# BIOAVAIBILITY EVALUATION AND MOLECULAR DOCKING OF *Cananga odorata* PLANT AS ANTI-INFLAMMATORY POTENTIAL AGAINST CROHN'S DISEASE

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## Abstract

Crohn's disease is a chronic inflammatory bowel disease (IBD) that affects the digestive tract. One of the potential targets for this disease is LRRK2. Kenanga (*Cananga odorata*) is known to have anti-inflammatory effects. The study aims to identify the potential of the secondary metabolite compounds found in *C. odorata* against LRRK2 in silico. The KnapSack database was used to identify the secondary metabolite compounds of *C. odorata*, SwissADME was used to find the compound with high bioavailability with the Boiled-EGG method, and PyRx with the AutoDock was used for molecular docking. According to the docking results, three compounds are potentially inhibiting LRRK2, namely (+)-Reticuline with a binding energy of -9.04 kcal/mol and a prediction of inhibition constant (pKi) of 237.71 nM, benzyl benzoate with a binding energy of -8.19 kcal/mol and a prediction of inhibition constant (pKi) of 994.29 nM and benzyl salicylate with a bonding energy of -8.22 kcal/mol and a prediction of inhibition constant (pKi) of 942.48 nM.

***Keywords:*** *Crohn disease; Cananga odorata; in silico; LRRK2; molecular docking*

## Introduction

Crohn's disease is a chronic disease that attacks the digestive tract and causes inflammation in the small and large intestines, characterized by increasing and decreasing symptoms. One of the IBDs that affects people between the ages of 15 and 35 is Crohn's disease (Sleiman *et al.*, 2022). Opposite to other inflammatory conditions, inflammatory bowel became not easy to overcome. As a result, an intestinal area gets damaged and the immune system is activated. Along with other symptoms, it causes pain, diarrhea, and fever. Not only can Crohn's disease have a severe impact on the lower portion of the small intestine, but it can also affect the large intestine, stomach, esophagus, or even the mouth (Saeid *et al.*, 2019). However, it then reappears as a pathophysiological condition affected by complex pathogenesis (Petagna *et al.*, 2020). The pathogenesis of Crohn's disease is based on tissue inflammation caused by an uncontrolled

immune response to the luminal bacterial antigen. Immune cells such as T-cells CD4 and CD8, B cells, CD14 monocytes, and NK cells are involved when the cells attack the intestines of patients with Crohn's disease (Ikezu *et al.*, 2020). Multidisciplinary medical treatment is used to treat Crohn's disease, with the main goals being symptom relief and mucous healing. Surgery is crucial in treating complications such as stenosis, perforation, fistula, and abscess. Over 80% of patients undergoing surgery are known to have post-operative relapses (Feuerstein and Cheifetz, 2017).

One of the potential biological targets for treating Crohn's disease is LRRK2 (Younis *et al.*, 2020). LRRK2 is frequently found in CD14+ monocytes in human blood tip mononuclear cells. Furthermore, multiple single nucleotide polymorphisms (SNPs) at the LRRK 2 gene have been linked to inflammatory illnesses such as Crohn's. Type II interferon (IFN-) can activate LRRK2 in human immune cells because the transcription factor activity is suppressed by Nuclear Factor of Activated T Cells (NFAT), which directly raises inflammatory gene activity. This shows that LRRK2 mediated the inflammatory response by lowering NFAT and activating inflammatory cells in type II interferon (Ikezu *et al.*, 2020). Thus, LRRK2 modules the host's immune response and has been associated with inflammation, cancer, and Crohn's disease pathophysiology (Bae and Lee, 2015). Therefore, LRRK2 has been shown to play an essential role in the innate immune response associated with inflammation. In particular, B lymphocytes, which are immune cells, require LRRK2 to regulate cell function and to execute binding activity in the molecule. B lymphocytes are active immune response cells that are part of the adaptive immune system (Li *et al.*, 2021).

