The Potency of Cinnamon as An Anti-Diabetic and Anti-Covid19 based on Its Mineral Content and Phenolic Compounds

N R P Hapsari\textsuperscript{1a}, C Wijayanti\textsuperscript{1b}, Subandi\textsuperscript{1c*}, Suharti\textsuperscript{2a}, R R Mariana\textsuperscript{2b}

\textsuperscript{1,2a}Chemistry Department of Mathematics and Science Faculty, State University of Malang, Jl. Semarang no 5, Malang, East Java, Indonesia
\textsuperscript{2b}Culinary Arts Department of Engineering, State University of Malang, Jl. Semarang no 5, Malang, East Java, Indonesia

email:kynadia14@gmail.com\textsuperscript{1a}, chandrawijayanti@gmail.com\textsuperscript{1b}, subandi.fmipa@um.ac.id\textsuperscript{1c}, suharti.fmipa@um.ac.id\textsuperscript{2a}, rina.riefqie.ft@um.ac.id\textsuperscript{2b}

Corresponding author

Abstract. The purpose of this study were to determine the mineral content (Cr, K and Ca) as well as total phenolic (TPC) and total flavonoids (TFC) in cinnamon, then to know the potency of some phenolic compounds in cinnamon as alpha amylase inhibitors and its binding activity to S protein of covid19. The mineral content was determined by the ICP method, while the TPC and TFC levels were determined spectrophotometrically. In silico analysis was carried out by docking techniques using human salivary alpha amylase and S covid19 protein as receptors and several polyphenol compounds in cinnamon as ligands. The results have shown that the levels of Cr, K, Ca, TPC and TFC of cinnamon, were 0.524 ppm, 4033ppm, 17453 ppm, 1.55% and 4.26%, respectively. The results of in silico analysis has shown that kaempferol 3-O-glucoside and quercetin in cinnamon are able to bind to human saliva α-Amylase on its active site with a binding affinity that are relatively the same as acarbose has. The docking analysis also has shown that kaempferol, quercetin and rutin of cinnamon were able to bind to the Receptor Binding Domain (RBD) of S protein of covid19, so that these compounds also have the potency to be anticovid19.

Keyword: cinnamon, anti-diabetes, anticovid-19, phenolic compounds, mineral content

1. Introduction

Diabetes mellitus (DM) has now become a global problem with a prevalence of more than 425 million people from the world's population, both with type 1 and type 2 DM [1]. If not treated immediately the prevalence of DM in the world is estimated to continue increase so that by 2045 it can reach 629 million sufferers [1]. DM itself is caused by increasing levels of glucose in the blood. The newest approach being investigated to regulate elevated blood glucose levels is to control the activity of the alpha-amylase enzyme.

In diabetes mellitus, changes in salivary alpha-amylase enzyme levels are caused by an increase in glucose levels in the blood and a decrease in glucose levels in the interstitial tissue [2]. This causes the body to maintain hemostasis by regulating glucose in the blood. This mechanism causes the pancreatic acinar cells in the islets of the pancreatic Langerhans and the
exocrine glands in the salivary glands to produce alpha-amylase enzymes [3]. The resulting alpha-amylase will hydrolyze starch into dextrans and monosaccharides so that glucose levels in the blood increase. Thus, alpha-amylase inhibition has the potential to treat diseases related to carbohydrate absorption, such as diabetes mellitus. In previous studies, alpha-glucosidase has been recommended by the American of Clinical Endocrinologists as a therapy for diabetes mellitus because it is safe and does not cause hypoglycemia. But alpha-glucosidase types such as acarbose can cause side effects such as liver poisoning [4]. Therefore, studies on alpha-amylase inhibition of bioactive compounds in cinnamon will be an alternative as a substitute for acarbose.

Besides, cinnamon has the potential to be an anti-diabetic based on its high bioactive mineral content. Minerals contained in various solid sugar preparations include chromium, potassium, and calcium, each of which has a role in increasing the activity of insulin receptor sensitivity and insulin production. The cause of diabetes mellitus type 2 is insulin resistance which causes the inability of insulin to control glucose utilization and storage [5]. Meanwhile, the cause of insulin resistance is a lack of intake of essential nutrients, one of which is chromium. Chromium has been identified as an insulin regulator by increasing insulin receptors [6]. In DM, potassium has a role to increase insulin sensitivity, so that blood glucose levels decrease [7]. Apart from potassium, calcium is also needed to open cell channels in pancreatic cells, so the entry of calcium into cells causes the body to release a lot of insulin to move glucose molecules in the blood enter into every cell in the body [8].

