



## In-Silico Study and Antioxidant Capacity from Jamaican Cherry, Red Ginger, Thyme Combination as Multi-target Nutraceutical for Chronic Obstructive Pulmonary Disease

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### ARTICLE INFO

#### Article history:

Received 31 July 2025

Revised 02 May 2026

Accepted 14 June 2026

Published online 30 June 2026

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**Citation:** Sayyidah S, Nurhasanah N, Tjaja LAP, Yunarto N. In-Silico Study and Antioxidant Capacity from Jamaican Cherry, Red Ginger, Thyme Combination as Multi-target Nutraceutical for Chronic Obstructive Pulmonary Disease. *Jurnal Kefarmasian Indonesia*. 2026;16(1):75-94.

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### ABSTRACT

Chronic obstructive pulmonary disease (COPD) is one of the health concerns in Indonesia with 4.8 million people suffer from COPD. Global Adult Tobacco Survey Indonesia reported 70.2 million active smokers in 2021. This trend raises concerns about the future trajectory of COPD cases in the country. COPD is a chronic condition that impairs the lower respiratory system due to progressive stimuli that initiate oxidant-antioxidant imbalance contributes to dysregulated inflammation cascade response. Some natural ancient plants that had been used to relieve respiratory discomfort are Ginger (*Zingiber officinale* var. Rubrum) and Thyme (*Thymus vulgaris*). In order to give synergetic mechanism to imboost antioxidant capacity also mitigate COPD symptoms, this research combine both plants with Jamaican Cherry (*Muntingia calabura*) leave as a powder drink formulation. This study is conducted to analysis the potential of these combination through *in-silico* along with antioxidant capacity evaluation from each formulation. Total 75 compounds that meet Lipinski rules from the plants had been screened to identify the overlapping genes. Based on Network Pharmacology and validated with molecular docking analysis the potential targets based on the best degree value were IL-8(-11.2 kcal/mol), TNF- $\alpha$  (-8.9 kcal/mol), MMP-9(-7.7 kcal/mol) and IL-6(-7 kcal/mol). The highest binding affinity compound was 3'-hydroxydaidzein from Jamaican Cherry. The powder drink formulation made through wet granulation and antioxidant evaluated using DPPH(1,1-diphenyl-2-picrylhydrazyl) method. The antioxidant capacity was IC<sub>50</sub> 39.99 ppm; 36.10 ppm ; and 28.30 ppm for F1, F2 and F3 respectively compared to ascorbic acid 13.03 ppm. To conclude, this natural combination nutraceutical has potential as supportive natural remedy for COPD.

**Keywords:** COPD; Ginger; *Muntingia calabura*; Nutraceutical; Thyme

## INTRODUCTION

Non-communicable diseases (NCDs) are responsible for roughly 70% of deaths globally, with Chronic Obstructive Pulmonary Disease (COPD) standing as the fourth most common cause of mortality and accounting for an estimated 3.5 million fatalities worldwide in 2021.<sup>1</sup> Within Indonesia, the disease burden is equally alarming, with approximately 4.8 million people equivalent to 5.6% of the national population living with COPD, underscoring its significance as a major public health concern.<sup>2</sup> A key driver of this prevalence is tobacco use, which continues to exert a dominant influence on respiratory health outcomes. Data from the Ministry of Health of the Republic of Indonesia (2021) indicate that smoking-related disease burden affects up to 6.8 million Indonesians.<sup>3</sup> Complementing this, the Global Adult Tobacco Survey (GATS) documented that 34.5% of adults representing approximately 70.2 million individuals are active tobacco users, while 74.2% are regularly exposed to secondhand smoke.<sup>4</sup> Collectively, these figures point toward a persistent and escalating trajectory of COPD risk within the country.<sup>5</sup>

At its core, COPD is a long-term, progressive condition of the respiratory system defined by irreversible airflow obstruction arising from sustained airway inflammation and tissue remodeling.<sup>6</sup> From a molecular standpoint, repeated exposure to cigarette smoke and other harmful particulates triggers oxidative stress, disrupting the homeostatic balance between oxidative and antioxidative mechanisms. This imbalance subsequently activates critical pro-inflammatory signaling cascades, namely nuclear factor-kappa B (NF- $\kappa$ B), mitogen-activated protein kinase (MAPK), and the NLRP3 inflammasome.<sup>7</sup> Downstream activation of these pathways drives the overproduction of inflammatory mediators including TNF- $\alpha$ , IL-6, and IL-17 which perpetuate chronic inflammation and compromise immune regulation. Concurrent dysregulation of the protease–

antiprotease equilibrium accelerates extracellular matrix breakdown, ultimately giving rise to emphysema and irreversible airway remodeling.<sup>8</sup> Furthermore, structural alterations such as goblet cell hyperplasia, excessive mucus production, and deteriorating mucociliary function collectively aggravate airflow obstruction and impair pulmonary gas exchange.<sup>9,10</sup>

Existing pharmacological interventions for COPD encompassing corticosteroids,  $\beta_2$ -agonists, and antimuscarinic drugs are largely limited to managing symptoms rather than correcting the underlying pathological mechanisms.<sup>10</sup> Prolonged corticosteroid therapy is further complicated by the development of steroid resistance in advanced disease stages, a phenomenon attributable to diminished histone deacetylase-2 (HDAC2) activity under conditions of oxidative stress.<sup>11</sup> Adverse systemic effects associated with long-term corticosteroid use including immunosuppression, bone density loss, and heightened cardiovascular risk pose particular concerns for older patient populations.<sup>12</sup> These therapeutic shortcomings emphasize the pressing need for alternative or adjunctive treatment approaches capable of simultaneously addressing multiple pathogenic mechanisms while maintaining a favorable safety profile.

In this context, natural products have attracted growing interest as multi-target therapeutic candidates owing to their complex phytochemical profiles. Nevertheless, despite considerable research into individual medicinal plants, the potential synergistic or additive effects of combining multiple phytochemicals in the management of COPD remain largely unexplored. Notably, no published study has yet systematically examined the combined therapeutic potential of *Zingiber officinale*, *Muntingia calabura*, and *Thymus vulgaris* for COPD, nor characterized their collective mechanisms through a network pharmacology framework a gap that the present study seeks to address.

The rationale for selecting these three plant species lies in their mechanistic complementarity with respect to COPD pathogenesis. *Zingiber officinale* harbors key bioactive constituents gingerol, shogaol, and zingerone that are well documented for their antioxidant and anti-inflammatory activities, particularly via suppression of NF- $\kappa$ B signaling pathways.<sup>13-15</sup> *Muntingia calabura* leaves are rich in flavonoids and phenolic compounds capable of attenuating inflammatory processes, including those mediated by IL-17, while also demonstrating marked antioxidant potential.<sup>16-18</sup> *Thymus vulgaris*, in turn, is recognized for its antimicrobial and antioxidant properties, with additional evidence supporting its capacity to promote mucociliary activity and facilitate mucus clearance in respiratory disorders.<sup>19,20</sup> On this basis, the combined use of these plants is hypothesized to produce complementary therapeutic effects by concurrently targeting oxidative stress, persistent inflammation, and mucociliary dysfunction three central features of COPD pathogenesis.

Given the multifactorial etiology of COPD, therapeutic strategies targeting multiple molecular pathways are more likely to yield meaningful clinical outcomes. Network pharmacology offers a systems biology framework that enables comprehensive analysis of bioactive compound-target interactions within complex disease networks, making it particularly well-suited for investigating multifactorial conditions such as COPD. Accordingly, the present study sought to evaluate the binding affinity and molecular target profiles of selected bioactive compounds from *Zingiber officinale*, *Muntingia calabura*, and *Thymus vulgaris* through an in silico network pharmacology approach, while also exploring the development of a nutraceutical powder formulation with antioxidant properties as a potential adjunctive strategy for COPD management.

