Molecular docking studies of 4-ethyl-2-methoxyphenol and 1,3-cyclopentanedione compounds from gemor (*Nothaphoebe coriacea*) with glucagon like-peptide-1 (GLP-1) receptor

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Abstract. Gemor (*Nothaphoebe coriacea*) is a plant that grows in wetland forests. Many studies have revealed the potential of this plant for health and medicine, among others as an antioxidant, anti-inflammatory, antidiabetic, and others. However, the mechanism is unknown or not yet discovered. Previous studies have shown that gemor bark contains active compounds. One of them is 4-ethyl-2-methoxyphenol (PubChem ID 62465) and 1,3-cyclopentanedione (PubChem CID 77466) compounds. This research will prove that 2 compounds act as antidiabetic by influencing Glucagon like-Peptide-1 (GLP-1) Receptor. Molecular docking was carried out on 2 these compounds. The protein is taken from RCSB PDB (4ZGM). Ligand and protein preparation, analyzed and visualized docking results were carried out with the Chimera 1.14. Molecular docking using SWISSDOCK. The results show that the 4-ethyl-2-methoxyphenol compound can be bound by 6 residues (SER 84, CYS 85, TRP 87, ALA 92, VAL 95, and Pro 96); 1,3-cyclopentanedione bind by 7 residues (GLY 45, CYS 46, TYR 42, SER 49, CYS 71, VAL 83 and PRO 73). Gibbs energy for 4-Ethyl-2-methoxyphenol and 1,3-Cyclopentanedione, against GLP-1 Receptor each -6.10 kcal/mol and -5.37 kcal/mol. The conclusion is that 4-Ethyl-2-methoxyphenol and 1,3-Cyclopentanediene compound has the potential as an antidiabetic by binding mechanism with residues of GLP-1 receptor.

Keywords: *Nothaphoebe coriacea*, 4-ethyl-2-methoxyphenol, 1,3-cyclo pentanedione, GLP-1
1. Introduction
South Kalimantan is a province that has 103,556 ha of wetland and has a biodiversity that is potential to be developed for medicines. Some wetland plants have proven to be beneficial, for example the kelakai (*Stenochlaena palustris*) uses are used for antimetalotoxic, antiglycation, antioxidant, and protective skin from exposure to UV radiation [1-3]. In addition, the pasak bumi (*Eurycoma Longifolia* Jack.) plant and Dayak onion (*Eleutherine palmifolia* (L.) merr) are also used as antioxidants and photoprotective [4-5].

Gemor (*Nothaphoebe coriacea*) is also a wetland plant that is included in the type of Non-Timber Forest Products. It is used as raw material for making mosquito coils, incense and glue [6]. Previous studies have shown that the leaf of this plant has the potential as an antioxidant and anti-peroxide lipid [6,7]. Gemor leaf also plays a role in the metabolism of glucose in the liver due to exposure to Cadmium [8]. However, the pathomechanism is unclear.

Research Suhartono *et al.* [9] states that gemor contains bioactive compounds such as phenolic compounds, alkaloids, terpenoids, and steroids. Previous research also mentioned that gemor bark contains active compounds, such as 4-ethyl-2-methoxyphenol and 1,3-cyclopentanedione [10]. Both of these compounds are thought to be involved in glucose metabolism through the Glucagon-like Peptide-1 (GLP-1) Receptor pathway.

GLP-1 receptors were expressed in pancreatic beta cells. GLP-1 activated receptors stimulate the adenylate cyclase pathway. This activation causes increased synthesis and release of insulin. As a result, GLP-1 receptors have become a target for developing drugs commonly referred to as GLP1R agonists to treat diabetes mellitus [11].

Gemor in previous studies is involved in glucose metabolism. Yet, the mechanism is unknown. The study aims to know the in silico interaction of 4-ethyl-2-methoxyphenol and 1,3-cyclo pentanedione as antidiabetic agent. The use of the GLP-1 receptor protein is expected to explain the mechanism of 4-ethyl-2-methoxyphenol and 1,3-cyclo pentanedione as antidiabetic.

