Molecular Docking of Zingerone and Gamma-Mangostin to Inhibit MAO-B and Catechol-O-Methyltransferase (COMT) in the Treatment of Parkinson's Disease

Docagem Molecular de Zingerone e Gamma-Mangostin para Inibir MAO-B e Catecol-O-Metiltransferase (COMT) no Tratamento da Doença de Parkinson

Acoplamiento Molecular de Zingerona y Gamma-Mangostín para Inhibir MAO-B y Catecol-O-Metiltransfereasa (COMT) en el Tratamiento de la Enfermedad de Parkinson

Abstract
Currently, there is no drug that has proven neuroprotective properties in Parkinson's disease. The best-known drug is levodopa, which acts as inhibitors of the MAO-B and COMT enzymes involved in dopamine degradation. Although levodopa is the "gold standard" of treatment, as the disease progresses, most patients develop complications from the therapy and side effects. In this sense, the combination of two abundant substances and phytotherapics as alternatives to the use of traditional medicines is approached, namely Zingerone and Gamma-Mangostin. In which they presented favorable results in molecular docking.

Keywords: Parkinson; Zingerone; Gamma-Mangostin; Catecol-O-Metiltransferase.

Resumo
Atualmente, não existe nenhum medicamento que tenha propriedades neuroprotetoras comprovadas na doença de Parkinson. O medicamento mais conhecido é a levodopa que atua como inibidores nas enzimas MAO-B e COMT envolvidas na degradação da dopamina. Apesar da levodopa ser o "padrão ouro" no tratamento, à medida que a doença progrediu, a maioria dos pacientes desenvolveu complicações da terapia e efeitos colaterais. Neste sentido, é abordado a junção de duas substâncias abundantes e fitoterápicos como alternativas ao uso dos medicamentos tradicionais que é o Zingerone e o Gamma-Mangostin. Nos quais apresentaram resultados favoráveis na docagem molecular.

Palavras-chave: Parkinson; Zingerone; Gamma-Mangostin; Catecol-O-Metiltransferase.

Resumen
Actualmente, no existe ningún fármaco que tenga propiedades neuroprotectoras comprobadas en la enfermedad de Parkinson. El fármaco más conocido es la levodopa, la que actúa como inhibidor de las enzimas MAO-B y COMT implicadas en la degradación de la dopamina. Aunque la levodopa es el "estándar de oro" del tratamiento, a medida que avanza la enfermedad, la mayoría de los pacientes desarrollan complicaciones a causa de la terapia y los efectos secundarios. En este sentido, se aborda la combinación de dos sustancias abundantes y fitoterapéuticos como alternativas al uso de las medicinas tradicionales, a saber, la Zingerona y la Gamma-Mangostín. En el cual presentaron resultados favorables en acoplamiento molecular.

Palabras clave: Parkinson; Zingerona; Gamma-Mangostín; Catecol-O-Metiltransferasa.
1. Introduction

ThParkinson's disease is a degenerative disease of the brain, accompanied by symptoms of impaired motor function such as slowness of movement, tremors, rigidity and loss of balance in addition to a wide range of non-motor disorders characterized by decreased cognitive functions, mental disorders, sleep disturbances, pain and sensory disturbances. Movement disorders, in particular dyskinesia (involuntary movements) and dystonia (painful involuntary muscle contractions), contribute to speech and motor disorders and limit the patient's ability in many areas of life. In many cases, the progression of these symptoms leads to disability and the need for assistance. Many people with Parkinson's disease also develop dementia during the course of the disease (Aversano, et al., 2022; Liu, et al., 2022a; Wang & Wang, 2022; Dadu, et al., 2022; Carbunaru, et al., 2018; Farfán, et al., 2021; Doregowska & Rudzińska-Bar, 2019).

Although Parkinson's disease is a movement disorder more common, there are other movement disorders, such as multiple system atrophy, supranuclear palsy progressive, ataxia and dystonia. Some movement disorders share symptoms with Parkinson's disease, such as tremors, slowness of movement and rigidity. All disorders of the movement are characterized by problems in providing diagnosis and treatment of patients, as well as medication ments, especially in low- and middle-income countries (Chaudhuri, et al., 2022; Albin, 2022).

Although there is no cure for Parkinson's disease, its symptoms can be improved with medication, surgery and other therapies. The most used and effective drug is levodopa and are not always available everywhere (Lenka, et al., 2022).