## METHODS

### 1. Compound Collection and Filtering

Chemical constituents of *Zingiber officinale*, *Muntingia calabura*, and *Thymus vulgaris* were identified through peer-reviewed phytochemical studies and supported by public databases including PubChem and CMAUP. Only previously reported compounds were included.<sup>2</sup> Structural information and canonical SMILES were retrieved from PubChem and converted into SDF format using Open Babel. Drug-likeness screening was performed using SwissADME based on Lipinski's Rule of Five with the following criteria:

- Molecular weight  $\leq 500$  Da
- LogP  $\leq 5$
- Hydrogen bond donors  $\leq 5$
- Hydrogen bond acceptors  $\leq 10$

A total of 75 compounds was initially identified. After Lipinski filtering, 65 compounds passed the criteria and were selected for further analysis. Compounds with poor gastrointestinal absorption or more than one Lipinski violation were excluded from further analysis.

### 2. Target Prediction

Potential molecular targets were predicted using CMAUP and SwissTargetPrediction to improve prediction coverage and reduce bias. The inclusion criteria were:

- Probability  $\geq 0.1$  in SwissTargetPrediction
- High-confidence interactions (CMAUP)

Duplicate targets were removed before further analysis. Duplicate targets from both platforms were merged and standardized.

### 3. COPD Gene Collection

COPD-associated genes were retrieved from DisGeNET and GeneCards using the keyword: "Chronic Obstructive Pulmonary Disease" Filtering criteria:

- DisGeNET score  $\geq 0.1$
- GeneCards relevance score  $\geq 10$

A total of 929 COPD-associated genes were obtained after filtering and duplicate removal.

#### 4. Network Construction

The intersection between compound-related targets and COPD-associated genes was identified using Venn diagram analysis. A total of 278 overlapping genes were obtained and used to construct the network using Cytoscape 3.10.3. Topological analysis was performed using the CytoHubba plugin with the Maximal Clique Centrality (MCC) algorithm. The top 10 hub genes were selected based on the highest MCC scores.

#### 5. Protein-Protein Interaction and Enrichment Analysis

PPI analysis was performed using STRING with a minimum confidence score  $\geq 0.7$ . Functional enrichment analysis (GO and KEGG) was conducted using DAVID with:

- p-value  $< 0.05$
- FDR  $< 0.05$
- Benjamini-Hochberg correction

#### 6. Molecular Docking Preparation

Protein structures were obtained from the Protein Data Bank (RCSB). Only structures with resolution  $< 2.0 \text{ \AA}$  were selected. Protein preparation was performed using AutoDock Tools by removing water molecules, adding hydrogen atoms, and assigning Gasteiger charges. Ligands were minimized using Open Babel in PyRx.

#### 7. Docking Validation

Docking validation was performed using native ligands. The docking protocol was considered valid when  $\text{RMSD} \leq 2.0 \text{ \AA}$ . Grid box parameters were defined based on native ligand binding sites. For proteins without native ligands, binding sites were predicted using the COACH tool.

#### 8. Virtual Screening

Virtual screening was conducted using AutoDock Vina in PyRx. Binding affinity was evaluated based on the lowest binding energy (kcal/mol).

#### 9. Interaction Analysis

Protein-ligand interactions were analyzed using Discovery Studio

Visualizer to identify hydrogen bonds and hydrophobic interactions. Intersection analysis between compound-predicted targets and COPD-associated genes was performed using a Venn diagram approach. The overlapping genes were identified as potential therapeutic targets and were subsequently used for network construction and protein-protein interaction (PPI) analysis.

#### 10. Nutraceutical Formulation Study Material

Jamaican cherry leaves were purchased and extracted at Research Center for Medicinal and Aromatic Plants (Balitro) Kemtan, Cimanggu Bogor. Determination were conducted at Padjajaran University Central Laboratory. Ginger liquid (dissolved) was purchased at PT. Phytochemindo. Thyme extract was made and determined by Unit Pelaksana Fungsional Pelayanan Kesehatan Tradisional Tawangmangu RSUP Dr. Sardjito. Excipients including PVP (polyvinylpropylene) K30, maltodextrin and lactose-monohydrate Caesar Loretz GmbH. The liquid stevia (Beeru) was purchased at Beeru official store. The analysis material including Methanol (merck), DPPH (1,1-diphenyl-2-picrylhydrazyl) and Vitamin C (Sigma Aldrich).

#### Equipment.

Mortar and stamper, digital weighing scale (Ohaus), analytical weighing scale (AND), beaker glass (PyRex), mesh 12, mesh 140, Heating and Drying Oven (Memmert), whatmann filter paper, Spectrophotometer UV-Vis (Spectroquant Pharo 300), pH meter (APC).

#### Procedure

The nutraceutical formulation was conducted at the Compounding and Dispensing Pharmacy Laboratory of STIKes Widya Dharma Husada Tangerang. The formulation of powder nutraceutical can be seen at the table below.

**Table 1.** Nutraceutical Powder Drink Formulation

Material	Formula % (b/v)			Usability
	FI	FII	FIII	
Jamaican cherry extract	1	2	3	Active ingredients
Ginger Liquid	16	16	16	
Thyme Extract	3	2	1	
PVP	4.5	4.5	4.5	Binder
Maltodextrin	2	2	2	Filler
Lactose	70.5	70.5	70.5	Filler
Stevia	3	3	3	Sweetener

### Plant Extracts

Fresh Jamaican cherry leaves were dried at room temperature. 1000 grams of Jamaican cherry leaf then powdered and soaked in 5 liters of 50% ethanol for 3 days which the residues were filtrated every 24 hours. The collected filtrate was evaporated using a rotary evaporator at 50°C until a concentrated extract was obtained. On the other hand, thyme extract was made from the whole plant part of the thyme herb. After the plant was collected, cleaned and dried at room temperature, 1000 grams of simplicia was then macerated using ethanol 70%. The length of maceration and evaporation temperature parameter were same as Jamaican cherry extract process.

### Phytochemical Screening

This procedure was done according to the Indonesian Herbal Pharmacopeia 2<sup>nd</sup> Edition, including secondary metabolites screening such as alkaloids, polyphenols, flavonoids, tannin, saponin, and terpenoids.<sup>27</sup>

### Nutraceutical Formulation

This nutraceutical was made using wet granulation method<sup>28</sup>. Binder solution volume: 15mL, mixing time 10-15 minutes mixing speed 200 rpm, drying temperature 60°C. Relative humidity: ambient conditions PVP was added into warm water in a mortar, let the PVP absorbed the water then mix with stamper gently. Add the active ingredients, and then mix the mixture until it is homogeneous. After that, add lactose and continue mixing, then add Maltodextrin gradually. Last, add stevia

into the mixture and sieve with mesh number 12. Dry the sieved mixture using oven at 60°C for 60 minutes. Repeat the sieving process with mesh 40 and put it in a cool place, and keep it from direct sunlight.

### Physical Evaluation

The physical evaluation of nutraceutical powder includes organoleptic test, water content, flow rate and repose angle, dissolution rate, pH test, and homogeneity.

### Organoleptic

Organoleptic evaluation was done by visual observation, which comprises shape, color, smell, and taste.

