ORIGINAL PAPER

An in Silico Approach Reveals the Potential Function of Cyanidin-3-o-glucoside of Red Rice in Inhibiting the Advanced Glycation End Products (AGES)-Receptor (RAGE) Signaling Pathway

Ayu Tri Agustin[1,2], Anna Safitri[2,3], Fatchiyah Fatchiyah[1,2]

[1]Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang, Indonesia

[2]Research Center of Smart Molecule of Natural Genetics Resource, Brawijaya University, Malang, Indonesia

[3]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang, Indonesia

Corresponding Author: Fatchiyah Fatchiyah, Research Center of Smart Molecule of Natural Genetics Resource, Brawijaya University, and Malang, Indonesia. Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang, Indonesia. Tel: +62-341-575-841. Email: fatchiya@ub.ac.id. ORCID ID: https://orcid.org/0000-0001-6241-9665.

doi: 10.5455/aim.2020.28.170-179

ACTA INFORM MED. 2020 SEP 28(3): 170-179

Received: Jul 05, 2020

Accepted: Auh 26, 2020

ABSTRACT

Introduction: Advanced glycation end products (AGEs) contribute to the pathogenesis of chronic inflammation, diabetes, micro and macrovascular complications, and neurodegenerative diseases through the binding with RAGE. Natural compounds can act as an alternative in disease therapy related to the AGEs-RAGE interactions. Cyanidin-3-O-glucoside is one of the potential anthocyanins found in red rice. Cyanidin-3-O-glucoside in red rice may interfere with the AGEs-RAGE signaling so that the potential mechanism of their interaction needs to be elucidated. **Aim**: This study aimed to investigate the potency of cyanidin-3-O-glucoside in red rice as an inhibitor of AGE-RAGE signaling pathway through *in silico* analysis. **Methods**: Our study used the 3D structures of AGEs and Cyanidin-3-O-glucoside compounds from PubChem and Receptor for AGEs (RAGE) from the RCSB Protein Data Bank (PDB) database. The molecular interactions of those compounds and RAGE were established using Hex 8.0 software, then visualized using Discovery Studio 2016 software. **Results**: Argypirimidine, pentosidine, pyrralline, and imidazole bound to the ligand-binding domain of RAGE with the binding energy of -247 kcal/mol, -350.4 kcal/mol, -591.1 kcal/mol, and -100.4 kcal/mol, respectively. The presence of cyanidin-3-O-glucoside in the imidazole-RAGE-cyanidin-3-O-glucoside complex could inhibit the interaction of imidazole-RAGE with a binding energy of -299 kcal/mol, which was lower than of imidazole-RAGE complex. The establishment of AGEs-Cyanidin-3-O-glucoside-RAGE complex showed that cyanidin-3-O-glucoside, which bound first to Argypirimidine and Pyrralline, could bound to RAGE at the same residue as those two AGEs did with the binding energy of -411.8 kcal/mol and -1305 kcal/mol, respectively. Based on the binding site location and energy, cyanidin-3-O-glucoside might have a biological function as an inhibitor of AGEs-RAGE interactions, which was more likely through the establishment of AGEs-cyanidin-3-O-glucoside-RAGE. **Conclusion**: This study suggests that cyanidin-3-O-glucoside in red rice can be a potential AGEs-RAGE inhibitor, leading to the regulation of the pro-inflammatory and oxidative damage in the cellular pathway.

Keywords: argypirimidine, cyanidin-3-O-glucoside, imidazole, pentosidine, pyrralline

1. INTRODUCTION

Advanced glycation end products (AGEs) are the biomarkers of hyperglycemia and pro-inflammatory, which result from the non-enzymatic glycation of protein and sugar (1). The endogenous formation of AGEs involves arginine, lysine, and sulfur-containing amino acids, which are prone to glycoxidation; lipids; as well as glucose, ribose, mannose, and reactive triose intermediates that are sensitive to oxidation and degradation (2,3). AGEs can also be produced from exogenous sources, such as high fat and high sugar diets processed in high temperature (4). Different AGEs compounds can be classified as fluorescent cross-linking AGEs, such as pentosidine, glyoxal-lysine dimer, methylglyoxal-lysine dimer; and non-fluorescent non-cross-linking AGEs such as pyrralline, argypirimidine, and imidazole (5). AGEs, especially argypirimidine, imidazole, pentosidine, and Pyrralline, bind to the C domain of Receptor for AGEs (RAGE) (6)cardiovascular disease, stroke, neuropathy, and nephrop-