Non-pharmacological treatments, such as rehabilitation, can help improve the patient's condition. right types of physical rehabilitation, including strength training, walking and balance exercises and hydrotherapy can help improve the functionality and quality of life of people with Parkinson's disease (Harro, et al., 2022; Carroll, et al., 2021).

In this work, a molecular docking study is carried out to enable a phytotherapeutic alternative for possible treatment of the disease. The method consists of joining two substances, Zingerone and Gamma-Mangostin, to inhibit the enzymes Monoamine oxidase B (MAO-B) and Catechol-O-Methyltransferase (COMT). As validation follows its comparison with Levedopa.

The article is carried out without any commercial or financial relationship that could be interpreted as a potential conflict of interest. And which in turn is divided into five sections, section 2 deals with the substances present, while section 3 emphasizes the docking technique used in the work. In section 4 we describe the results obtained and finally the conclusion.

2. Chemical Structures

In this work we present a molecular docking approach that makes use of five components: Levedopa, Zingerone, Gamma-Mangostin, MAO-B enzyme and COMT enzyme. The same are covered in this section.

2.1 Levodopa

For nearly 50 years, levodopa (L-DOPA, the levorotatory isomer of the amino acid deoxyphenylalanine) has been the most effective treatment for Parkinson's disease. In terms of effectiveness, it is ahead of any other antiparkinsonian drug and even neurosurgical intervention. It provides the most guaranteed antiparkinsonian effect, causing improvement in almost 100% of patients with Parkinson's disease. Not a single Parkinson's disease patient who seeks to maximize the period of his active life can avoid its intake. Levodopa is considered the "gold standard" for the treatment of Parkinson's disease, its structure is shown in the Fig 1. Increases patient life expectancy (Hansen, et al., 2022; Olszewska, et al., 2022; Fahn & Poewe, 2014).
Furthermore, after ingestion, levodopa enters the brain and is converted into dopamine by the functioning nerve cells, compensating for its deficiency. Current medications contain a combination of levodopa with an enzyme inhibitor. In the early stages of Parkinson’s disease, even small doses of levodopa often have a serious effect, almost completely eliminating the symptoms of parkinsonism. Unfortunately, a few years after starting levodopa treatment in a significant proportion of patients, the drug reaction changes: the duration of action of a single dose decreases (Hansen, et al., 2022; Chen, et al., 2020).

The patient takes the prescribed single dose of levodopa, begins to act after a few minutes - the patient begins the "on" period, characterized by a decrease in parkinsonism symptoms for a few hours, later the effect of the drug weakens, there is a period of "shutdown" with decreased motor activity. Sometimes "on" and "off" are accompanied by violent involuntary movements of a different nature. Stiffnesses also occur when walking, when for a few seconds or minutes the patient is unable to move. For patients with this disorder, turning around or passing through a relatively narrow door can be particularly difficult (Jost, 2022; Hansen, et al., 2022).

Many patients, as the effect of a single dose of levodopa wears off, experience depression, anxiety, sweating, palpitations, increased pain, and non-motor fluctuations (Hansen, et al., 2022; Liu, et al., 2022b; Toloraia, et al., 2022; Lambea-Gil, et al., 2021).

At the maximum dose of levodopa, rapid movements may occur, mainly involving the upper half of the body. This is a kind of limiter, requiring the weakening of dopaminergic therapy, as increasing the dose will lead to an increase in dyskinesias (Shiller & Lemay, 2017; Hong, et al., 2020; Hansen, et al., 2022).

"Off" periods and dyskinesia can be distressing for patients, and they may be tempted to alleviate their condition by taking an emergency dose of levodopa or another antiparkinsonian medication. Often, in a vicious circle, this leads to a worsening of the instability of the patient's condition. Therefore, any change in the treatment regimen, especially with fluctuations, must be agreed with the treating physician. Correction of fluctuations and dyskinesias is a difficult task, even for an experienced specialist, and can only be resolved with close cooperation between the physician and the patient (Hansen, et al., 2022; Kessel, et al., 2019).

### 2.2 Zingerone

Ginger is not just a delicious spice in oriental cuisine, but a product that is in high demand in supermarkets. Popular rumor calls it an all-powerful remedy that strengthens the immune system and attributes to it a long list of indications, although officially ginger is not a medicine (Zhang, et al., 2022).