Other studies suggest that diabetes treatment should not only focus on insulin secretion but also on the enormous protective antioxidants of b-cells of pancreas, thus helping in the repair of b-cells damaged by secondary oxidative stress to hyperglycemia [9] and can help protect and repair. beta cells in the pancreas that produce insulin. Oxidative stress can be inhibited by giving antioxidants, that at small concentrations can significantly inhibit or prevent oxidation of the substrate caused by free radicals [10]. Antioxidants can come from a variety of sources, including endogenous system enzymes, phenolic compounds (especially flavonoids), that are the largest phytochemical group in plants [11]. Phenolic compounds are a natural bioactive compound that is widely found in fruits and vegetables, while flavonoids are the largest group of polyphenols which are also very effective as antioxidants [12]. Flavonoids have a role to scavenge free radicals and repair pancreatic tissue damage caused by DNA alkylation due to alloxan induction [13].

Another study also stated that bioactive compounds such as antioxidant compounds were found to interfere with the binding of the coronavirus, namely SARS-CoV to host cells. It is known that SARS-CoV, has similarities with SARS-CoV-2 or virus of COVID-19, in its mechanism of entering host cells, namely by using the ACE2 receptor protein. So, to prevent the coronavirus from binding to ACE2, some antioxidant compounds were used which were found to block the entry of the virus into cells [14]. By understanding the role of ACE2 in the process of entry of SARS-CoV-2 into its host cells, research using cell culture has shown that antioxidants inhibit coronavirus infection by reducing its replication via suppressing synthesis on its protein surface, and reducing host cell death caused by infection of this virus. So, the polyphenol are thought to have potential as anti-covid-19. The purpose of this study were to determine the mineral content (Cr, K and Ca) as well as total phenolic (TPC) and total flavonoids (TFC) in cinnamon, then to know the potency of some phenolic compounds in cinnamon as alpha amylase inhibitors and its binding activity to S protein of covid19 through in silico analysis.
2. Materials and Method

2.1 Place of research

The research was conducted in the Biochemistry Laboratory, Department of Chemistry, State University of Malang for the implementation of the TFC level test and in silico molecular docking test. Testing of mineral content such as chromium, potassium, and calcium is carried out at the Analyst Services Laboratory of PT. Biochemlab Angler, Surabaya.

2.2 Tools and materials

The tools used in this study are laboratory common glassware and special instruments, including an analytic balance (Sartorius Element ELT103) with an accuracy of 0.001 gram, UV-Vis (Ultraviolet-Visible) spectrophotometry borrowed from the Chemistry Lab, State University of Malang, hot plate, and Inductively Coupled Plasma (ICP) at PT. Biochemlab Angler, PyMol (Python Molecular Viewer) software for docking preparation and visualization of ligand binding positions with receptors, PyRx 0.8 software for docking, and Discovery Studio Software for visualizing the interaction of ligand compounds with receptors.

The materials used in this study were cinnamon randomly obtained at a herbal shop in Malang City, HNO3 pa solution, aquasteril, FolinCiocalteu reagent, 10% Na2CO3 solution, 70% ethanol, 5% NaNO2 solution, 10% AlCl3 solution in acetic acid, glacial, 1 M NaOH solution, quercetin, and gallic acid (Sigma product), the 3d structure of the human salivary alpha-amylase receptor(PDB no. 1XV8) P04745 (AMY1_HUMAN), the 3d structure of Chain E of the Spike glycoprotein receptor Severe acute respiratory syndrome coronavirus 2 (2019-nCoV) (SARS-CoV-2) (PDB no E6M0J) P0DTC2 (SPIKE_SRAS2) obtained from UniProt Bank Protein Data database, the 3d structure of ligand compounds obtained from PubChem database.

