad170.

Safran, M. *et al.* (2021) 'Bab 2 Rangkaian GeneCards', p. 27-56.

Shofi, M. (2022) 'Studi In Silico Senyawa Kuarsetin Daun Kencana Ungu (Ruellia tuberosa L.) Sebagai Agen Antikanker Payudara', *Jurnal Sintesis: Penelitian Sains, Terapan dan Analisisnya*, 2(1), p. 1-9. doi: 10.56399/jst.v2i1.13.

Suhendi, H. *and* Supriadi, A. (2020) 'Sistem Pakar Diagnosa Gangguan Kecemasan Menggunakan Metode Certainty Factor Berbasis Website', *Naratif : Jurnal Nasional Riset, Aplikasi dan Teknik Informatika*, 2(2), p. 13-23. doi.org/10.53580/naratif.v2i2.94.

Sundara, A. K. *et al.* (2022) 'Review Article : Aromaterapi Sebagai Terapi Stres Dan Gangguan Kecemasan', *Jurnal Buana Farma*, 2(2), p. 78-84. doi: 10.36805/jbf.v2i2.396.

Syed, S. A. *and* Nemeroff, C.B. (2017) 'Early Life Stress, Mood, and Anxiety Disorders', *Chronic Stress*, 1. doi: 10.1177/2470547017694461.

Szklarczyk, D. *et al.* (2021) 'Database STRING pada Tahun 2021 : dapat Disesuaikan Jaringan Protein-Protein, dan Fungsional Karakterisasi Gen/ Pengukuran yang Diunggah Pengguna Set', 49, p. 605-612.

Tan, L. T. H. *et al.* (2015) 'Traditional Uses, Phytochemistry, and Bioactivities of Cananga odorata (ylang-ylang)', *Evidence-based Complementary and Alternative Medicine*, 2015. doi: 10.1155/2015/896314.

Ulfianasari, E., Winahyu, K. M. *and* Nainar, A. A. A. (2022) 'Cyberbullying dan kecemasan remaja : Sebuah studi deskriptif', *Jurnal Ilmiah Keperawatan Indonesia*, 6(1), p. 80–89).

Vildayanti, H., Puspitasari, I.M. and Sinuraya, R.K. (2018) 'Review: Farmakoterapi Gangguan Anxietas', *Farmaka*, 16(1), p. 196-213.

Wulandari, A. S., Ferawati, D. *and* Nurhayani, O. (2019) 'Morfologi dan Mutu Fisik Benih Kenanga (Cananga odorata (Lam.) Hook.f. & Thomson forma genuina) Morphology and Physical Quality of Cananga Seeds (Cananga odorata (Lam.) Hook.f. & Thomson forma genuina)', *Jurnal Silvikultur Tropika*, 10(2), p. 95–99.

Yassir, M. *and* Asnah, A. (2019) 'Pemanfaatan Jenis Tumbuhan Obat Tradisional Di Desa Batu Hamparan Kabupaten Aceh Tenggara', *BIOTIK: Jurnal Ilmiah Biologi Teknologi dan Kependidikan*, 6(1), p. 17. doi: 10.22373/biotik.v6i1.4039.

Zhou, Y. *et al.* (2017) 'The Effects of NR3C1 Polymorphisms and Paternal/ Maternal Parenting Styles on Chinese Adolescent Anxiety Disorders', *Acta Psychologica Sinica*, 49(10), p. 1287. doi: 10.3724/sp.j.1041.2017.01287.