### Flow rates and Repose Angle

25 grams of sample was placed into a closed funnel at the flow tester meanwhile, millimeter paper was prepared as a base to collect the sample. Count the time start when the funnel opened to allow the powder to flow down into the paper until all the sample converged at the paper. Measure the height and diameter of sample. The repose angle can be calculated as  $\tan(\theta)$  from the height divided with half of diameter.

### Water Content

Put 2 grams of sample in a closed container (weight measured). Put it in an oven at a temperature of 105°C for about 3 hours, let it cool down then weight the whole place. Repeat the same procedure with 1 hour inside the oven. This step was repeated until the weight was constant. Count the percentage of the weight differences between the initial weight and the constant weight.

### Dissolution rate

Add 5 g of the sample in 50 ml of warm water and stir until homogeneous. Count the time until the powder completely dissolved.

### Homogeneity Evaluation

Dissolved 1 g of sample with 10 ml of warm water. Add one drip of the mixture into the object glass then covered with cover glass. Observe the homogeneity under the microscope.

#### DPPH Assay

DPPH and Reference Standard Preparation. The antioxidant capacity was measured using DPPH assay according previous method with slight modification.<sup>29</sup> 5 mg of standard DPPH was dissolved in 100 mL of methanol to make a 50 µg/mL DPPH standard solution. The reference standard was made from 5 mg of Vitamin C in 50 mL of methanol to create serial vitamin c concentration at 5, 10, 15, 20, and 25 µg/mL. 1 mL from each concentration of vitamin C was mixed with 2 mL of DPPH 50 µg/mL while methanol was used as a blank. The mixture was incubated for 30 minutes then measured at 517 nm.

The scavenging activity through IC<sub>50</sub> value was calculated by interpolating linear regression equation from calibration curve. X axis as concentration while Y axis represented as percentage of immersion.

#### Powder Nutraceutical Scavenging Activity

50 mg of sample was dissolved with 50 mL of methanol with sonication for 10 minutes to obtain 1000 µg/mL solution. Serial dilutions of sample were made at 20, 40, 60, 80, and 100 µg/mL. 1 mL from each concentration was mixed with DPPH 50 µg/mL solution. The next step was the same as described for vitamin C scavenging activity. All computational analyses were conducted under standardized parameters to ensure reproducibility.

## RESULTS AND DISCUSSION

### In-silico study

#### 1. Active Compound Collection and Filtering

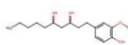
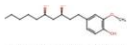
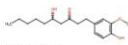
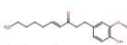
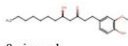
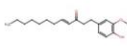
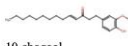
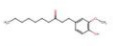
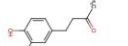
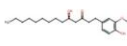
Chemical constituents of *Muntingia calabura*, *Thymus vulgaris*, and *Zingiber officinale* were collected from previously

reported phytochemical studies, primarily derived from 50% ethanol extracts.

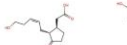
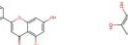


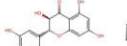
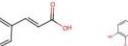


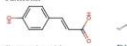
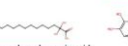


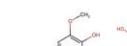



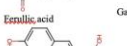
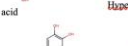


A total of 42 compounds from Jamaican cherry, 22 compounds from thyme, and 11 compounds from red ginger were initially identified. After applying Lipinski's Rule of Five using Swiss ADME as a proxy for oral bioavailability, 34 compounds (Jamaican cherry), 20 compounds (thyme), and 11 compounds (red ginger) were retained for further analysis. To avoid redundancy, identical compounds present across different plant species were identified and removed prior to downstream analysis.

Although the experimental extraction in this study used 70% ethanol, compound identification was based on literature data (50% ethanol extract). Both solvent systems are widely used for extracting polar-semi-polar compounds such as flavonoids and phenolics; therefore, the selected compounds remain representative and relevant. The representative structures from each plant can be seen at tables below.

**Table 2.** Red Ginger Compounds<sup>17,30</sup>

Red Ginger Compounds			
			
			
			

**Table 3.** Thyme Compounds<sup>35,36</sup>

Thyme Compounds			
			
			
			
			
			

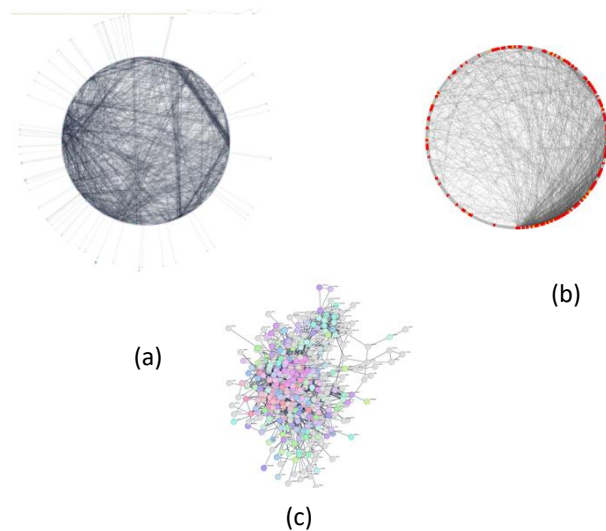
**Table 4.** Jamaican cherry Compounds <sup>19,31-34</sup>

Kersen Compounds			

The amount of each component as per Table 5 shows below.

Table 5. Target Amount Each Substance	
Substance	Target Genes
Jamaican cherry	1849
Thyme	117
Red Ginger	87
COPD	929

All the target was inputted into Cytoscape with 0,9 confidence. The new network can be seen in Picture 1.



**Figure 1.** Network Pharmacology of Jamaican cherry-Ginger-Thyme's target towards COPD. (a) COPD's network. (b) Jamaican cherry-Ginger-Thyme's Network. (c) Intersection Network Pharmacology

### Protein-Protein Interaction (PPI) and Target Intersection

Predicted targets from all compounds were compiled and compared with COPD-associated genes obtained from DisGeNET and GeneCards.

A Venn diagram-based intersection analysis was performed to identify overlapping targets between compound-related targets and COPD-associated genes.

A total of 278 overlapping genes were identified, representing potential therapeutic targets relevant to COPD.

These overlapping genes were subsequently used to construct the PPI network using Cytoscape 3.10.3 and further analyzed using the CytoHubba plugin. There were 278 genes target between the herbs combination and COPD network. Next, we used installed plug in MCODE then choose the best *p*Value.<sup>37</sup> Picture 2 shows there were 35 related genes.

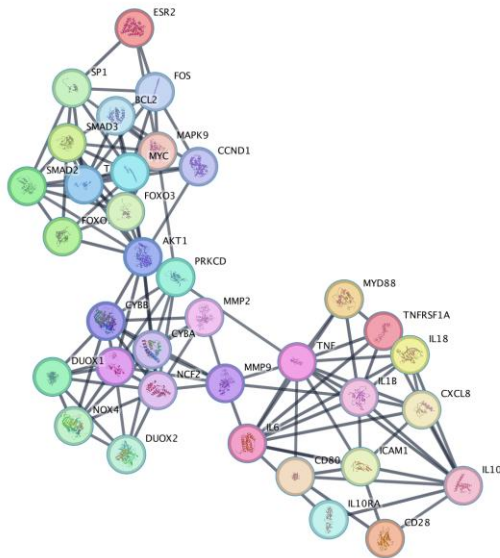


Figure 2. The Best Clustered Network

The topological parameters analysis can be found at Table 6 below.