2.3 Procedure

a. Determination of chromium, potassium, and calcium levels

The determination of chromium, potassium, and calcium levels was carried out using dry digestion by adding a solution of HNO3 p.a. Digestion is carried out until the vapor or solution becomes clear and the volume is concentrated to less than 50mL, then diluted with 1:1 aquasteril : HNO3, until the volume reaches 100mL, filtered then analyzed the levels of chromium, potassium, and calcium using ICP. The concentration is calculated based on the standard calibration curve.

b. Determination of total phenolic content

Analysis of the total phenolic content of the sample preparation was carried out by extracting the refined cinnamon sample using mortal and pastel, then maceration using 10mL of 70% ethanol solvent for 4 minutes, then vortexed at room temperature. Decantation is carried out to take the filtrate. Then the sample was added with 0.75 mL of 20% Na2CO3 and then measuring up to 5 mL with distilled water. Then incubated for 2 hours and then measured with a UV-Vis spectrophotometer at λ = 765 nm.

The phenol concentration in the sample is determined by the gallic acid calibration curve. The linearity of the gallic acid calibration curve was made by making a stock solution of gallic acid with a concentration of 0; 5; 10; 15; 20 and 25 ppm.

A calibration curve is created then a linear regression equation is determined and the correlation coefficient is used to evaluate linearity. Based on the value of the correlation coefficient, it can be seen whether the linearity is good or not.
c. **Determination of total flavonoid levels**

   Analysis of total flavonoid levels of sample preparation was carried out by extracting a sample of cinnamon that had been mashed using mortal and pastel, then macerated using 10mL of 70% ethanol solvent for 4 minutes, then vortexed at room temperature. Decantation is done to take the filtrate.

   Next, the sample was added with 2 mL of distilled water 150 mL 5% NaNO2. Samples were incubated for 5 minutes. Added with 10% AlCl3 as much as 150 μL and incubated for 6 minutes. 2 mL of 1M NaOH was added to the sample and then added distilled water to a volume of 5 mL. Total flavonoid levels were measured by a UV-Vis spectrophotometer at λ = 510 nm. The concentration of flavonoids in the sample was determined by a quercetin calibration curve. The linearity of the quercetin calibration curve was made by making a quer cetin stock solution with a concentration of 0; 5; 10; 15; 20; 25; 30; 35; 40; and 45 ppm.

   A calibration curve is created then a linear regression equation is determined and the correlation coefficient is used to evaluate linearity. Based on the value of the correlation coefficient, it can be seen whether the linearity is good or not.

d. **In silico test of Cinnamon Bioactive compound of cinnamon as ligand and human salivary alpha-amylase as receptors**

   The 3D structure of the Human Salivary α-Amylase receptor: P04745 (AMY1_HUMAN) was obtained from UniProt's Protein Data Bank database in PDB file format. The structure used is Human Salivary α-Amylase 1XV8 (chain A / B, positions 16-511).

   The 3D structure of ligand compounds: acarbose, kaempferol, and quercetin were obtained from the PubChem database in Sybil Data Files (SDF) format.

   In silico testing using the docking technique was carried out by sterilizing the Human Salivary α-Amylase receptor which aims to remove water content and all ligands contained in these receptors. This process is carried out using PyMol (Python Molecular Viewer) software.

   The molecular docking process is carried out to identify the activity of ligand compounds that have potential as candidates for Human Salivary α-Amylase inhibitors in silico. This process is carried out using the AutoDock Vina program in pyrx 0.8 software, the results obtained are the binding affinity value.

   The docking results obtained through the PyRyx software then identified the binding position between the ligand compound and the receptor through visualization using the PyMol software.

e. **In silico test of the SARS-CoV-2 protein spike glycoprotein receptors using a docking technique**

   The 3D structure of the Spike glycoprotein Severe acute respiratory syndrome coronavirus 2 (2019-nCoV) (SARS-CoV-2) P0DTC2 (SPIKE_SARS2) receptor was obtained from the UniProt Bank Protein Data Database in PDB file format. The structure used is chain E.

   The 3D structure of the ligand compounds: catechin, cinnamaldehyde, eugenol, kaemferol, linalool, quercetin, and routine were obtained from PubChem database in Sybil Data Files (SDF) format.

   In silico testing using a docking technique was carried out by sterilizing the Spike glycoprotein receptor severe acute respiratory syndrome coronavirus 2 (2019-nCoV) (SARS-CoV-2) which aims to remove water content and all ligands that are present in the receptor. This process is carried out using PyMol (Python Molecular Viewer) software.