athy. Different studies have been done to employ AGEs as drug targets for the diseases therapy. In previous study, we have found bioactive peptide from Ethawah goat milk for anti-diabetic that may work through inhibition of AGE receptor function. However, the mechanism of bioactive peptides inhibits AGE- AGE receptor (RAGE. RAGE consists of an extracellular region with one V-type and two C-type of immunoglobulin domains (7). RAGE exists in almost all cells, including immune cells, vascular cells, adipocytes, podocytes, cardiomyocytes, neurons, and others (8)detoxification, intracellular disposition, extracellular release, and induction of signal transduction. These processes modulate the response to hyperglycemia, obesity, aging, inflammation, and renal failure, in which AGE formation and accumulation is facilitated. It has been shown that endogenous anti-AGE protective mechanisms are thwarted in chronic disease, thereby amplifying accumulation and detrimental cellular actions of these species. Atop these considerations, receptor for advanced glycation endproducts (RAGE. The binding of AGEs with RAGE contributes to the development of metabolic disease through the activation of NF-κB, which can induce the secretion of pro-inflammatory cytokines, such as TNF-α, IL-1α, and IL-6 (9). The excess production of AGEs can cause strokes, cardiovascular disease, diabetic retinopathy, autonomic neuropathy, and other vascular complications of diabetes in chronic hyperglycemic states (8,10)detoxification, intracellular disposition, extracellular release, and induction of signal transduction. These processes modulate the response to hyperglycemia, obesity, aging, inflammation, and renal failure, in which AGE formation and accumulation is facilitated. It has been shown that endogenous anti-AGE protective mechanisms are thwarted in chronic disease, thereby amplifying accumulation and detrimental cellular actions of these species. Atop these considerations, receptor for advanced glycation endproducts (RAGE.

Several drugs used in disease therapy target the AGEs and RAGE signaling. Atorvastatin acts as a modulator of AGEs through its antioxidant activity, which can inhibit the formation of AGE and prevent macrovascular complications. Rosiglitazone was reported to reduce RAGE expression in the experimental models of myocardial fibrosis. However, the side effects of these drugs are not yet clearly understood (10). Foods with certain nutritional composition and bioactive compounds are the alternative option to control or prevent disease manifestations. *In vitro* study showed that anthocyanin compounds in Rosella extract could reduce the levels of AGEs (n-carboxymethyl-lysine), leading to the prevention of NF-κB activation and TNF-α expression (11). Red grape skin extract was reported to decrease the levels of fructosamine, N^{ε}-(carboxymethyl) lysine (CML), and protein oxidation effectively so that the inhibition of AGEs formation occurred (12)RGSE was screened for its potential as an antioxidant using various in vitro models.Methods: Antioxidant activity was measured by 2,2-diphenyl-1-picrylhydrazyl (DPPH. The inhibitory effect on the AGE formation was also found in the anthocyanin extracts of red raspberry (59.1%) and strawberry (42.8%) at 100 μg/mL (13).

One of the diets consumed as a staple food for energy needs is rice (*Oryza sativa* L.) (14). Red rice has a glycemic index (GI) of 68. It is lower than white rice, which has a GI of 72. Foods with high GI can increase blood glucose quickly, and vice versa (15). Red rice is also rich in anthocyanin compounds. One of the anthocyanins in red rice is cyanidin-3-glucoside (up to 67%), which has antioxidant, anti-inflammatory, and anti-cancer activity (16,17). Previous study examined the role of bioactive peptides from Etawah crossbreed goat milk in inhibiting AGE-RAGE interactions. Bioactive peptides that bind to RAGE can block AGEs from interacting with the functional side of RAGE so that damage to the signal transduction cascade at the cellular level does not occur (6)cardiovascular disease, stroke, neuropathy, and nephropathy. Different studies have been done to employ AGEs as drug targets for the diseases therapy. In previous study, we have found bioactive peptide from Ethawah goat milk for anti-diabetic that may work through inhibition of AGE receptor function. However, the mechanism of bioactive peptides inhibits AGE- AGE receptor (RAGE. The study of the plant bioactive compounds with inhibitory activity against AGE-RAGE interactions is still limited. Therefore, we aimed to identify the potential function of cyanidin-3-O-glucoside of red rice in the prevention of an AGEs-RAGE signaling by *in silico*.