Table 6. Topological Analysis

Genes	Betweenness Centrality	Closeness Centrality	Degree
AKT1	0,457810682	0,58620689	13
TNF	0,343678464	0,51515151	11
MMP9	0,155754946	0,44736842	8
IL6	0,074951193	0,43037974	10
MAPK9	0,061309554	0,38202247	9
CYBA	0,060712497	0,47887323	10
NCF2	0,060712497	0,47887323	10
NCF4	0,060712497	0,47887323	10
IL10	0,046371276	0,38202247	9
CYBB	0,043719032	0,47222222	9
PRKCD	0,041554114	0,38636363	5
IL1B	0,037144555	0,425	9
TP53	0,03643635	0,44738421	10
SMAD3	0,032824602	0,44155844	9
MYC	0,025591959	0,43037974	8
ICAM1	0,02067524	0,36956521	6
SMAD2	0,013152486	0,425	7
FOS	0,013104242	0,34	7
SP1	0,012215805	0,34	7
CD80	0,012199728	0,36170212	4
CCND1	0,011161993	0,41463414	5
BCL2	0,00731894	0,41975308	5
FOXO3	0,006826622	0,425	6

FOXO1	0,006470116	0,41975308	5
IL18	0,001114082	0,36956521	6
CXCL8	0,000742721	0,36956521	6
NOX4	0,000356506	0,34343434	6
DUOX1	0,000356506	0,34343434	6
CD28	0,000297089	0,28571428	3
MMP2	0	0,38636363	5
TNFRSF1A	0	0,36170212	4
MYD88	0	0,35789473	4
DUOX2	0	0,34	5
IL10RA	0	0,31192660	2
ESR2	0	0,29059829	3

Topological analysis should be performed in order to analyze which gene. Betweenness is defined as the flow of information through a particular node in the network; centrality exposes distance of the flow of information between two nodes, while degree represents how many interactions between different nodes and edges of the network. If the nodes have high degree and betweenness, it determine critical hubs in the PPI.<sup>38</sup> All these genes were then analyzed through David Bioinformatics <https://davidbioinformatics.nih.gov/> to explore the possibilities of gene enrichment.

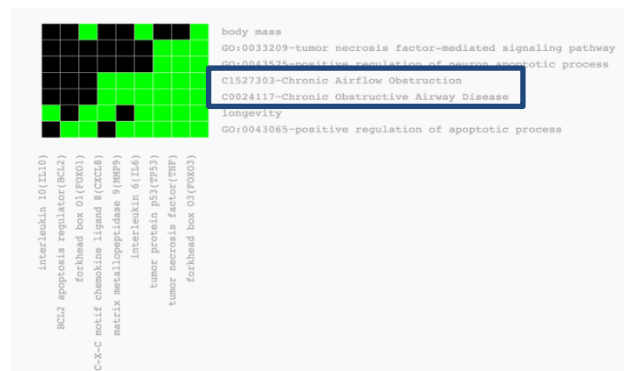


Figure 3. Cluster Annotation from David Bioinformatics related to COPD.

In terms of this annotation, six genes were revealed related to COPD. They were IL-6, TNF, FOXO3, TP53, CXCL-8 or IL-8 and MMP-9 as per below picture.

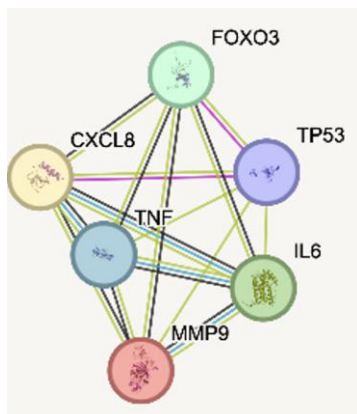
**Related Terms Evidence**

Kappa: 1.0

Summary Table	Chronic Obstructive Airway Disease	
	+	-
Chronic Obstructive Airway Disease	6	0
	0	28

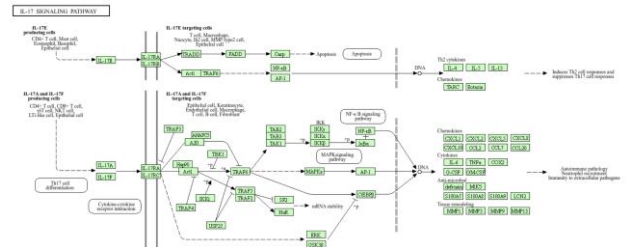
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Chronic Obstructive Airway Disease & Chronic Obstructive Airway Disease
<a href="#">interleukin 6(IL6)</a>
<a href="#">tumor necrosis factor(TNF)</a>
<a href="#">forkhead box O3(FOXO3)</a>
<a href="#">tumor protein p53(TP53)</a>
<a href="#">C-X-C motif chemokine ligand 8(CXCL8)</a>
<a href="#">matrix metalloproteinase 9(MMP9)</a>



**Figure 4.** Target Genes from Herbal Combination of Jamaican cherry-Red Ginger-Thyme

Based on KEGG Pathways enrichment results above, it was concluded that these herbal combination of Jamaican cherry-Red Ginger-Thyme has potential to interfere the COPD through this pathway. This findings supported by the previous researchers that shows IL-17a was the pivotal pathway related to COPD progression.<sup>39</sup>



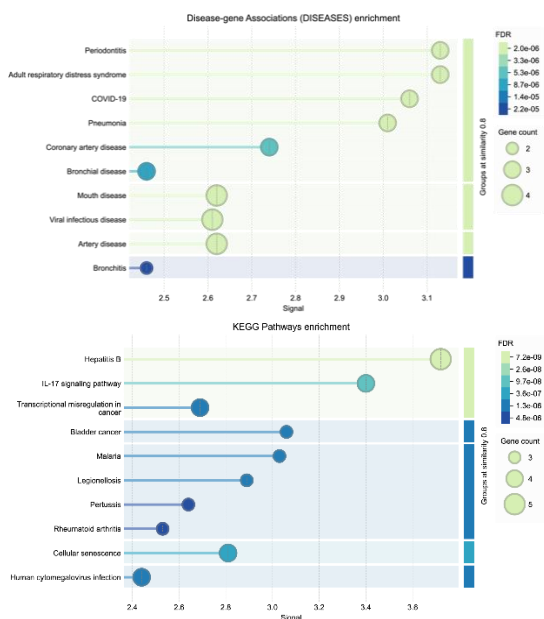
**Figure 6.** IL-17 Signalling Pathway

Since selected pathways was IL-17 signaling, the potential related genes were including IL-6, TNF- $\alpha$ , MMP-9, dan CXCL-8 or known as IL-8. IL-17 signaling pathway initiating signaling any other pathway such as NF- $\kappa$ B signaling to release cytokines that induce inflammation. In mouse pulmonary inflammation and fibrosis models, IL-17A both affected the regulation of the collagen synthesis and secretion in alveolar epithelial cells through TGF- $\beta$ 1-dependent manner and suppressed autophagy supporting cells death in inflammatory lung tissue.<sup>39</sup>

These analyses were then confirmed through molecular docking and virtual screening using PyRx. All four related genes were docked with all the ligands from each of the herbal compounds. All of those four genes were approved through in vivo and in vitro research that involved COPD progression.<sup>40-43</sup>

The proper genes crystal structure was saved into pdb format from (<https://www.rcsb.org/>). The preparation included removing unnecessary material such as water and het atoms. The hydrogen polar only was added as well as repair the missing atom and add the charges.<sup>25</sup>

Each ligand was also prepared before the screening started. The docking method was



**Figure 5** Disease and Pathway

validated with each native ligand with AutoDock 4.0. The native ligand for IL-6, IL-8, MMP-9 and TNF was C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>, Azelaic Acid, C<sub>15</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub> (N~2~-[2R]-2-[[formyl(hydroxy)amino]methyl]-4-methylpentanoyl]-N,3-dimethyl-L-valinamide) and C<sub>32</sub>H<sub>32</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub> (6,7-dimethyl-3-[(methyl{2-[methyl({1-[3-(trifluoromethyl)phenyl]-1H-indol-3yl)methyl]amino}ethyl)-amnio)methyl]4H-chromed-4-one) respectively which can be found inside the validation report at RCSB databases. The grid parameter can be found in the table below.