   The molecular docking process was carried out to identify the activity of ligand compounds that have potential as candidates for the spike glycoprotein receptor inhibitor for severe acute respiratory syndrome coronavirus 2 (2019-nCoV) (sars-CoV-2) in silico. This process is carried out using the AutoDock Vina program in pyrx 0.8 software, the results obtained are the binding affinity value.
The docking results obtained through the PyRyx software then identified the similarity of the binding position between the ligand compound and the receptor through visualization using the PyMol software. The docking results obtained through the PyRyx software then identified the similarity of the binding position between the ligand compound and the receptor through visualization using the PyMol software.

3. Result and discussion

There are 5 results of this study, namely (1) chromium, potassium, and calcium content of cinnamon (2) total phenolic content (TPC) of cinnamon, (3) total flavonoid content (TFC) of cinnamon, (4) results of molecular docking analysis of polyphenol or flavonoid compound in cinnamon as ligand against Human Salivary α-amylase as receptor, and (5) the results of docking analysis of polyphenol or flavonoid compounds in cinnamon as ligand against protein S of Covid-19 as receptor.

3.1 Chromium, potassium, and calcium levels of cinnamon

One of the antidiabetic potentials of solid sugar preparations is determined by the high levels of minerals it contains. Based on the results of measuring mineral content using ICP which can be seen in Table 1.

| Mineral   | Mineral Content (ppm) of | Cinnamon | White crystal sugar |
|-----------|--------------------------|----------|---------------------|
| Chromium  | 0.524                    | 0.132    |
| Potassium | 4033                     | 625      |
| Calcium   | 17453                    | 59.7     |

When compared the mineral content in cinnamon with white sugar crystals, which were also analyzed in this study were as shown in Table 2.

Table 2. Comparison of Mineral Content between Cinnamon and White Crystal Sugar

According to Table 2, the mineral content (chromium, potassium, and calcium) of cinnamon are much higher than white crystal has. In addition, when compared to the other herbs such as ginger (Cr = 0.007 ppm; Ca = 16 ppm; K = 415 ppm)[15], the mineral content of cinnamon are still much higher. Based on this data, cinnamon has the most likely potential to be further explored as an antidiabetic.

3.2 Total phenolic Content (TPC) of cinnamon

Determination of total phenolic content in cinnamon extract using the Folin-Ciocalteu method (spectrophotometrically) with gallic acid as the standard solution at wave length of 765 nm. The standard solution of gallic acid used is by concentration of 0; 5; 10; 10; 15; 20 and 25 ppm. The results of the measurement of the gallic acid standard solution are then presented in the standard calibration curve in Figure 1.
Based on the standard calibration curve in Figure 1, a linear regression equation is obtained, namely $y = 0.0525x - 0.067$ with an R value of 0.9915. Where the R value is closer to 1, it can be said that the concentration of gallic acid and its absorbance shows a linear relationship.

According to the regression equation and absorbance of the cinnamon extract solution can be determined the TPC of cinnamon as can be seen in Table 3.

### Table 3. Total Phenolic Content (TPC) of Cinnamon

| Sample    | Absorbance of Sample | TPC (ppm) | TPC (%) |
|-----------|----------------------|-----------|---------|
| Cinnamon  | 0.747                | 15,505    | 1,551   |

In addition, when compared to other herbs (0.197%) [16], the TPC cinnamon is higher. The higher of TPC, the higher the benefits of phenolic as an anti-oxidant. The presence of a hydroxyl group that is substituted on the benzene ring of phenolic compound plays an important role in the ability of the compounds to release hydrogen atoms that involved in redox reactions with FolinCiocalteu's reagent. The more hydroxyl groups and double bonds that are conjugated to a phenolic compound, the more potential these compounds are involved in redox reactions and as anti oxidant agent[17].

#### 3.3 Total Flavonoid Content (TFC) of Cinnamon

Determination of total flavonoid content (TFC) in cinnamon extract has been done using a UV-Vis spectrophotometer at wavelength of 510 nm with quercetin as a standard solution.

The variation in concentration of quercetin standard solution are 0; 5; 10; 15; 20; 25; 30; 35; 40; and 45 ppm, and the absorbance of the quercetin standard solution are then presented in the standard calibration curve as can be seen in Figure 2.
Based on Figure 1, a linear regression equation is obtained, namely \( y = 0.0167x + 0.0215 \) with an \( R \) value of 0.9993. Where the \( R \) value which is close to 1, and show a linear relationship. By using the standard curve and the absorbance of cinnamon ethanol extract, can be find out the TFC of the cinnamon as can be seen in Table 4.