Ylang-ylang, also known as *Cananga odorata*, is a medicinal plant of the Annonaceae family that grows in many countries in Asia, including the Philippines, Malaysia, Indonesia, and Madagascar (Kumar *et al.*, 2022). The ylang-ylang essential oil can be obtained from the flower of *C. odorata*. It is used in the food, perfume, and aromatherapy industries (Teng *et al.*, 2015). According to some studies, *C. odorata* plant extract has analgesic activity and anti-inflammatory properties (Maniyar and Devi, 2015).

To date, the therapeutic properties of plants have been investigated without explicitly indicating molecular activity (Pinzi and Rastelli, 2019). *In silico* studies can explain the molecular and cellular mechanisms that occur when these active plant chemicals are activated. In drug development research, this study in silico uses computer technology and databases (Joshi *et al.*, 2022). In order to discover and develop new effective, efficient, and safe drugs, it is essential to understand the mechanisms of the enzyme reaction and the molecular mechanism of action of enzyme inhibitors (Rufer, 2021). The research will use molecular docking methods to find predictions of interactions between secondary metabolite compounds *C. odorata* and LRKK2. The computational drug design relies on docking proteins and ligands, where computer simulations can create several models of docking proteins and ligands (Khan *et al.*, 2020). The research focuses on discovering a drug candidate from the secondary metabolite compound of the plant *C. odorata* that can be used to treat Crohn's disease.

## Methods

### Tools and Materials

This study was conducted using online databases such as KNApSAcK (http://www.knapsackfamily.com/), PubChem (https://pubchem.ncbi.nlm.nih.gov/), SwissADME (http://www.swissadme.ch/), Protein Data Bank (https://www.rcsb.org/), and Proteins.Plus (https://proteins.plus/). The software used in this study is Avogadro, BIOVIA Discovery Studio Visualizer version 4.5, and PyRx version 0.8.

**Data collection of bioactive compounds and bioavailability predictions**

The secondary metabolite of *C. odorata* was obtained from KNApSAcK by entering the scientific name of the plant taken. Then PubChem used Pubchem to see the SMILES code. Subsequently, bioavailability predictions were performed by entering the secondary *C. odorata* metabolite SMILEs code into SwissADME. The Boiled-Egg method was used to predict compounds with high bioavailability (Daina and Zoete, 2016).

**Docking Protein Target**

The structural component of the LRRK2 protein is obtained from the Protein Data Bank with the PDB ID 5IL7. Before molecular docking, first, a protein preparation with Discovery Studio 2020 to separate between protein and ligan (Nailis *et al.*, 2021). Then, validate the method by redocking the ligan compound with the target protein. Molecular docking is done on the Grid Box specified at coordinates X = 29, 5832; Y = 43,0435; and Z = 45,0891 with a size of 50x50x50 and a distance of 0,375 Å.

Secondary metabolite compounds that passed Boiled-Egg were prepared using Avogadro using MMF94s methods. Then, the test compound was docked along with LRRK2 protein using AutoDock 4 with PyRx 0.8. Lamarckian and Genetic Algorithm (LGA) were used as parameters with numbers of GA runs 100, the maximum number of energy evaluations was set medium, 150 population size, with a mutation rate of 0.02, and crossover rate of 0.80 (Muchlisin *et al.*, 2022). Interactions between secondary metabolite compounds and LRRK2 proteins were analyzed using Proteins.Plus web server.

**Results and Discussion**

**List and bioavailability predictions of secondary metabolite compounds of *C. odorata***

From the search of compounds carried out on the online database of KNApSAcK obtained 46 compound secondary metabolites of *C. odorata* (Table 1). This database has been developed to systematize crude drug systems by providing information about species-metabolite relations and the medicinal usage of plants based on traditional and modern knowledge (Wijaya *et al.*, 2016). This database contains 101,500 species–metabolite relationship information, encompassing 20,741 species and 50,048 metabolites (Ma *et al.*, 2021).