**Table 7** The Binding Affinity with IL-6

Plants	Compound	Kcal/mol
Jamaican cherry	3'-Hydroxydaidzein	-6,5
	Kaempferol	-6,5
	Quercetin	-7,2
Thyme	Eriodictyol	-6,9
	Taxifolin	-7
	Apigenin	-6,8
Red Ginger	6-gingerol	-5,5
	10-gingerol	-5,6
	(3S,5S)-[6]-Gingerdiol	-5,1

**Table 8** Grid Parameter

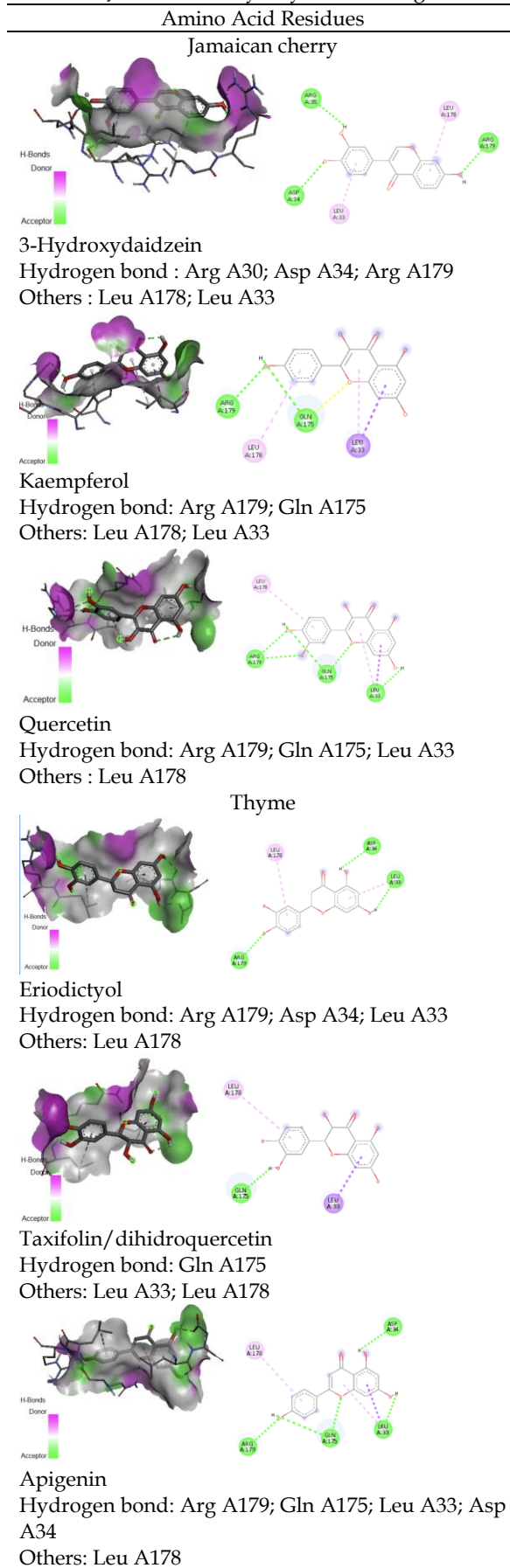
Gen	RCSB	Grid Parameter	
		Center	Dimensions
IL-6	1ALU	X : -0,024	X : 22,146
		Y : -25,79	Y : 26,041
		Z : -1,84	Z : 21,105
IL-8	5D14	X : 2,39	X : 25
		Y : 17,146	Y : 25
		Z : -3,842	Z : 25
MMP-9	1GKC	X : 65,248	X : 28,202
		Y : 30,084	Y : 24,275
		Z : 117,718	Z : 28,027
TNF-α	2AZ5	X : -19,223	X : 32,914
		Y : 74,616	Y : 50,696
		Z : 33,99	Z : 29,483

The virtual screening for all the compounds with four target genes was done using Vina PyRx with the validated grid parameter above.

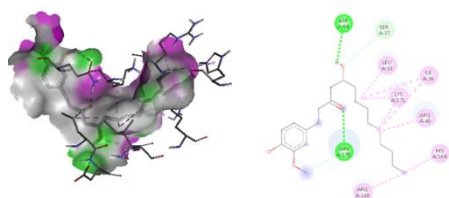
**Table 9.** The Binding Affinity with IL-8

Plants	Compound	(Kcal/mol)
Jamaican cherry	3'-Hydroxydaidzein	-11,2
	Formononetin	10,8
	Quercetin	-10,3
Thyme	Eriodictyol	-10,9
	Narigenin	-10,6
	Taxifolin	-10,3
Red Ginger	6-gingerol	-7,9
	10-gingerol	-7,5
	(3S,5S)-[6]-Gingerdiol	-7,7

**Table 10** Visualization of IL-6 and Selected Ligands from Jamaican cherry-Thyme-Red Ginger

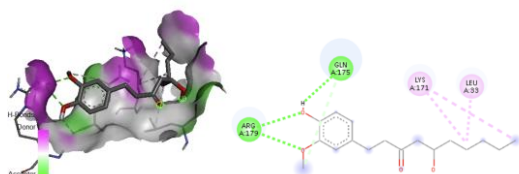


Red Ginger



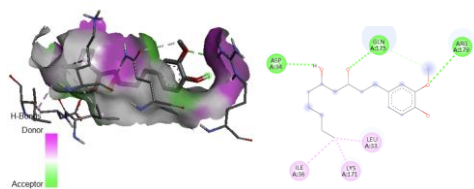
10-Gingerol

Hydrogen Bond : Asp A34, Gln A172, Ser A169  
Others : Leu A33; Ile A36; Lys A175; Arg A40; His A164; Arg A168



6-Gingerol

Hydrogen Bond : Gln A175; Arg 179  
Others : Lys A171; Leu A33



(3S,5S)-[6]-Gingerdiol

Hydrogen Bond : Asp A34; Gln A175; Arg A179  
Others : ILE A36; Lys A171; Leu A33

Table 8 shows the binding affinity between selected ligands from each plant with interleukin-6 while Table 9 shows the visualization and interaction between ligands and IL-6.

IL-6 is an important biomarker which the elevation is in tune with the exacerbation.<sup>40</sup> IL-6 is a pleiotropic cytokine that plays a key role in regulating immune responses, inflammation, and the development of chronic diseases such as COPD.<sup>44</sup> Therefore, inhibiting IL-6 activity is a potential target in anti-inflammatory therapy.

The results of molecular docking visualization show that the active compounds are able to interact with the IL-6 (Interleukin-6) receptor through hydrogen bonds and other bonds such as covalent and non-covalent. The ligands that show the lowest energy binding

affinity based on each plant are -7.2 kcal/mol; 6.9 kcal/mol and -5.6 kcal/mol respectively, namely quercetin from Jamaican cherry plants, eriodictyol from thyme and 10-gingerol from red ginger.