2. Materials and Methods

2.1 Ligand and protein preparation
4-Ethyl-2-methoxyphenol (CID 62465) and 1,3-Cyclopentanedione (CID 77466) ligand structures were obtained from Pub Chem (https://pubchem.ncbi.nlm.nih.gov). Both ligands were optimized for molecule docking preparation. Optimization by adding hydrogen atom and ligand charges. Protein receptor GLP-1 is obtained from RCSB Protein Data Bank (https://www.rcsb.org/search) with PDB code 4ZGM. Protein is prepared by removing the natural ligand residue present in the protein. The preparation of ligands and proteins is used by the Chimera 1.14 program (https://www.cgl.ucsf.edu/chimera/download.html).

2.2 Molecular docking
Simulation of reactions between Ethyl-2-methoxyphenol (CID 62465) and 1,3-Cyclopentanedione (CID 77466) ligand compounds with GLP-1 protein the SWISSDOCK program (http://www.swissdock.ch/) is used. The docking result is the Gibbs free energy value (ΔG).

2.3 Analysis and visualization
Analysis and visualization of docking results used the Chimera 1.14 program (https://www.cgl.ucsf.edu/chimera/download.html). Visualization is used to explain interactions between ligands and receptor protein residues.

3. Results and Discussion
Molecular docking results showed interactions between ethyl-2-methoxyphenol and 1,3-Cyclopentanedione compounds with GLP-1 protein. The interaction can be seen in Figure 1.
Figure 1 shows that ethyl-2-methoxyphenol and 1,3-Cyclopentanedione compounds are bind to different GLP-1 receptor residues. Residues that bind the two compounds can be seen in table 1.

Table 1. GLP-1 receptor residues binding and Gibbs Energy.

| Protein                | Ligand                          | Amino Acid Residue Binding | ΔG (kcal/mol) |
|------------------------|---------------------------------|---------------------------|---------------|
| GLP-1 receptor 4ZGM    | 4-ethyl-2-methoxyphenol (CID 62465) | SER 84, CYS 85, TRP 87, ALA 92, VAL 95, and PRO 96 | -6.10         |
|                        | 1,3-Cyclopentanedione (CID 77466) | GLY 45, CYS 46, TYR 42, SER 49, CYS 71, VAL 83 and PRO 73 | -5.37         |

Table 1 data shows that the Gibbs energy of the 4-ethyl-2-methoxyphenol compound is more negative than 1,3-Cyclopentanedione. This means that GLP-1 residues more strongly bind or interact with 4-ethyl-2-methoxyphenol compounds. Interaction can explain the antidiabetic potential of gemor plants.

GLP-1 is predominant in beta cells and alpha cells in the pancreas. This hormone only works when glucose concentration above basal concentration. The GLP-1 receptor is a peptide hormone, consisting of 30-31 amino acids. GLP-1 receptors function to inhibit glucagon release so that blood glucose is lower.

GLP-1 is an incretin hormone that acts as an antidiabetic by stimulating insulin secretion and increasing beta cell neogenesis. In addition, GLP-1 can inhibit beta cell apoptosis, inhibit glucagon secretion, and induce satiety. Thus, the binding of 4-ethyl-2-methoxyphenol and 1,3-Cyclopentanedione to GLP-1 is thought to activate GLP-1, thereby increasing insulin secretion and inhibiting glucagon [12].
Increased insulin secretion causes an increase in cell membrane permeability to glucose. Furthermore, glucose will be catalyzed by hexokinase/glucokinase into glucose-6-phosphate. This molecule is the meeting point of carbohydrate, lipid, and protein metabolism [12].

**4. Conclusion**

4-ethyl-2-methoxyphenol and 1,3-Cyclopentanedione are compounds contained in gemor which have the potential as antidiabetic. These compounds can interact with the GLP-1 receptor residue thereby activating the inhibition of glucagon release. It can reduce blood glucose levels.

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