The use of ginger is offered in many ways: to improve immunity, from nausea, diarrhea and digestive problems,
against inflammations (including those of the skin - as an antiseptic for acne), from colds, for all kinds of "cleansing" of the body (and especially the blood vessels). Ginger compresses are suggested to be applied for rheumatism, headaches and back pain, and the essential oil is indicated for inhalation, baths, rubs and massages to treat psycho-emotional disorders, acute respiratory illnesses and problems with the musculoskeletal system (Zhang, et al., 2022; Dissanayake, et al., 2020; Onyiba, 2022).

Ginger is on the US Food and Drug Administration's (FDA) list of relatively safe substances, but the World Health Organization says nothing about its potential as a drug (Kuanar, et al., 2022).

It is the rhizome, which is often incorrectly called ginger root, and is used for food and medicine. One hundred grams of raw ginger contains about 11-12% of the daily value of manganese, magnesium and vitamin B6, and in dry spice the proportion of vitamin B6 and magnesium is small, but manganese can reach 70% of the daily value. In a teaspoon. A little less calcium in ginger, there are other vitamins (including a lot of vitamins C, E) and minerals, but their percentage of the daily norm for a person is very small. In terms of nutritional value, ginger has a little more fiber than protein and a little more protein than sugars, so it's unlikely to harm a person (although it's hard to eat a lot of it) (Wang, et al., 2019; Taghavi, et al., 2021).

Among the specific components of ginger are gingerol (in raw ginger, possibly responsible for the pungency) and its product zingerone (which gives dried or cooked ginger a sweet taste), Figure 2, named in his honor. Ginger also contains the enzyme zingibain, which regulates many processes in the plant by breaking down (Verma & Bisen, 2022) proteins.

**Figure 2 - Three-dimensional representation of Zingerone.**

Source: Authors.

### 2.3 Gamma-Mangostin

Among the compounds that can be extracted from mangosteen bark, the most abundant is the polyphenolic xanthone known as alpha-mangostin, followed by several other xanthones, such as Beta-mangostin, Gartanine and Gamma-Mangostin (Mahmudah, et al., 2021; Do & Cho, 2020b).

Gamma-Mangostin has a powerful anti-inflammatory effect on structural brain cells. This suggests the possibility of its use in inflammatory diseases of the brain, e.g. Alzheimer's disease and Parkinson's disease, promoting the protection of nerve cells from destruction and reducing inflammation caused by the destruction of neurons (Do & Cho, 2020a; Do & Cho, 2020b).

Inflammatory processes are recognized as the cause of most degenerative and fatal diseases, including cardiovascular disease, cancer, rheumatoid arthritis, lupus, Crohn's disease and ulcerative colitis (Chang & Yang, 2012; Krishnamachary, et al., 2019).
Allopathic anti-inflammatory drugs are known to reduce inflammation by inhibiting inflammatory enzymes such as cyclooxygenase-2 (COX-2). Unfortunately, these drugs also destroy the enzyme cyclooxygenase-1 (COX-1), which is necessary for the production of group 1 prostaglandins, which are an important part of cellular immunity and reduce blood viscosity (Attiq, et al., 2018; Ju, et al., 2022).

Gamma-Mangostin, on the other hand, selectively blocks COX-2 and does not affect the work of COX-1, so it does not cause any known side effects (Chang & Yang, 2012; Nakatani, et al., 2002). For this reason, it was chosen as the substance for this work.

**Figure 3** - Three-dimensional representation of Gamma-Mangostin.

2.4 MAO-B enzyme

It is common to start the treatment of Parkinson's disease with drugs that have a weaker effect, but are also neuroprotective, that is, delay the course of the disease. These are called MAO-B Inhibitors, glutamate antagonists and dopamine agonists. These are specific groups of drugs that the neurologist chooses, according to the main symptoms, the specific patient and their form of disease and associated diseases (Goetz, et al., 2002) (Kuusisto, et al., 2010) (Hauser, et al., 2016).

**Figure 4** - Three-dimensional representation of MAO-B.
Blockade of the brain enzyme MAO B, Fig 4, being fundamental at an early stage, is addressed in this research. It is worth noting that the use of a weaker dose is due to the side effects of the drug.