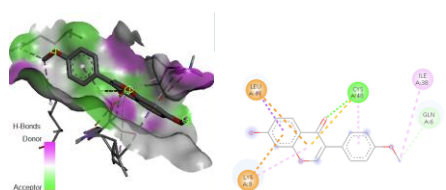
Quercetin has been widely used as an anti-inflammatory agent. This study found that quercetin at a dose of 10 mg/kgbw improved COPD by reducing cellular influx and cytokine levels, reducing oxidative damage, and demonstrating improved lung histopathology compared to the negative group.<sup>45</sup>

Eriodictyol content in thyme has also been shown to have antioxidant and anti-inflammatory activity, repairing acute lung damage induced by LPS in experimental animals.<sup>46</sup> Meanwhile, the 10-gingerdiol content in red ginger can inhibit the production of nitric oxide, IL-1b, IL-6, and TNF- $\alpha$  at a concentration of 20  $\mu$ M. This is due to the presence of a long alkyl chain, which increases anti-inflammatory activity, although this does not occur with the 6-gingerol compound.<sup>47</sup>

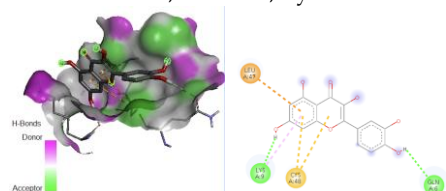
The second gen that successfully docked with ligands was IL-8. The molecular docking result as per Table 10 shows that the highest affinity between ligand and IL-8 from Jamaican cherry extract as much as -7.7 Kcal/mol was 3'-Hydroxydaidzein. Thyme has Narigenin and Eriodictyol as -7.4 Kcal/mol and red ginger with gingerol compound with -6.5 Kcal/mol binding affinity.

**Table 7.** Visualization of IL-8 and Selected Ligands from Jamaican cherry-Thyme-Red Ginger

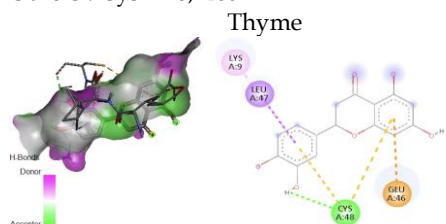
Amino Acid Residue
Jamaican cherry
3-Hydroxydaidzein
Hydrogen Bond : Cys A48
Others : Leu A47; Lys A9



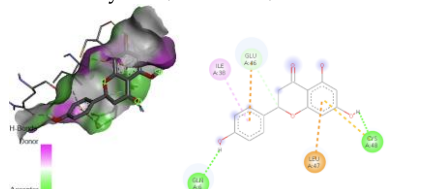
**Formononetin**  
Hydrogen Bond : Cys A48; Gln A6  
Others :Ile A38; Leu A47; Lys A9



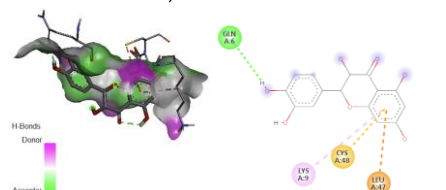
**Quercetin**  
Hydrogen Bond : Gln A6; Lys A9  
Others : Cys A48; Leu A47



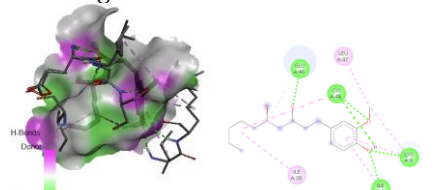
**Thyme**  
Eriodictyol  
Hydrogen Bond : Cys A48  
Others :Lys A9; Leu A47; Glu A46



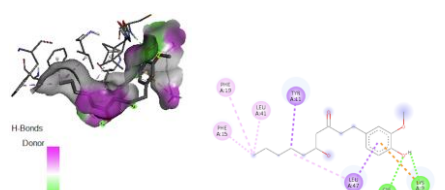
**Narigenin**  
Hydrogen Bond : Glu A46; Cys A48; Gln A6  
Others :Ile A38; Leu A47



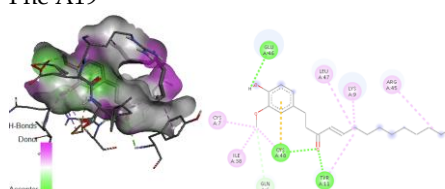
**Taxifolin**  
Hydrogen Bond : Gln A6  
Others :Lys A9; Cys A48; Leu A47



**(3S,5S)-[6]-Gingerdiol**  
Hydrogen Bond : Glu A46; Cys A48; Lys A9; Ile A8  
Others : Leu A47; Ile 38



**6-Gingerol**  
Hydrogen Bond : Cys A48; Lys A9  
Others : Leu A47; Tyr A11; Leu A41; Phe A15; Phe A19



**10-Gingerol**  
Hydrogen Bond : Glu A46; Cys A48; Tyr A11; Gln A6  
Others : Leu A47; Lys A9; Arg A45; Cys A7; Ile A38

Red ginger has been shown to suppress the expression of IL-8, TNF- $\alpha$ , IL-6, and IL-1 $\beta$  and influence ROS production by inhibiting NF- $\kappa$ B activation.<sup>37</sup> One of the compounds in red ginger, 6-shogaol, can inhibit the above expression through JNK phosphorylation in HMC-1 cells.<sup>38</sup>

Considering several interactions between ligands and target genes, there was organic components interact with proteins through chemical bonds and non-covalent interactions. Hydrogen bonds and hydrophobic interactions are important in evaluating the binding affinity and effectiveness of drug molecules, which meet pharmacological needs. Hydrogen bonds play a crucial role in receptor-drug interactions and the structural integrity of many biological components, including proteins and DNA. Ligands bound to receptors interact directly with proteins by creating and releasing water molecules.<sup>30</sup>