**Table 1. List of secondary metabolite of C. odorata**

| No. | Compound Name | Compound Code |
|---|---|---|
| 1. | (-)-Coreximine | Mol 1 |
| 2. | (-)-Germacrene D | Mol 2 |
| 3. | (-)-Ushinsunine beta-N-oxide | Mol 3 |
| 4. | (+)-Cuparene | Mol 4 |
| 5. | (+)-gamma-Gurjunene | Mol 5 |
| 6. | (+)-Reticuline | Mol 6 |
| 7. | 1,6-Diazafluoranthene | Mol 7 |
| 8. | 1,8-Cineole | Mol 8 |
| 9. | 2-Bornene | Mol 9 |
| 10. | 4-Methylanisole | Mol 10 |
| 11. | 4-Terpineol | Mol 11 |
| 12. | allo-Aromadendrene | Mol 12 |
| 13. | alpha-Caryophyllene (obsol.) | Mol 13 |
| 14. | alpha-Gurjunene | Mol 14 |
| 15. | alpha-Pinene | Mol 15 |

| | | |
|---|---|---|
| 16. | alpha-Terpineol | Mol 16 |
| 17. | alpha-Terpinolene | Mol 17 |
| 18. | alpha-Ylangene | Mol 18 |
| 19. | Anaxagoreine | Mol 19 |
| 20. | Anonaine | Mol 20 |
| 21. | Benzyl benzoate | Mol 21 |
| 22. | Benzyl salicylate | Mol 22 |
| 23. | beta-Caryophyllene | Mol 23 |
| 24 | beta-Cedrene | Mol 24 |
| 25. | beta-Myrcene | Mol 25 |
| 26. | beta-Nerol | Mol 26 |
| 27. | beta-Pinene | Mol 27 |
| 28. | beta-Terpineol | Mol 28 |
| 29. | Cadinene | Mol 29 |
| 30. | Canangone | Mol 30 |
| 31 | Cananodine | Mol 31 |
| 32. | Cleistopholine | Mol 32 |
| 33. | delta-Cadinene | Mol 33 |
| 34. | gamma-Eudesmol | Mol 34 |
| 35. | gamma-Muurolene | Mol 35 |
| 36. | gamma-Terpineol | Mol 36 |
| 37. | Geranyl acetate | Mol 37 |
| 38. | Isocamphane | Mol 38 |
| 39. | Isoeugenol | Mol 39 |
| 40. | Isosafrole | Mol 40 |
| 41. | Isosylvestrene | Mol 41 |
| 42. | Linalool | Mol 42 |
| 43. | Micheline A | Mol 43 |
| 44. | N-trans- Feruloyltyramine | Mol 44 |
| 45. | Sampangine | Mol 45 |
| 46. | Thujopsene | Mol 46 |

The next step was to predict the bioavailability of the secondary metabolite compounds of *C. odorata* using the BOILED-Egg method using SwissADME (Figure 1). The results obtained 25 compounds with high bioavailability (Table 2). The yellow zone, often known as egg yolk, represents the physical chemical space of the molecules most likely to be absorbed by the digestive tract, whereas the white region represents the physical chemical space of the molecules least likely to be absorbed by the intestinal tract (Daina and Zoete, 2016). SwissADME is involved in manufacturing and developing new anti-inflammatory compounds to better understand and apply them in the development cycle of new drugs (Bakchi *et al.*, 2022). This method is in line with a descriptive graphical approach that distinguishes molecules that are well absorbed by the intestine and poorly absorbed in the intestines, as well as molecules that are absorbable by the brain and that cannot be absorbed into the brain (Daina *et al.*, 2017). The method is based on two parameters: lipophilicity and polarity. The lipophilicity of a compound was measured using a partition coefficient (P) with a LogP value calculated using the Wildman–Crippen (WLogP) method, and the polarity of the compounds, measured using the calculated topological polar surface area (tPSA) (Daina and Zoete, 2016).