**Table 4. Total Flavonoid Content of Cinnamon**

| Sample  | Absorbance | TFC (ppm) | TFC (%) |
|---------|------------|-----------|---------|
| Cinnamon | 0.732      | 42,545    | 4.255   |

Based on Table 4 the total flavonoid content of cinnamon is 4.255%, this value is higher than total flavonoid levels of other herbs that have high antioxidant content such as ginger (0.845%) [16]. The higher the total flavonoid levels, the higher the benefits of flavonoids as antioxidants. Flavonoid compounds have an important role in counteracting free radicals and chelating metal ions. Cinnamon contains lots of flavonols consisting of catechin compounds and their derivatives, kaempferol, and quercetin [18].

The effectiveness of flavonoids as antioxidants is largely determined by the presence of an ortho-hydroxy structure in ring B of the C2-3 double bond conjugated with the C4 oxo functional group, the OH group on C3 in the C ring, and the OH group on C5 in the A ring (Figure 2). The combination of C3-OH and C5-OH groups with C4-carbonyl and C2-3 double bonds can increase the activity of free radical scavenging [19]. Based on this data, cinnamon can be used as additional therapy and has potency to prevent DM.

![Figure 3. Potential of flavonoids as radical scavengers](image)

### 3.4 The results of docking analysis of compound activity in cinnamon against human salivary alpha amylase

As has been proven by previous researchers that cinnamon contains kaemferol and quercetin [18], then in this study will analyze the bond profile of the two compounds against human salivary alpha amylase, using acarbose as a positive control, because acarbose is competitive inhibitor of Human Salivary \( \alpha \)-Amylase [20].

The molecular docking technique was used to determine the interaction type of quercetin and kaempferol as ligands against Human Salivary \( \alpha \)-Amylase receptor.

First, we need to look for the 3D structure of the enzyme in the protein data bank (pdb), as shown in Fig 4.
Figure 4. 3D Human Salivary α-Amylase structure (P04745: AMY_HUMAN) visualized using PyMol software

The next step is to find the position of ligand bindings to human salivary alpha amylase, as can be seen in Figure 5. According to Figure 5, the binding of quercetin and kaempferol on Human Salivary α-Amylase occupies the same position as the binding position acarbose. Based on this binding position, it can be said that quercetin and kaempferol has potency as acarbose, namely as competitive inhibitors of Human Salivary α-Amylase.

Figure 5. Binding position of (a) Acarbose, (b) Quercetin, (c) Kaempferol 3-O-glucoside at the Human Salivary α-Amylase visualized with PyMol software
Further analysis was carried out to determine the amino acid residues of Human Salivary α-Amylase salivary that involved in the binding to quercetin, and kaempferol compounds, and the results are shown in Figure 6 and Table 5.

![Figure 6](image_url)

Figure 6. The amino acid residues of alpha amylase that involved in the bonding with the ligand of (a) Acarbose, (b) Quercetine, (c) Kaempferol 3-O-glucoside, visualized by PyMol software