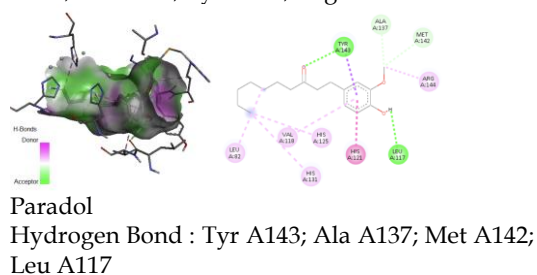
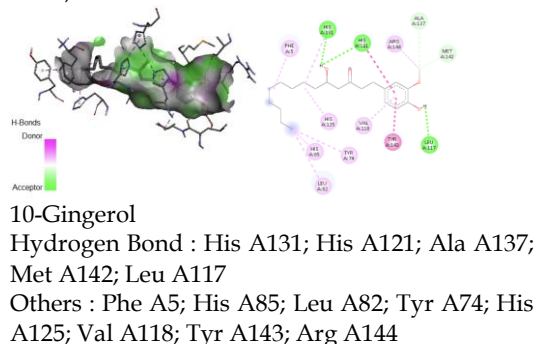
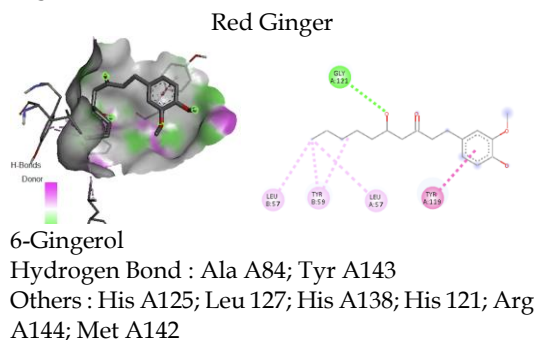
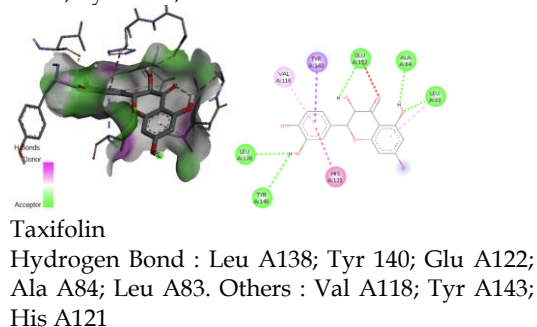
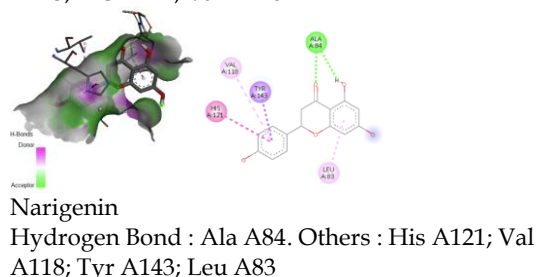
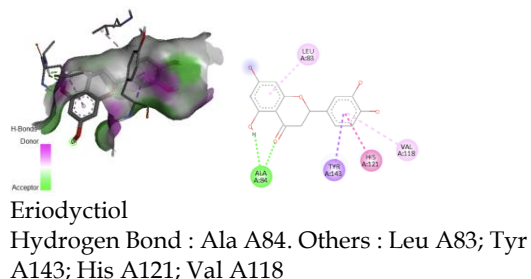
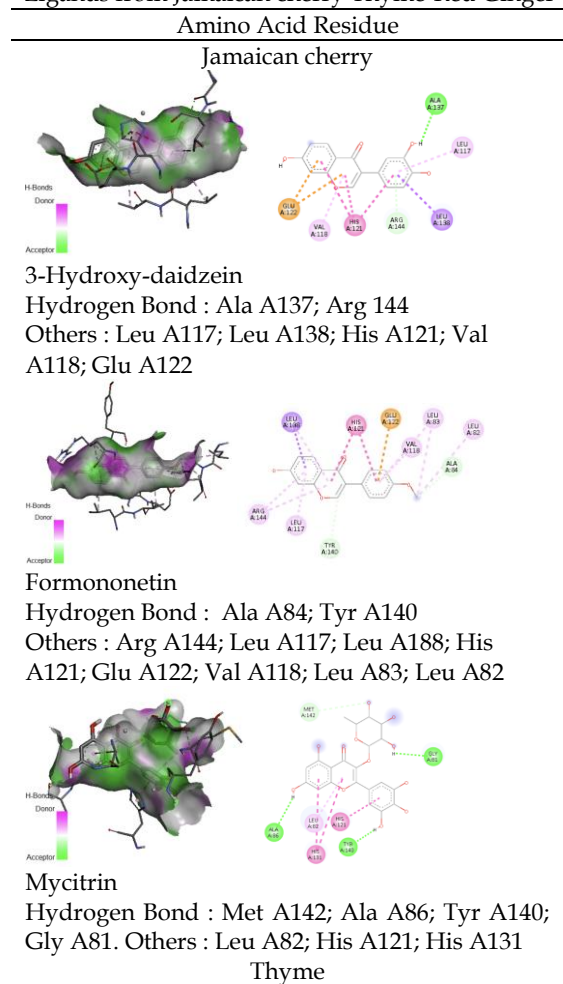
In line with the results in Table 6 and Table 10, several supporting studies include thyme extract having an anti-inflammatory effect on primary epithelial cells of human airway (bronchial/tracheal) epithelial cell lines and human lung cancer cell line (H460) induced by LPS can suppress transcription of NF- $\kappa$ B p65 and NF- $\kappa$ B p52 and reduce the expression of IL-1beta and IL-8, as well as Muc5ac secretion

thereby reducing mucus hypersecretion.<sup>35</sup> Thyme can also support the frequency of ciliary movement (Cilia beating frequency, CBF) which is disturbed in COPD conditions through analysis of cAMP and Ca<sup>2+</sup> levels as well as CBF using MucilAir 3D human.<sup>36</sup> Thus, thyme can support the condition of COPD patients by reducing mucus secretion and improving ciliary movement which is disturbed due to mucus hypersecretion.

**Table 8.** MMP-9 Binding Affinity Value

Plants	Compound	Kcal/mol
Jamaican cherry	3'-Hydroxydaidzein	-7,7
	Formononetin	-7,5
	Mycitrin	-7,3
Thyme	Eriodictyol	-7,4
	Narigenin	-7,4
	Taxifolin	-7,3
Red Ginger	6-gingerol	-6,5
	10-gingerol	-6,5
	Paradolol	-6,3

**Table 9.** Visualization of MMP-9 and Selected Ligands from Jamaican cherry Thyme-Red Ginger



Others : Arg A144; His A121; His A131; Val A118;  
Leu A82

MMP-9 is a zinc-dependent endopeptidase. Therefore, if the ligands from these three plants have a high affinity for Zn<sup>2+</sup> ions, these molecules will effectively prevent the polypeptide from binding to MMP, thus potentially acting as MMP-9 inhibitors.<sup>49</sup> Zinc is known to be a trace element required for the activity of enzymes and transcription factors. Flavonoids can act as chelating agents to suppress Zn<sup>2+</sup>.<sup>50</sup>

Next is TNF- $\alpha$ , or Tumor Necrosis Factor- $\alpha$ , which is a factor that stimulates tumor necrosis. TNF- $\alpha$  binds to two different receptors and is involved in numerous signaling pathways, such as cell survival, differentiation, and proliferation. However, excessive signaling activation involving TNF- $\alpha$  can lead to inflammation.<sup>43</sup>

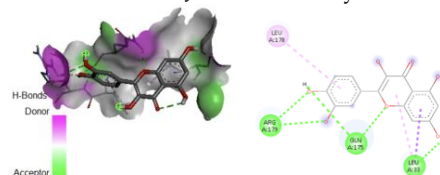
Antioxidant compounds such as quercetin have been shown to suppress oxidants such as reactive oxygen species (ROS), superoxide dismutase (SOD), GSH, GPx, and GST formed in 3T3-L1 cells induced by TNF- $\alpha$ .<sup>45</sup> Furthermore, compounds contained in red ginger, such as several types of shogaols, gingerols, and other phenolics, act as antioxidants by donating electrons or hydrogen atoms to free radicals<sup>29</sup> as well as Jamaican cherry has been shown to reduce TNF- $\alpha$  expression in COPD animal models at a dose of 3.5 mg/Kgbw of mice.<sup>20</sup>

Table 10 TNF- $\alpha$  Binding Affinity Value

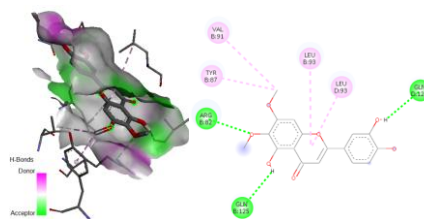
Plants	Compound	(Kcal/mol)
Jamaica	Quercetin	-8,8
n cherry	Cirsiliol	-7,6
Thyme	Eriodictyol	-8,9
	Narigenin	-8,3
Red	6-gingerol	-6,9
Ginger	Zingerone	-6,3
	(3S,5S)-[6]-Gingerdiol	-6,2

Table 11. Visualization of TNF- $\alpha$  and Selected Ligands from Jamaican cherry-Thyme-Red Ginger