**Molecular Docking**

The method was validated before docking was carried out by redocking the native ligand to the LRKK2 protein (5IL7). From the redocking results, the RMSD value was obtained. This value indicates the capability of the method to be used to replicate the original position of the native ligand. A method is considered valid if it has an RMSD value < 2 Å (Muchlisin *et al.*, 2022)

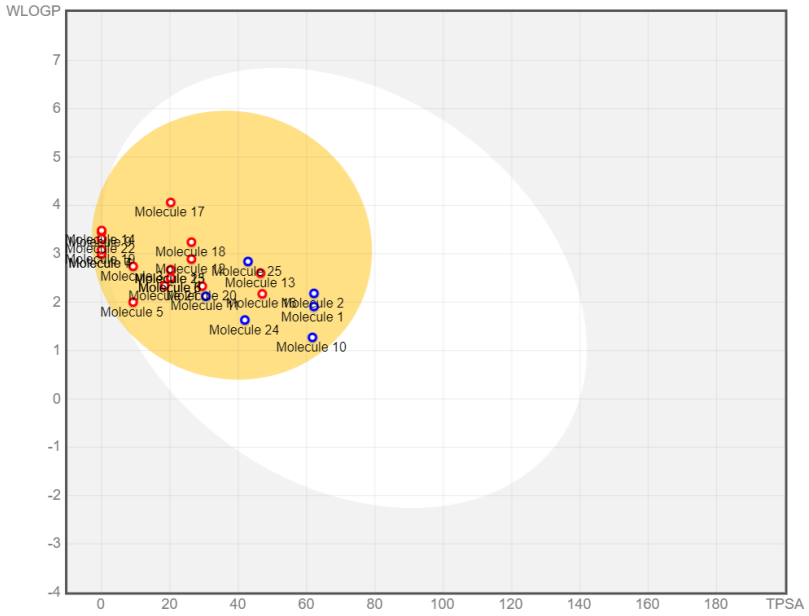



**Figure 1. Bioavailability prediction of of the secondary metabolite of *C. odorata* by using BOILED-Egg method**

**Table 2. Bioavailability prediction of of the secondary metabolite of *C. odorata* by using BOILED-Egg method**

| No. | Bioavailability Prediction | Total Compound | Compound Code |
|---|---|---|---|
| 1. | High | 25 | Mol 1, Mol 6, Mol 8, Mol 9, Mol 10, Mol 11, Mol 15, Mol 16, Mol 17, Mol 19, Mol 20, Mol 21, Mol 22, Mol 25, Mol 26, Mol 32, Mol 34, Mol 37, Mol 38, Mol 39, Mol 40, Mol 41, Mol 42, Mol 43, Mol 45 |
| 2. | Low | 21 | Mol 2, Mol 3, Mol 4, Mol 5, Mol 7, Mol 12, Mol 13, Mol 14, Mol 18, Mol 23, Mol 24, Mol 27, Mol 28, Mol 29, Mol 30, Mol 31, Mol 33, Mol 35, Mol 36, Mol 44, Mol 46 |

To predict the affinity of the secondary metabolite of *C. odorata*, docking was carried out to the target protein. The docking result will produce binding affinity data, producing a stable complex between ligand and protein. This complex shows more negative free binding energy, and a low pKi indicates a high inhibitor potential. Binding energy (kcal/mol) is used to compare and study the binding affinities of different compounds or ligands to their target molecules. The lower the binding energy, the greater the ligand's affinity to the target, so the ligand with the highest affinities can be selected for further research (Rahman *et al.*, 2021).

Based on the data obtained (Table 3), it is seen that the ligand acting as a comparator has a binding energy of -7.33 kcal/Mol and a pKi of 4.24 µM. Compared to the 25 metabolite compounds, only

three compounds, (+)-Reticuline (-9.04 kcal/mol and 237.71 nM), benzyl benzoate (-8.19 kcal/mol and 994.29 nM) and benzyl salicylate (-8.22 kcal /mol and 942.48 nM), have lower binding energies and pKi than the ligans. So, it can be concluded that both predicted compounds have the potential to inhibit LRRK2.