2. METHODS

Protein and Ligand Preparation

Proteins and ligands were obtained from the database of RCSB Protein Data Bank (PDB) (http://www.rcsb.org/structure/3O3U) and PubChem (http://pubchem.ncbi.nl.nih.gov/) . The RAGE (PDB ID: 3O3U) was used in this study. The ligands and water molecules incorporated in its 3D structures were removed using Discovery Studio Ver. 4.1 software. The ligands were cyanidin-3-O-glucoside (CID 12303203) and several AGEs, namely, argypirimidine (CID 17750123), imidazole (CID 795), pyrraline (CID 122228), and pentosidine (CID 119593). The energy minimization was performed for each ligand using PyRx Ver. 0.8 software. The SDF file format of each ligand was converted to PDB format using Open Babel.

Ligand-Protein Docking and Visualization

Each of AGE (argypirimidine, imidazole, pyrraline, and pentosidine) was assessed for the ability to bind RAGE and or cyanidin-3-O-glucoside. We would like to compare the interactions that occurred between the AGE-RAGE complex with and without the presence of cyanidin-3-O-glucoside. The possibility of cyanidin-3-O-glucoside to bind AGE, leading to the prevention of AGEs interaction with RAGE, was also investigated. Therefore, the docking of AGE-RAGE, AGE-cyanidin-3-O-glucoside, AGE-RAGE-cyanidin-3-O-glucoside, and AGE-cyanidin-3-O-glucoside-RAGE were established using Hex 8.0 software with Shape + Electro + DARS mode. Amino acid residues, types and binding energies of receptor-ligand interactions were also identified using this software. The visualization of the molecular interactions was performed using Discovery Studio Ver. 4.1 software.

3. RESULTS

The Possible Interactions formed in the Binding of AGEs-RAGE

Interactions between AGEs (argypirimidine, pentosidine, pyrralline, and imidazole) and RAGE had maintained by hydrogen and hydrophobic bonds (Table 1A). Residues involved in argypirimidine-RAGE interactions were LYS42, LYS46, GLY1213, LEU1214, and ARG1218 (Figure 1A). Pentosidine could bind to ALA52, ASN1025, and PRO1215 of RAGE (Figure 1B). In the pyrralline-RAGE complex, the amino acid residues involved were TRP62, ALA63, TRP230, LEU262, and LEU299 (Figure 1C). There were four amino acid residues of RAGE that capable of interacting with imidazole, namely ALA63, ASP65, MET330, and TRP340 (Figure 1D). The binding energy of the AGEs-RAGE interaction from the lowest to the highest was the complex of pyrralline-RAGE, pentosidine-RAGE, argypirimidine-RAGE, and Imidazole-RAGE with the energy of -591.1 kcal/mol, -350.4 kcal/mol, -247 kcal/mol, and -100.4 kcal/mol, respectively.