Amino Acid Residue  
Jamaican cherry

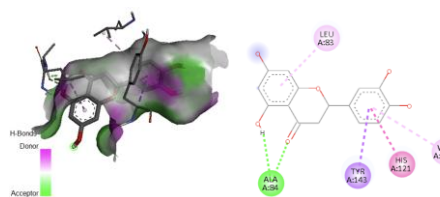


Quercetin  
Hydrogen Bond : Arg A179; Gln A175; Leu A33.  
Others : Leu A178

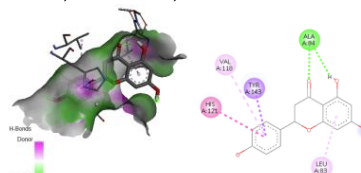


Cirsiliol  
Hydrogen Bonds: Arg B82; Gln B125; Gln D125.  
Others : Leu D93; Leu B93; Val B91; Tyr B87

Thyme

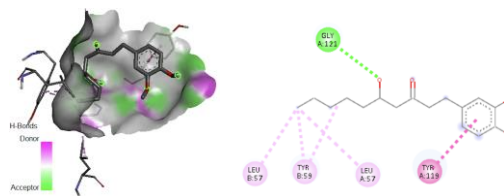


Eriodictyol  
Hydrogen Bond : Ala A84. Others : Leu A83; Tyr A143; His A121; Val A118

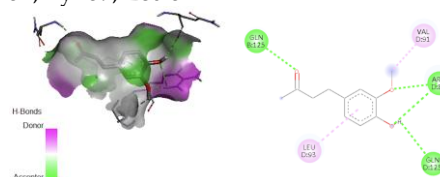


Narigenin  
Hydrogen Bond : Ala A84. Others : His A121; Val A118; Tyr A143; Leu A83

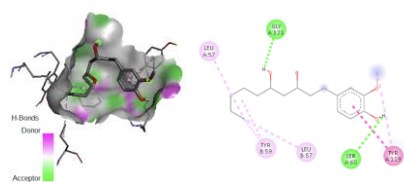
Red Ginger



6-Gingerol  
Hydrogen Bond : Gly A121. Others : Tyr 119; Leu 57; Tyr 59; Leu 57

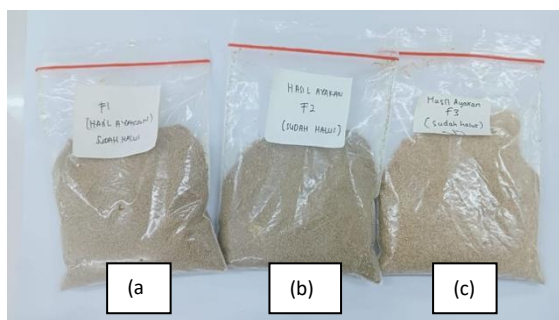


Zingerone  
Hydrogen Bond : Gln 125; Arg 82; Gln D125.  
Others : Val 91; Leu 93



(3S,5S)-[6]-Gingerdiol  
Hydrogen Bond : Gly A121; A60  
Others :Tyr A119; Leu B57; Tyr B59; Leu A57

Jamaican cherry has also been shown to reduce MMP-9 expression in a mouse model exposed to cigarette smoke.<sup>48</sup>



Picture 7 Formulation Appearance (a), (b) and (c)

Table 12 Powder Evaluation

Organoleptic	Water content (%)	Flow Rate	Angle (°)	Dissolution Rate (s)	pH
Ginger aromatic, stable powdery, brown-greenish	2,41	3,92	18	8,54	4,07
Ginger aromatic, stable powdery, dark brown-greenish	2,38	2,8	18,7	9,97	3,85
Ginger aromatic, stable powdery, light brown-greenish	2,40	2,64	19,5	10,34	4,45

In this study, organoleptic evaluation were conducted visually on the Powder Drink formulation including color, aroma, taste, and form. Observations of the three formulations showed no changes in color, shape, taste, or aroma.

Based on Table 16, after 7 days of observation, average water content for FI, FII and FIII were 2.41, 2.38, and 2.40 respectively. The water content specification for powder product is ≤3%.<sup>51</sup> This indicates that all formulas meet the requirements. Based on the flow rate test carried out, all three formulations have a

flow rate categorized as cohesive. The flow time test properties are >10 g/sec for free-flowing, 4-10 for easy-flowing, 1.4-4 for cohesive, and <1.4 for very cohesive.<sup>51</sup> The angle of repose evaluation result shows <20° while the standards ranging from 25° to 45°.

Dissolution evaluation was conducted to determine how long it takes for the powder to completely dissolve in water. From the test results carried out on the powder, formulations FI, FII, and FIII dissolved completely without any residue. Dissolution time requirement of less than 5 minutes.<sup>51</sup>

pH testing is conducted to measure whether a substance is acidic or basic. Since the pH result is within 3.85 – 4.46, and the pH range for powder drink formulation is between 4-7<sup>28</sup> therefore, only FI and FIII that meet the requirement. It could be because FII contains the same concentration of thyme and Jamaican cherry extract, which resulting the formulation more acidic.

Both flow rate and angle of repose did not meet the requirement although the water content was fine. It could be because strong cohesive forces between particles, which cause the formation of clumps that have resistance to flow. Since in this research we used only the differences of extract concentration between the formulation, therefore in the next research we could find any combination of excipients to reach the best formulation.

Table 13 Homogeneity Evaluation

Formulation	Result
FI	
FII	
FIII	

Homogeneity evaluation is conduct to determine the presence of granules or homogeneity. This showed no granules

that means our formulation has good homogeneity.

**Table 14** Antioxidant Activity as IC<sub>50</sub> Value

Formulation	IC <sub>50</sub> (ppm)
F1	39,99
F2	36,10
F3	28,30

The IC<sub>50</sub> value is determined through a linear regression equation from the calibration curve, namely the percentage of attenuation as the y-axis and the antioxidant concentration as the x-axis. The IC<sub>50</sub> value is calculated by entering the value of 50% into the regression equation as the y-value, then calculating the x-value as the IC<sub>50</sub> concentration. Based on table 18, the results of the analysis of antioxidant activity using the DPPH method show that F1 has an IC<sub>50</sub> value of 39.99 ppm, which is categorized as very strong. In F2, the nutraceutical powder drink preparation which has an IC<sub>50</sub> value of 36.10, the strongest is in F3 with an IC<sub>50</sub> value of 28.30 ppm, which is categorized as very strong. The F3 contain more Jamaican cherry extract that shows the best IC<sub>50</sub>. Further research related to hedonic is possible.

As previously explained, these three herbal combinations have excellent potential in terms of antioxidants and each component has an anti-inflammatory effect.

## CONCLUSION

This study demonstrates that the combination of Jamaican cherry (*Muntingia calabura*), red ginger (*Zingiber officinale*), and thyme (*Thymus vulgaris*) exhibits promising antioxidant activity and favorable in-silico interactions with key COPD-related targets, including TNF- $\alpha$ , IL-6, IL-8, and MMP-9. The network pharmacology and molecular docking analyses suggest that this combination may modulate multiple inflammatory pathways associated with COPD pathogenesis. However, these findings are based on computational predictions and preliminary in vitro

antioxidant evaluation, and therefore do not directly confirm therapeutic efficacy.

In addition, the absence of benchmarking data, such as co-crystal ligand comparison and standard antioxidant controls, limits the ability to interpret the results comparatively.

Therefore, the proposed nutraceutical formulation should be considered as a potential candidate for further investigation rather than a confirmed therapeutic option.

Future studies, including detailed pharmacological validation, in vitro mechanistic assays, and in vivo studies, are required to confirm its biological activity and clinical relevance. These findings provide a scientific basis for further development of multi-target nutraceutical approaches in COPD.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

## Acknowledgments

We would like to thank the Ministry of Education through LLDIKTI IV that had supported our research.

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