In Silico Study: Potential Prediction of *Curcuma longa* And *Cymbopogon citratus* Essential Oil As Lipoxygenase Inhibitor

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ABSTRACT. Inflammation is the human body response when pathogens enter and attack the immune system. One of the effects of inflammation is the activation of the Lipoxygenase (LOX) gene. The bioactive from essential oil such as *Curcuma longa* and *Cymbopogon citratus* that has potential pharmacologist activity can be used to curve the inflammation. This research aimed to investigate the role of *Curcuma longa* and *Cymbopogon citratus* essential oil through the LOX gene activity. The study adapted by in silico study. Several chemical substances, including 3,7-dimethyl-1,3,6-octatriene, camphor, eugenol, curzerenem, and isoborneol, were retrieved from the PubChem database. The PyRx 0.8 was used to minimize and convert the sdf file to a pdb format file of ligands. Those compounds were predicted their interaction using STITCH online server. Ligands and protein were docked by HEX Cuda 8.0.0 program, 3D and 2D views were evaluated using Discovery studio ver.19.0.0 and LigPlot+ ver 2.2, respectively. We found fourteen amino acid residues from LOX which bound the chemical compounds. A hydrogen bond supported those interactions with a variety of energy binding. To sum up, the essential oil from *Curcuma longa* and *Cymbopogon citratus* has a potential function as inhibitor LOX by inhibiting fourteen active sides of the LOX gene.

Keywords: *Curcuma longa*, *Cymbopogon citratus*, essential oil, inflammation, lipoxygenase

INTRODUCTION

The herbal essential oil has become a popular product for relaxation. Several plants were used to produce the essential oil, such as *Pogostemon cablin*, lemongrass, geranium, orchids, rose, and rosemary. Every essential oil has specific functions. Lemongrass or *Cymbopogon citratus* has been reported to contain some bioactive substances, such as alkaloids, flavonoids, steroid, and terpenoids. Bioactive compounds in lemongrass essential oil are geraniol, citral, citronellal, and citronellol [1–4]. Those compounds have functioned as antifungal, antioxidant, anti-inflammation, antidiabetic, antimicrobial, and anti-tumor [5–10].

Turmeric or *Curcuma longa* is an herbal medicine used in the community containing active compounds such as alkaloids, flavonoids, tannins, and phytosterols [11–12]. Turmeric's flavonoid and alkaloid compounds are widely explored for various treatments for anti-cancer, antimicrobial, antioxidant, and antimutagenic properties [11–14]. *Curcuma* oil has been proved to have an anti-inflammatory effect in some experimental

conditions [14]. Both *C. citratus* and *C. longa* have been known as therapeutic medicine, while the study on this function in the inflammation process is still limited.

Inflammation is a condition in the body characterized by the appearance of pro-inflammatory signals. During the inflammation, the body will produce a different protein with a specific function [15]. One of the genes which play a role in inflammation condition is lipoxygenase gene (LOX). LOX will affect the human body when inflammation occurred and leads to chronic inflammation. The LOX pathway that works during the process is leukotrienes and hydroperoxy fatty acids [16,17]. Nowadays, LOX has become a target for inflammatory therapy [18]. The previous study showed LOX as an anti-cancer [19]. There are pharmacological inhibitors of lipoxygenases (LOX) used because of their ability to decrease some of the cellular and tissue level effects of the inflammatory reaction [20]. In this study, the reduction of inflammatory reactions in the body was conducted by inhibiting LOX as an inflammatory mediator involved during the inflammatory process. Plant derivatives were used

therapy from secondary metabolites such as phenolic acids to reduce the toxicity of the drugs (20)-(21). We analyzed the potential of the *C. longa* and *C. citratus* essential oils as LOX inhibitors.

METHODS

Sample preparation and molecular modeling

Several chemical substances, including 3,7-dimethyl-1,3,6-octatriene, camphor, eugenol, curzerene, and isoborneol, were retrieved from the PubChem database with accession number CID5281553, CID2537, CID3314, CID572766, and CID64685, respectively. The PyRx 0.8 was used to minimize and convert the sdf file to a pdb format file of ligands. Those compounds' interaction was predicted using STITCH online server and resulted from LOX as a targeted protein. Ligands and protein were docked by HEX Cuda 8.0.0 program, 3D and 2D views were evaluated using Discovery studio ver.19.0.0 and LigPlot+ ver 2.2, respectively.

RESULTS AND DISCUSSIONS

Interaction of 3,7-dimethyl-1,3,6-octatriene bioactive compound with LOX formed energy binding around -199.0kJ/mol. That interaction showed one amino acid residue binds to the 3,7-dimethyl-1,3,6-octatriene in LEU153 of LOX? (Figure 1 and Table 1). However, Camphor and LOX's interaction revealed five amino acid residues that binding to the bioactive compound. The amino acid residues are GLU250, CYS248, PRO252, LYS521, and THR249, with energy binding -156.3kJ/mol (Figure 1 and Table 1). The bioactive Eugenol and protein LOX were docked and showed energy binding about -196.7kJ/mol. Those interactions reported four amino acid residues (ARG370, PHE450, PHE544, VAL243), bound with the eugenol (Figure 1 and Table 1). The Curzerene showed activity as a LOX inhibitor, which provided binding energy -227.4kJ/mol. The potential inhibitor of curzerene showed to inhibit the active site of LOX in amino acid residues ASP333, GLY332, ILE330, LEU153, TRP144 (Figure 1 and Table 1). Isoborneol-LOX complex demonstrated an amino acid residue that was ILE330 with the energy binding of -153.0kJ/mol (Figure 1 and Table 1).