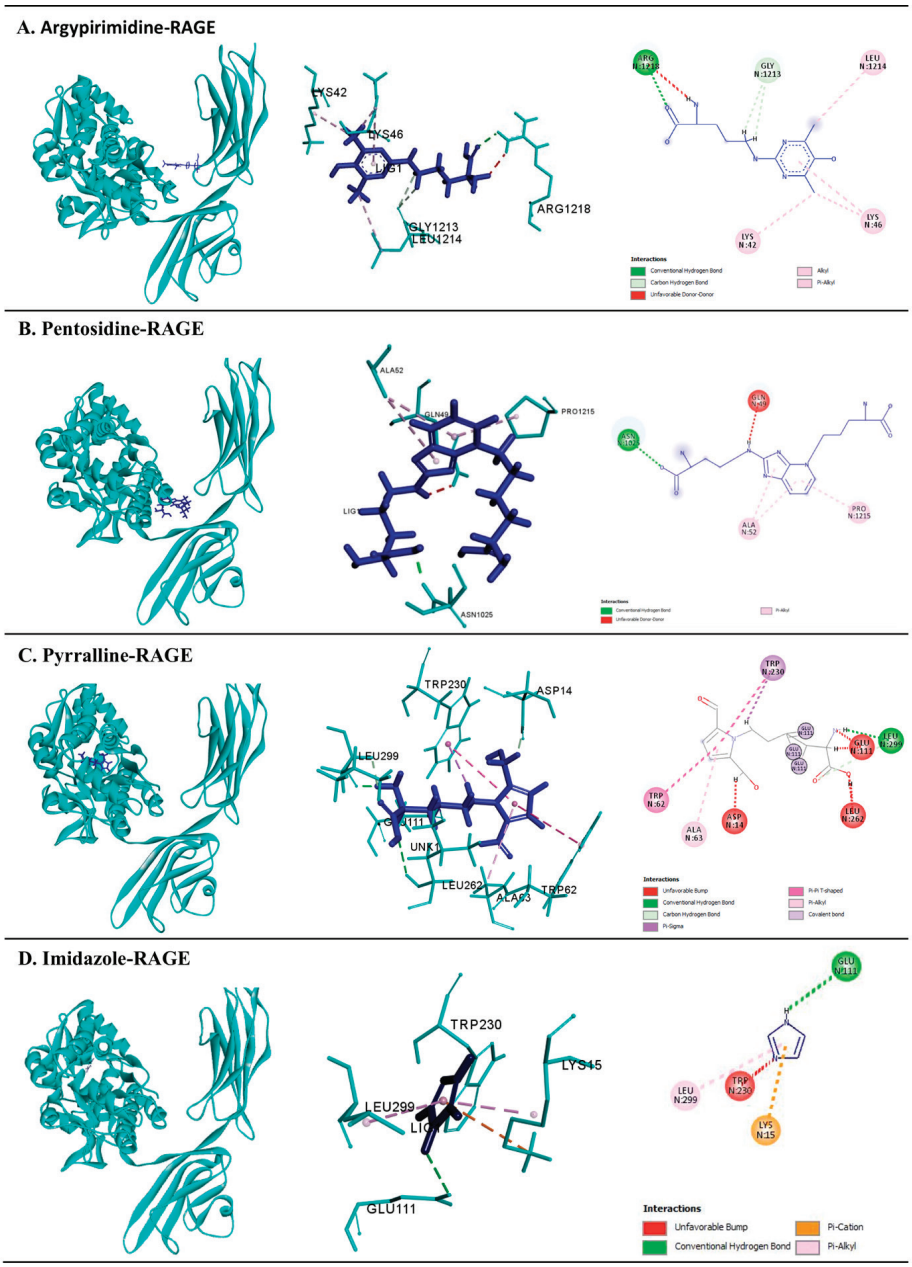

Figure 1. Visualization of AGEs-RAGE molecular docking; (A) Argypirimidine-RAGE; (B) Pentosidine-RAGE; (C) Pyrralline-RAGE; (D) Imidazole-RAGE. AGEs are shown in dark blue color. RAGE is shown in light blue color.

The Interaction of AGEs-RAGE Complex with Cyanidin-3-O-glucoside

The binding of AGEs-RAGE complex with Cyanidin-3-O-glucoside was identified by the bonds formed, the type of bond, and the binding energy (Table 1B). The AGEs-RAGE-cyanidin-3-O-glucoside complex analysis showed that argypirimidine, pentosidine, pyrralline, and imidazole could still bind to RAGE at the same position as in the complex of AGEs-RAGE (Figure 2A-C). Interestingly, cyanidin-3-O-glucoside could bind to the ALA63 of RAGE in the imidazole-RAGE-cyanidin-3-O-glucoside complex. Imidazole was reported to interact in this residue as well. This result indicated that cyanidin-3-O-glucoside was able to compete with imidazole in binding the RAGE (Figure 2D). The docking of the imidazole-RAGE complex with cyanidin-3-O-glucoside had the energy binding of -299 kcal/mol, which was lower than the energy needed in the interaction of imidazole and RAGE. Therefore, cyanidin-3-O-glucoside is easy to interact with the Imidazole-RAGE complex.