| Ligand compounds       | Amino acid residue | Distance (Å) | Type of interactions               |
|------------------------|-------------------|--------------|------------------------------------|
| Acarbose               | ARG B:267         | 2.32         | Unfavorable Donor-Donor            |
|                        | 3.07              | Conventional Hydrogen Bond |
|                        | ASP B:317         | 2.47         | Conventional Hydrogen Bond         |
|                        | 2.89              | Unfavorable Acceptor-Acceptor  |
|                        | PHE B:348         | 4.43         | Pi-Alkyl                           |
|                        | ALA A:310         | 3.73         | Carbon Hydrogen Bond               |
|                        | ARG A:267         | 3.16         | Conventional Hydrogen Bond         |
|                        | ASP A:317         | 1.97         | Conventional Hydrogen Bond         |
|                        | ARG 346           | 3.14         | Conventional Hydrogen Bond         |
|                        | GLY B:351         | 2.36         | Conventional Hydrogen Bond         |
|                        | ALA B:310         | 2.72         | Conventional Hydrogen Bond         |
| Quercetine             | ARG A:346         | 2.35         | Unfavorable Donor-Donor            |
|                        | ARG A:267         | 2.19         | Unfavorable Donor-Donor            |
|                        | HIS A:305         | 3.21         | Conventional Hydrogen Bond         |
|                        | PHE A:348         | 4.45         | Pi-Pi Stacked                      |
|                        | 4.07              | Pi-Pi Stacked |
|                        | ASN A:350         | 3.26         | Conventional Hydrogen Bond         |
| Kaempferol 3-O-glucoside| HIS A:305         | 3.16         | Conventional Hydrogen Bond         |
|                        | GLY A:304         | 2.40         | Conventional Hydrogen Bond         |
|                        | ALA A:310         | 3.49         | Pi-Sigma                           |
|                        | ALA B:310         | 5.00         | Pi-Alkyl                           |
|                        | PHE A:348         | 4.10         | Pi-Pi Stacked                      |
|                        | 4.58              | Pi-Pi Stacked |
|                        | GLY B:351         | 3.21         | Conventional Hydrogen Bond         |
|                        | ARG A:346         | 3.22         | Conventional Hydrogen Bond         |
|                        | 2.30              | Unfavorable Donor-Donor            |
|                        | THR A:314         | 2.87         | Conventional Hydrogen Bond         |
Based on Figure 6 and Table 5, it can be seen that in the binding to human salivary alpha amylase, kaemferol and quercetin involve some of the same amino acid residues as acarbose, although with slightly different bond types and distances. Intermolecular interactions such as hydrogen bonds and hydrophobic interactions play an important role in the stabilization of protein-ligand interaction, as well as affecting their binding affinity.

The next in silico analysis is the determination of binding affinity between ligand and receptor using the Autodock Vina program in the PyRx 0.8 software, and the results can be seen in Table 6.

| Table 6. Data of Binding Affinity of Acarbose, Quercetin dan Kaempferol against Human Salivary α-Amylase Enzyme |
|-----------------------------------------------|
| **Ligand** | **Binding Affinity (kcal/mol)** against human salivary alpha amylase |
|          | Mode 0 | Mode 1 | Mode 2 | Mode 3 | Mode 4 | Mode 5 | Mode 6 | Mode 7 | Mode 8 | Average |
| Acarbose  | -9.0   | -8.9   | -8.8   | -8.5   | -8.4   | -8.4   | -8.3   | -8.3   | -8.3   | -8.6    |
| Quercetin | -8.6   | -8.5   | -8.5   | -8.4   | -8.3   | -8.3   | -8.1   | -8.1   | -8.0   | -8.3    |
| Kaempferol| -9.0   | -8.8   | -8.5   | -8.3   | -8.2   | -8.2   | -8.0   | -8.0   | -7.7   | -8.3    |

In molecular docking studies, the more negative of binding affinity, it means that the binding between the ligand - protein is stronger. Based on Table 6, the docking results between quercetin and kaempferol with Human Salivary α-Amylase show that quercetin and kaempferol has average binding affinity (-8.3 kcal/mol, and -8.3 kcal/mol), is close to the average binding affinity of acarbose (-8.6 kcal/mol). Based on this, it can be predicted that between quercetin and kaempferol with Human Salivary α-Amylase to form a stable protein-ligand complex. Based on this in silico data both the quercetin dan kaempferol, that can be found in cinnamon are potential as a competitive inhibitor of the salivary human alpha amylase enzyme, so the cinnamon also potential as anti diabetes agent.

3.5 The in silico analysis results of the active compounds in cinnamon as anticovid-19

It has been proven by previous research that cinnamon contains kaemferol, routine and quercetin which are also shown to be active in inhibiting the growth of a type of RNA virus[21], but its activity against the Covid-19 virus is not yet known. In this study, a docking study was carried out using the 3 compounds as ligand and chain E spike protein of SARS-CoV-2 as receptor. The result of the binding position between the kaempferol, quercetin, and routine ligand compounds with the SARS-CoV-2 glycoprotein spike were visualized using PyMol software, and can be seen in Figure 7.
Figure 7. Ligand Binding position of (a) Kaempferol, (b) Quercetin, and (c) Rutine at the chain E of Spike glycoprotein of SARS-CoV-2, visualized with PyMoL software

According to Figure 7, the binding site all of the three ligands in Spike glycoprotein of SARS-CoV-2 are relatively the same. This can also be seen in the amino acid residues of the Spike protein which are involved in its bonding with the various ligands, as can be seen in Figure 8 and Table 7.