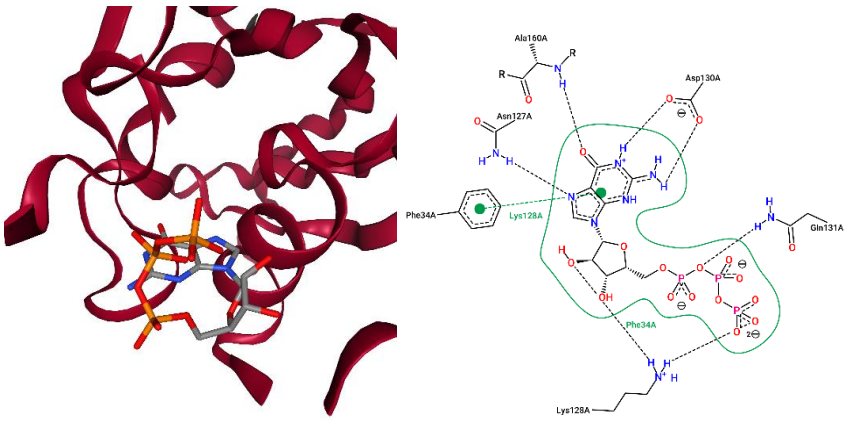
**Table 3. Molecular docking results of native ligand and secondary metabolite compounds of *C. odorata* against LRKK2**

| No. | Compound Code | Binding Energy (kcal/mol) | Predicting Inhibition Constant (pKi) |
|---|---|---|---|
| 1. | Mol 1 | -7,93 | 1,54 µM |
| 2. | Mol 6 | -9,04 | 237,71 nM |
| 3. | Mol 8 | -6.05 | 36,65 µM |
| 4. | Mol 9 | -5,34 | 121,25 µM |
| 5. | Mol 10 | -5,15 | 166,86 µM |
| 6. | Mol 11 | -6,51 | 16,82 µM |
| 7. | Mol 15 | -6,18 | 29,34 µM |
| 8. | Mol 16 | -6,66 | 13,04 µM |
| 9. | Mol 17 | -5,56 | 84,27 µM |
| 10. | Mol 19 | -6,12 | 32,85 µM |
| 11. | Mol 20 | -7,29 | 4,57 µM |
| 12. | Mol 21 | -8,19 | 994,29 nM |
| 13. | Mol 22 | -8,22 | 942,48 nM |
| 14. | Mol 25 | -4,93 | 243,72 µM |
| 15. | Mol 26 | -5,37 | 115,9 µM |
| 16. | Mol 32 | -7,43 | 3,55 µM |
| 17. | Mol 34 | -8,14 | 1,07 µM |
| 18. | Mol 37 | -6,61 | 14,38 µM |
| 19. | Mol 38 | -5,72 | 63,84 µM |
| 20. | Mol 39 | -6,56 | 15,41 µM |
| 21. | Mol 40 | -6,77 | 10,87 µM |
| 22. | Mol 41 | -5,75 | 60,58 µM |
| 23. | Mol 42 | -5,63 | 74,62 µM |
| 24. | Mol 43 | -8,07 | 1,21 µM |
| 25. | Mol 45 | -7,31 | 4,35 µM |
| 26. | Native Ligand | -7,33 | 4,24 µM |