The Interaction of AGES with Cyanidin-3-O-glucoside

Chemical bonds and binding energy of the interaction of AGEs-cyanidin-3-O-glucoside are presented in Table 2A. The hydrogen and hydrophobic bonds stabilized the binding of cyanidin-3-O-glucoside and each of the four AGEs (Figure 3A1-D1). The binding energy needed in those interactions from the lowest to the highest was -164 kcal/mol (argypirimidine-cyanidin-3-O-glucoside complex), -163,2 kcal/mol (pentosidine-cyanidin-3-O-glucoside complex), -150,3 kcal/mol (pyrralline-cyanidin-3-O-glucoside complex), and -95,7 kcal/mol (imidazole-cyanidin-3-O-glucoside complex). Of four AGEs, the binding of argypirimidine and cyanidin-3-O-glucoside was the strongest due to the highest amount of chemical bonds, and the two hydrogen bonds stabilized them.

The Binding Analysis of AGEs-Cyanidin-3-O-glu-

coside Complex and RAGE

The molecular docking result for the AGEs-cyanidin-3-O-glucoside complex with RAGE is presented in Table 2B. Our study suggested that cyanidin-3-O-glucoside might compete with the two AGEs, argypirimidine and pyrraline. Cyanidin-3-O-glucoside was able to bind RAGE at the same residue as argypirimidine and pyrraline did. In argypirimidine-cyanidin-3-O-glucoside-RAGE complex, hydrophobic bonds maintained the interaction of argypirimidine with ALA52 and TYR341 of RAGE. Cyanidin-3-O-glucoside also established a hydrophobic interaction with the ALA52 and a hydrogen bond with TYR341 (Figure 3A2). In pyrralline-cyanidin-3-O-glucoside-RAGE complex, the TRP230 of RAGE was involved in the interaction with pyrrallinne through hydrogen bond. Cyanidin-3-O-glucoside had hydrophobic interactions with this residue as well (Figure 3C2). Cyanidin-3-O-glucose can bind to RAGE and compete with imidazole in the imidazole-RAGE-cyanidin-3-O-glucose complex. However, cyanidin-3-O-glucose, which was first bound to Imidazole, could not interact with RAGE at all (Figure 3D2).

Each of four AGEs that connected with cyanidin-3-O-glucoside had different binding sites in RAGE compared with the interactions that occurred in the AGEs-RAGE complex (Figure 3A2-D2). This study implied that the presence of cyanidin-3-O-glucoside could affect the AGEs-RAGE interaction. The complex of pyrralline-cyanidin-3-O-glucoside-RAGE, pentosidine-cyanidin-3-O-glucoside-RAGE, argypirimidine-cyanidin-3-O-glucoside-RAGE, and imidazole-cyanidin-3-O-glucoside-RAGE showed the binding energy of -1305 kcal/mol, -462.2 kcal/mol, -411.8 kcal/mol, and 108.4 kcal/mol, respectively (Table 2B). The binding of the pyrralline-cyanidin-3-O-glucoside-RAGE complex had the strongest bond because it required the smallest binding energy. In addition, its interactions were stabilized by six hydrogen bonds and more chemical bonds than other complexes. Therefore, cyanidin-3-O-glucoside could be a potential inhibitor of AGEs-RAGE interaction through its binding to RAGE at the same amino acid residue with AGEs showed in the complex of AGE-Cyanidin-3-O-glucoside-RAGE.