2.5 Catechol-O-Methyltransferase Enzyme (COMT)

Cognition is a complex process, representing the totality of all skills and mental processes associated with knowledge. The activity of dopaminergic neurons in the prefrontal cortex is the biological substrate underlying cognitive functions (Chau, et al., 2018; Lohani, et al., 2019).

One of the best-studied genes associated with cognitive impairment is the gene that encodes COMT, Fig 5, an enzyme that plays an important role in dopamine metabolism and in the modulation of various brain functions. The gene encoding COMT has a large number of variants, this phenomenon is called polymorphism. As a result of genetic mutations, the working process of dopamine systems in the prefrontal cortex of the cerebral hemispheres changes (Käänenmäki, et al., 2010; Hall & Guyton, 2011).

**Figure 5 - Three-dimensional representation of COMT.**

COMT is being studied as a target for many neuropsychiatric disorders, including dementia, schizophrenia, bipolar personality disorder, and Alzheimer's disease (Juárez-Cedillo, et al., 2021; Pigoni, et al., 2018).

Alzheimer's disease is the most common dementia associated with cognitive impairment. Cognitive impairment in Alzheimer's disease begins slowly, with a gradual deterioration in memory, thinking, and reasoning ability. Cognitive function is influenced by complex interactions between various genetic, epigenetic, developmental and environmental factors (Yan, et al., 2016).

COMT is an enzyme that activates catechol substrates involved in catecholamine metabolism. Its main function was to metabolize dopamine, catecholamines, regulate behavioral responses, emotions, learning processes and participate in the noceptive system, pain perception system (Vasileva, et al., 2021).

This enzyme is located in many structures of the brain, including the prefrontal cortex, whose functions are the processing of noceptive information from neurons in the spinothalamic tract. Neurons in this pathway provide information to the central nervous system about the occurrence of pain (Hall & Guyton, 2011).

With the development of stressful situations, the level of dopamine changes, if its level is excessive, disturbances in the work of neurons occur. If a person has a high activity of the COMT enzyme, he copes better with problems and stressful situations, and excess dopamine is inactivated. Furthermore, people with high COMT activity are able to react less strongly to pain because they have a higher threshold of pain excitability. They are easier to tolerate surgery, less likely to suffer from
tension headaches. People with low COMT enzyme activity have pronounced analytical skills in terms of devising a strategy, calculating the probability of events and also synthesizing the information received, good memory faster, but their capabilities are revealed only during the absence of stressful influence (Hall & Guyton, 2011).

COMT inhibitors are commonly used as an adjunct to levodopa in patients with Parkinson’s disease to relieve symptoms of exhaustion and pain (Li, et al., 2022).

3. Methodology

Molecular dynamics is a technique that simulates the complete physical behavior of the atoms of the system over time and from these simulations, calculates thermodynamic properties using the formalism of statistical mechanics (Alnajjar, et al., 2021).

Due to the effort involved in a detailed estimation of the affinity between two molecules in solution, molecular docking is an alternative to evaluate the properties of the docking in three-dimensional space and estimate its (Li, et al., 2021) binding affinity, as shown in the Figure 6.

**Figure 6 - Enzyme-Linker Interaction.**

![Enzyme-Linker Interaction](image)

Source: Authors.

Where the equilibrium constant is defined as the quotient of the concentration of the complex by the product of the concentrations of the reactants (ligand and target in a 1:1 ratio), according to the equation equation 1 (Saraiva, et al., 2020).

\[ K = \frac{[\text{complex}]}{[\text{binder}][\text{target}]} \]  

(1)

According to the equation 2, this equilibrium constant is associated with a change in free energy so that the more negative the change in energy, the greater the equilibrium constant and the greater the affinity (Reyes-García, et al., 2021) (Saraiva, et al., 2019).

\[ K = e^{-\frac{\Delta G}{RT}} \]  

(2)

In this research, the following compounds were used:

**Step 1:**
- MAO-B + Levedopa
- MAO-B + Zingerone + Gamma-Mangostin

Step 2:
- COMT + Levedopa;
- COMT + Zingerone + Gamma-Mangostin

To prepare the docking, these molecules were acquired from (PubChen, 2022) and subjected to simulations in (Tools, 2022). In the end, there are the receptor-ligand complexes formed and the energy released in the process. After docking, the results were submitted to (Systems, 2022), for a detailed visualization between such molecules subjected to the docking process.