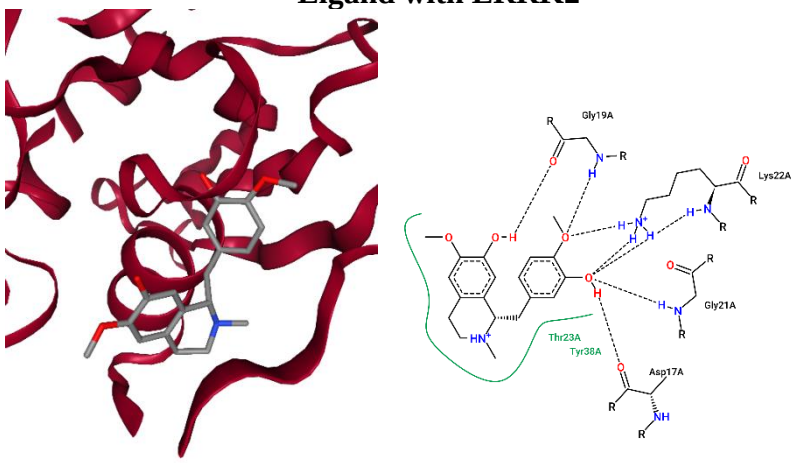
The interaction is the binding of amino acid residues that regulate the binding properties between protein and ligand (Boonserm *et al.*, 2021). In the study, the primary residues on the ligands that play a role in the active side inhibition of LRRK2, Ala160, Asn127, Asp130, Gln131, Lys128, and Phe34 for hydrogen bonds, whereas Lys128 and Phe34 for hydrophobic interaction. Of the 25 plant metabolite compounds of *C. odorata*, (+)-Reticuline, benzyl benzoate and benzyl salicylate have the same binding on one of the amino acids Lys but have different binding distances, although the three compound bind the remaining amino acid differently to the original ligand (Table 4). However, both are predicted to have lower binding energy and pKi compared to native ligand. Thus, it can be concluded that these compounds could act as competitive inhibitors of LRKK2 in the same way as native ligand, although they have different inhibitory mechanisms.

**Table 4. Hydrogen bound and hydrophobic binding of amino acid residues between secondary metabolite of *C. odorata* against LRRK2**

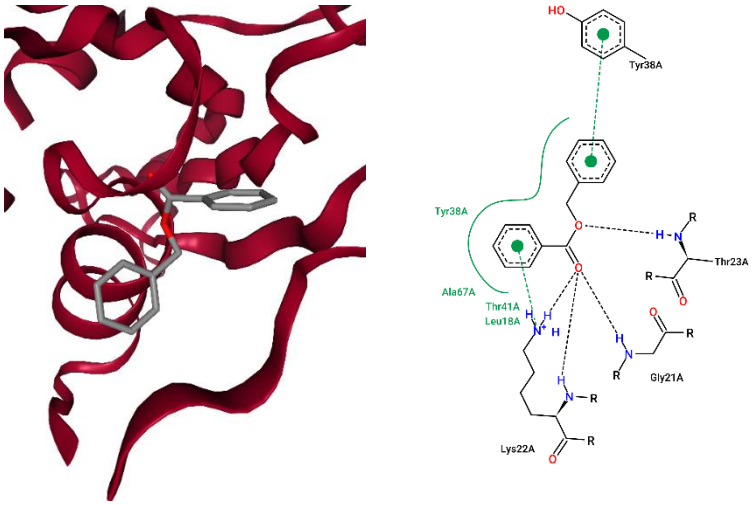
| No. | Compound Code | Hydrogen Bounf Binding on Amino Acid Residues | Hydrophobic Binding on Amino acid Residue |
|---|---|---|---|
| 1. | Mol 1 | Lys22, Gly21 | Thr23, Tyr38 |
| 2. | Mol 6 | Asp17, Gly19, Gly21, Lys22 | Thr23, Tyr38 |
| 3. | Mol 8 | Gly19 | Lys22, Thr41, Tyr38 |
| 4. | Mol 9 | - | - |
| 5. | Mol 10 | Gly19, Lys22 | Gly21 |
| 6. | Mol 11 | Thr23 | Tyr38 |
| 7. | Mol 15 | - | - |
| 8. | Mol 16 | Lys22 | - |
| 9. | Mol 17 | - | - |
| 10. | Mol 19 | Asp130 | Lys128 |
| 11. | Mol 20 | Arg39, Tyr38 | Thr23 |
| 12. | Mol 21 | Gly21, Lys22, Thr23, Thyr38 | Ala67, Leu18, Thr41, Tyr38 |
| 13. | Mol 22 | Gly21, Lys22, Thr23 | Tyr38 |
| 14. | Mol 25 | - | - |
| 15. | Mol 26 | Arg39, His37 | Gly21, Thr23 |
| 16. | Mol 32 | Arg39, Tyr38 | Tyr38 |
| 17. | Mol 34 | Gly21, Lys22 | Gly19, Thr23, Tyr38 |
| 18. | Mol 37 | Lys22, Thr41 | Tyr38 |
| 19. | Mol 38 | - | - |
| 20. | Mol 39 | Gly19, Gly21, Lys22 | Thr23 |
| 21. | Mol 40 | Gly19, Lys22, Thr41 | - |
| 22. | Mol 41 | - | - |
| 23. | Mol 42 | Gly21, Lys22 | Thr23 |
| 24. | Mol 43 | Ser24 | Thr23, Tyr38 |
| 25. | Mol 45 | - | - |
| 26 | Native Ligand | Ala160, Asn127, Asp130, Gln131, Lys128, Phe34 | Lys128, Phe34 |