![Figure 8](image_url)

Figure 8. The amino acid residues of E-chain of Spike protein SARS-CoV-2 which involved in binding to ligand of (a) Kaempferol, (b) Quercetin, and (c) Rutine, visualized by PyMoL software

| Ligand compounds | Amino acid residue | Distance (Å) | Type of interactions                      |
|------------------|--------------------|--------------|------------------------------------------|
| Kaempferol       | THR E:430          | 3.84         | Conventional Hydrogen Bond               |
|                  | ARG E:355          | 3.57         | Conventional Hydrogen Bond               |
|                  | PHE E:464          | 6.21         | Conventional Hydrogen Bond               |
|                  | LEU E:517          | 5.73         | Pi-Pi Stacked                            |
|                  |                    | 3.76         | Conventional Hydrogen Bond               |
Based on Figure 8 and Table 7, it can be seen that the amino acid residues of Chain E Spike protein SARS-CoV-2 that involved in binding to kaempferol, quercetin, and rutine, are located in RBD or near RBD of the protein, namely residues no 417-505, which plays an important role in binding with its receptors in the host cell, namely the ACE2 protein [22].

To see the bond strength of the ligands studied against the RBD region, their binding affinity has been analyzed using the Autodock Vina program in the PyRx 0.8 software, and the result are shown in Table 8.

| Ligand         | Binding Affinity (kcal/mol) against Chain E of Spike protein of SARS-CoV-2 |
|----------------|--------------------------------------------------------------------------------|
| Kaempferol 3-O-glucoside | -7.9 -7.7 -7.6 -7.4 -7.3 -7.1 -7.0 -7.0 -6.8 -7.3                  |
| Quercetin      | -8.5 -8.0 -7.9 -7.9 -7.8 -7.5 -7.2 -7.2 -7.2 -7.7                  |
| Rutin          | -8.7 -8.6 -8.5 -8.5 -8.4 -8.3 -8.3 -8.2 -8.2 -8.4                  |

Based on Table 8, the docking results shows that average binding affinity of kaempferol, quercetin and rutine were -7.3, -7.7, and -8.4 kcal/mol, respectively. Based on this data, and the data on Table 7, it can be predicted that all of three compounds that occured in the cinnamon can bind to RBD of chain E.S protein of Covid-19, with a relatively strong binding affinity, so cinnamon has the potential to be an anti-covid-19.

Based on the content of bioactive substances, Ca, K and Cr as well as the content of polyphenols and flavonoids, cinnamon has the potency to be an anti-diabetic agent. This is also supported by in silico analysis that kaempferol 3-O-glucoside and quercetin in cinnamon
have the same bonding pattern as acarbose to the alpha amylase enzyme. Meanwhile, the content of quercetin and routine of cinnamon has the potential to be anti-covid-19.

4. Conclusion
The results have shown that the levels of Cr, K, Ca, TPC and TFC of cinnamon, were 0.524 ppm, 4033 ppm, 17453 ppm, 1.55% and 4.26%, respectively. The results of in silico analysis has shown that kaempferol 3-O-glucoside and quercetin in cinnamon are able to bind to human saliva α-Amylase on its active site with the binding affinity that are relatively the same as acarbose has. The docking analysis also has shown that kaempferol, quercetin and rutin of cinnamon were able to bind to the Receptor Binding Domain (RBD) of S protein of covid19, so that these compounds also have the potency to be anticovid19.

Acknowledgment
The authors are very grateful for Rector of State University of Malang, for providing research fund to this study through 2020 PNBP funds.