The visualization of complex binding suggested that complex binding of ligands and LOX provides efficient inhibition. The hydrophobicity level of essential oil-LOX complexes presented differently from other complexes. Camphor and eugenol showed low levels because most of the ligand surface appears

light blue towards dark blue. The 3,7-dimethyl-1,3,6-octatriene, curzerene, and isoborneol released high levels of hydrophobicity with brown color on the surface.

Throughout the acute inflammatory response, the arachidonic acid (AA) pathway produces proinflammatory in neurodegenerative diseases, this AA pathway has become chronically hyperactivated. According to previous studies, the key regulatory enzymes in the eicosanoid pathway, i.e. 5-LOX and 5-, 12-, and 15-LOX, appear to have an important role in mediating the proinflammatory responses [23]. 5-LOX is a dioxygenase that has a function to convert Arachidonic acid to 5-(S)-hydroperoxy-eicosatetraenoic acid [22]. It means the LOX gene contributed to lead inflammation. The analysis shows that various binding sites prove that the raw materials are more effective than consumption only. Arachidonic acid is produced by membrane phospholipids part in the main pathway of pain and inflammation. Arachidonic acid was further metabolized by lipoxygenase and cyclooxygenase pathways. In lipoxygenase, 5-LOX produces leukotrienes, which play a major role in inflammation, gastrointestinal tract (GI) damage, and the primary disease. One of the leukotrienes is converted into lipoprotein A4 by 15-LOX, resolved inflammation conditions, and it has anti-tumor activity [22–24].

Inhibition the LOX carried out by essential oils from *Curcuma longa* and *Cymbopogon citratus* occurs on the active site of the LOX gene in fourteen amino acid residues (LEU153, GLU250, CYS248, PRO252, LYS521, THR249, ARG370, PHE450, PHE544, VAL243, ASP333, GLY332, ILE330, and TRP144) by in silico study. This inhibition will affect the inflammatory process in the human body. It can block various LOX parts and prevent natural arachidonic acid as the original substrate. The inhibition starts by inhibiting lipoxygenase catalyze through inhibiting hydroperoxy eicosatetraenoic acids (HPETEs) from arachidonic acid. Then the HPETEs decreased and converted into eicosanoid, a signal molecule and plays an essential regulatory role in immune reactions and other physiological processes. Generally, lipoxygenase has the ability to oxygenate fatty acids at specific positions [24].

Hydrogen bonds was also reported to promote ligand binding affinities with the proteins and stabilize it (25–29). The combination of phytochemical components will play a synergistic mechanism and improving the human system's biological activity [30–34].

1. 3,7-dimethyl-1,3,6-octatriene - LOX

2. Camphor-LOX

3. Eugenol-LOX

4. Curzerene- LOX

5. Isoborneol- LOX

Figure 1. The binding pose of *Curcuma longa* and *Cymbopogon citratus* essential oil with lipoxygenase protein, A. The 3D model of the ligand-protein complex, B. Interaction sites of ligand-protein complex, C. Hydrophobicity levels, D. The 2D view of the ligand-protein complex.

Table 1. Interaction essential oil of *Curcuma longa* and *Cymbopogon citratus* through lipoxydase protein

Ligand-Protein Complex	Binding energy (kJ/mol)	Interaction	Distance	Category	Type
1. 3,7-dimethyl-1,3,6-octatriene – LOX	-199.0	: UNK0:C7 - A: LEU153	4.86	Hydrophobic	Alkyl
		B:GLU250:HN - :UNK0:O1	2.44	Hydrogen Bond	Conventional Hydrogen Bond
		B:CYS248 - :UNK0	5.33	Hydrophobic	Alkyl
		B:PRO252 - :UNK0	5.49	Hydrophobic	Alkyl
2. Camphor-LOX	-156.3	:UNK0:C9 - A:LYS521	3.98	Hydrophobic	Alkyl
		:UNK0:C10 - A:LYS521	3.91	Hydrophobic	Alkyl
		:UNK0:C11 - A:LYS521	3.78	Hydrophobic	Alkyl
		B:THR249:OG1 - :UNK0:O1	2.92	Unfavorable	Unfavorable Acceptor-Acceptor
3. Eugenol-LOX	-196.7	A:ARG370:HE - :UNK0	2.66	Hydrogen Bond	Pi-Donor Hydrogen Bond
		A:PHE450 - :UNK0:C12	5.07	Hydrophobic	Pi-Alkyl
		A:PHE544 - :UNK0:C12	4.24	Hydrophobic	Pi-Alkyl
		:UNK0 - A:VAL243	5.19	Hydrophobic	Pi-Alkyl
		:UNK0 - A:ARG370	4.70	Hydrophobic	Pi-Alkyl
		A:ASP333:HN - :UNK0:O1	2.74	Hydrogen Bond	Conventional Hydrogen Bond
4. Curzerene- LOX	-227.4	A:GLY332:CA - :UNK0:O1	3.17	Hydrogen Bond	Carbon Hydrogen Bond
		:UNK0:C13 - A:ILE330	4.14	Hydrophobic	Alkyl
		:UNK0:C13 - B:LEU153	4.26	Hydrophobic	Alkyl
		B:TRP144 - :UNK0:C15	5.32	Hydrophobic	Pi-Alkyl
5. Isoborneol- LOX	-153.0	:UNK0:C10 - A:ILE330	4.76	Hydrophobic	Alkyl

CONCLUSION

The phytosterol compounds containing *C. longa* and *C. citratus* might have potential anti-inflammatory effects through lipoxygenase inhibitor activities.

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