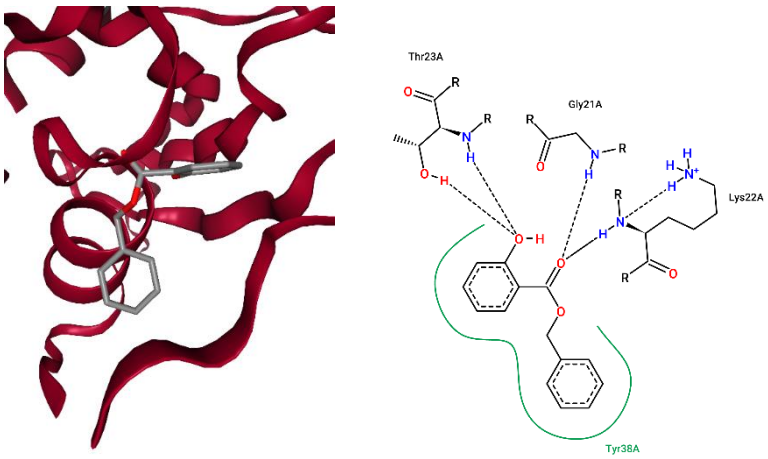

**Ligand with LRRK2**




**(+)-Reticuline with LRRK2**




**benzyl benzoate with LRRK2**




**benzyl salicylate with LRRK2**

**Figure 2. 3D and 2D interactions between native ligand, (+)-Reticuline, benzyl benzoate, and benzyle salicylate with amino acid residues on LRRK2**

The interaction between the ligand and the protein LRRK2 is required as a comparator to be associated with the inhibition mechanism of the selected compounds. The results of the analysis produced a compound, namely (+)-Reticuline, benzyl benzoate and benzyl salicylate, which are part of the metabolite *C. odorata* that has a response as a potentially anti-inflammatory compounds in Crohns' disease. Some studies show that benzyl benzoate can kill bacteria and have an anti-inflammatory effect (Singh, 2022). Based on the research results, the working mechanisms of (+)-Reticuline, benzyl benzoate and benzyl salicylate can suppress inflammatory activity in LRRK2 and be anti-inflammatory in the fight against Crohn's disease.

## Conclusion

According to the results of molecular docking analysis, it can be concluded that (+)-Reticuline, benzyl benzoate and benzyl salicylate, which are found in *C. odorata*, have a high potential as LRRK2 inhibitors. These are demonstrated by binding energy results, lower predictive constant inhibition (pKi), and different inhibitory mechanisms compared to native ligand that can act as LRRK2 inhibitors.

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