References
[1] International Diabetes Federation. 2018. *IDF Diabetes Atlas*. Edisi ke-8. International Diabetes Federation. Brussels.
[2] Malathi, L., Masthan, K.M.K., Balachander, N., Aravindha Babu, N. 2013. Estimation of salivary amylase in diabetic patients and saliva as diagnostic tool in early diabetic patients. *Journal of Clinical and Diagnostic Research*. [Online] 7 (11), 2634–2636. Available from: doi:10.7860/JCDR/2013/7574.3634.
[3] Chethan, J., Bb, P. & Hassan, S. 2016. Assessment of Salivary Alpha Amylase level in subjects with Diabetes mellitus - A Cross Sectional Study. 2(September), 79–82.
[4] The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). LiverTox, Clinical and Research information on Drug-induced liver injury-Acarbose. [Drug Record] http://livertox.nlm.nih.gov/Acarbose.htm#casereport. Last updated: 2016-03-24 01:30:41 PM (EST) (2016).
[5] Phung, O.J, Yin, R.V. 2015. Effect of chromium supplementation on glycated hemoglobin and fasting plasma glucose in patients with diabetes mellitus. *Nutrition journal*, 14:1.
[6] Stearns DM. 2000. "Is chromium a trace essential metal?". *BioFactors*. 11 (3): 149–62. doi:10.1002/biof.5520110301. PMID 10875302.
[7] Indriani, C. 2012. Hubungan Kadar Kalium dengan Kadar Gula Dewasa dan Anak-Anak dengan Solusi Herbal. Yogyakarta: Penerbit Nuga Medika.
[8] Frank H.U., Anatassios, G.P., Lau J., and Bess D.H. 2007. The Role of Vitamin D and Calcium in type 2 diabetes. A systematic Review and Meta Analysis. *J Clin Endocrinol Metab*. 92(6): 2017-2029.
[9] Robertson RP, Davis C, Larsen J. 2006. Pancreas and islet transplantation in type 1 diabetes. *Diabetes Care* 2006; 29:935.
[10] Isnindar dan Zahid, M.. 2013. Ulasan Ilmiah: Penggunaan Antibiotik Fluorokulinolon Sebagai Obat Hewan. *Buletin Pengujian Mutu Obat Hewan* 12(13): 22.
[11] Zhao X, Carey EE, Young JE, Wang W, Iwamoto T. 2007. Influence of organic fertilization, high tunnel environment, and postharvest storage on phenolic compounds in lettuce. *Hortscience*. 42(1): 71-76.
[12] Astawan, M. dan Kasih, A. 2008. Khasiat Warna Warni Makanan. Gramedia Pustaka Utama. Jakarta.
[13] Lugasi, A., & Hovari, J. 2003. Antioxidant properties of commercial alcoholic and nonalcoholic beverages. Nahrung/Food, 47, 79–86.

[14] Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J. 2020. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet.

[15] Shirin, A. and Jamuna, P. 2010. Chemical Composition and Antioxidant Properties of Ginger Root (Zingiber officinale). Journal of Medicinal Plants Research, 4(24), pp. 2674-2679.

[16] Adawiah, Sukandar, D., Muawanah, A. 2015. Aktivitas dan Kandungan Komponen Bioaktif Sari Buah Namnam. Jurnal Kimia VALENSI: Jurnal Penelitian dan Pengembangan Ilmu Kimia, 1(2), November 2015, 130-136.

[17] Widyawati, P.S. 2016. Determination of antioxidant capacity in Plucheia indica Less leaves extract and its fractions. International Journal of Pharmacy and Pharmaceutical Sciences, 8(9), 32-36.

[18] Amic, D.D., D. Beslo, and Trinajstic, Structure-radical scavenging activity relationship of flavonoids. Croatia Chem.Acta, 2003. 76(1): p. 55-61.

[19] Prasetyaningrum Utami, R., Baskara, R. 2012. Antioxidant Activity, Total Phenolic Content, and Antibacterial Activity Of Cinnamon Bark Oil and Oleoresin. Jurnal Teknosains Pangan Vol 1 No 1 Oktober 2012.

[20] Sirichai A, Orathai L, Ubonwan P, Aukkrapon M, Chaturong S. (2011). Inhibitory activity of cinnamon bark species and their combination effect with acarbose against intestinal alpha glucosidase and pancreatic alpha amylase. Plant Foods Hum Nutr 66:143–148.

[21] Ganesan, S., Faris, A. N., Comstock, A. T., Wang, Q., Nanua, S., Hershenson, M. B., & Sajjan, U. S. (2012). Quercetin inhibits rhinovirus replication in vitro and in vivo. Antiviral Research, 94(3), 258–271. doi:10.1016/j.antiviral.2012.03.005

[22] Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Wang, X. 2020. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. doi:10.1038/s41586-020-2180-5.