4. Results

To demonstrate the result found, this section will be divided into two steps, the first referring to the action of the ligands with the MAO-B enzyme and the second with the COMT enzyme. The results shown will be in the form of a table and final three-dimensional structure.

4.1 Step 1

The Table 1 shows the results of affinity docking between MAO-B receptor and Levedopa ligand. These values are determined through the fit energy using the equation 1. It is observed that it obtained a result of -6 Kcal/mol, reflecting the value of the gold standard used in the treatment of Parkinson's disease.

<table>
<thead>
<tr>
<th>Mode</th>
<th>affinity (Kcal/mol)</th>
<th>dist from rmsd lb</th>
<th>best mode rmsd u.b.</th>
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<td>52.397</td>
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<td>5.080</td>
<td>7.649</td>
</tr>
<tr>
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<td>6.663</td>
<td>7.899</td>
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<tr>
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<td>-5.6</td>
<td>52.293</td>
<td>52.911</td>
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<tr>
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<td>42.179</td>
<td>43.593</td>
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<tr>
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<td>-5.4</td>
<td>41.517</td>
<td>43.013</td>
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</table>

Source: Authors.

The Figure 7 shows the final state of the interaction after docking between MAO-B and Levedopa. Where the larger structure, in green, represents the MAO-B enzyme and the smaller structures is the Levedopa ligand.
Figure 7 - Final representation of MAO-B and levodopa docking.

Source: Authors.

In the Table 2 that represents the iteration affinity between MAO-B receptor and proposed ligand, a value of -7.9 kcal/mol is observed. This value compared to the Table 1 shows a more favorable balance in the production of the drug.

Table 2 - Affinity Result between MAO-B and Zingerone + Gamma-Mangostin.

<table>
<thead>
<tr>
<th>Mode</th>
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<td>36.656</td>
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<td>4</td>
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<td>7.839</td>
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<td>32.740</td>
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<td>32.818</td>
<td>35.346</td>
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</table>

Source: Authors.

The Figure 8 shows the three-dimensional binding of the proposed method with the MAO-B enzyme. In which the larger structure, in pink, represents the MAO-B enzyme and the smaller ones are the Zingerone and Gamma-Mangostin ligands.

Figure 8 - Final representation of MAO-B and Zingerone and Gamma-Magostin docking.

Source: Authors.
4.2 Step 2

Continuing, the Table 3 shows an affinity of -6 kcal/mol, again, between COMT receptor and Levedopa ligand.

**Table 3** - Affinity result between COMT and Levedopa.

<table>
<thead>
<tr>
<th>Mode</th>
<th>affinity (Kcal/mol)</th>
<th>dist from rmsd lb</th>
<th>best mode rmsd u.b.</th>
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</table>

Source: Authors.

The Figure 9 shows the image of the established crystallographic model. The larger structure, in gray, represents the COMT enzyme and the smaller one, the Levedopa ligand.

**Figure 9** - Final representation of the docking between COMT and Levopoda.

Source: Authors.

The Table 4 shows an affinity of -8.9 kcal/mol as a result between COMT receptor and ligands zingerone and gammamangositin.
Table 4 - Affinity result between COMT and zingerone and gamma-mangostin.

<table>
<thead>
<tr>
<th>Mode</th>
<th>affinity (Kcal/mol)</th>
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</table>

Source: Authors.

The Figure 10 shows the image of the established crystallographic model. The largest structure, in green, represents the COMT enzyme and the smallest are the Zingerone and Gamma-Mangostin ligands.

Figure 10 - Final representation of COMT + Zingerone + Gamma-Mangostin docking.

Source: Authors.

5. Conclusion

It is believed that this work, in molecular docking, constitutes a positive strategy to guarantee access to the treatment of Parkinson's disease, enabling an accessible medication for society.

The strategy is to establish a treatment consisting of blocking the enzyme that degrades dopamine, in order to control the production of dopamine and maintain the effect of dopamine in the brain.

According to the results in the affinity tables, it is observed that the proposed strategy presents better results when comparing the treatment of MAO-B and COMT with levodopa.

The computationally approached method is an alternative to the use of levodopa, which has side effects with prolonged use.

Because the proposed method does not present side effects, it can be applied in higher doses at the beginning of the treatment of Parkinson's disease.

As future work, it is suggested to apply it in human beings under the supervision of specialists. Subsequently, large-
scale drug development.

Acknowledgments

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PubChen. (2022). data deposited or computed by computer.