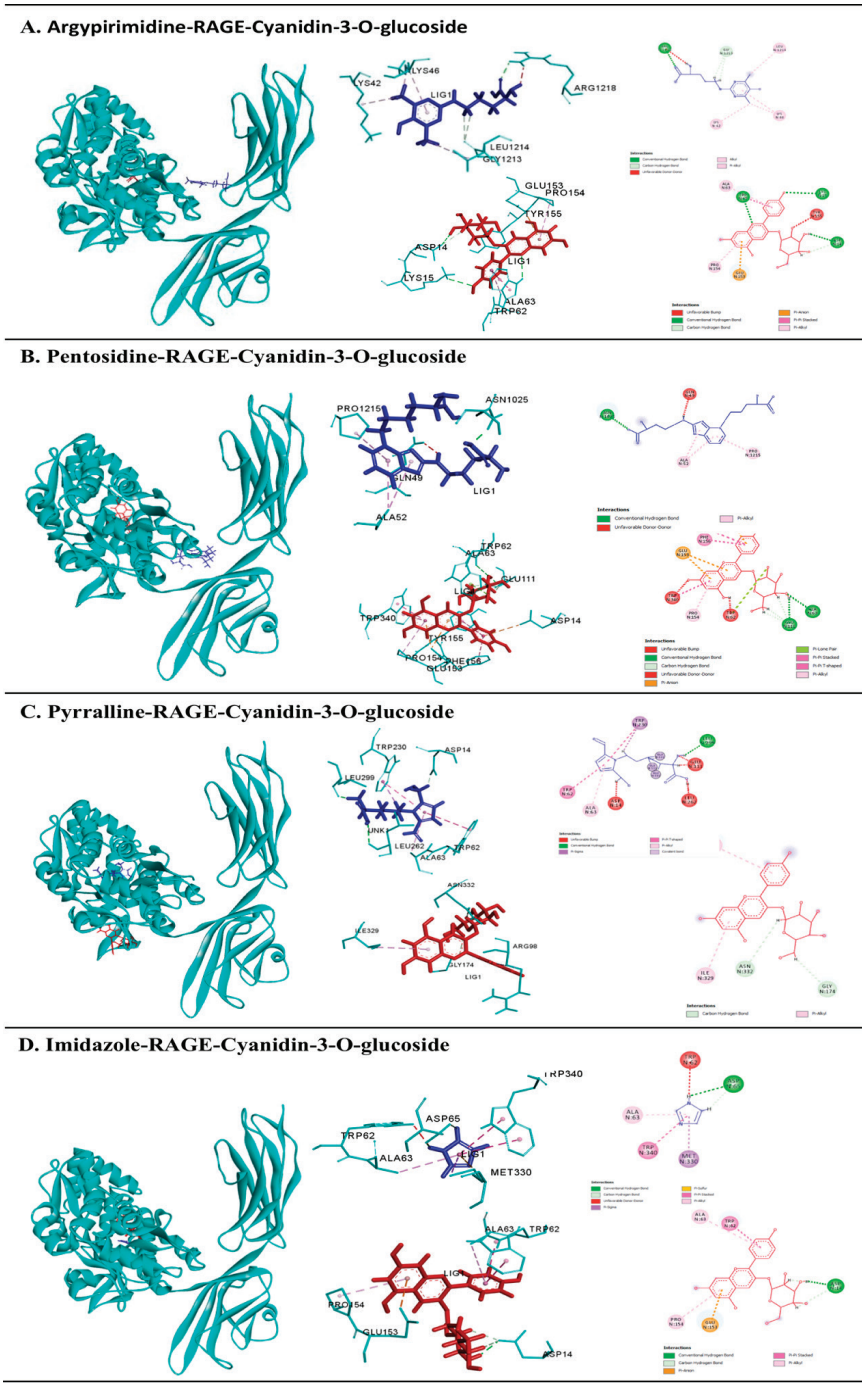

Figure 2. Visualization of AGEs-RAGE-Cyanidin-3-O-glucoside molecular docking. AGEs are shown in dark blue color. RAGE is shown in light blue color. Cyanidin-3-O-glucoside is in red color.

4. DISCUSSION

RAGE is a transmembrane protein, which consists of three different extracellular domains (a V-type domain (residue 23-116), C1 domain (residue 124-221), and C2 domain (residue 227-317)), a transmembrane helix (residue 343-363), and a cytoplasmic tail (364-404) (18)including vascular diseases, cancer, neurodegeneration and diabetes. Its oligomerization is believed to be important in signal transduction, but RAGE oligomeric structures and stoichiometries remain unclear. Different oligomerization modes have been proposed in studies involving different truncated versions of the extracellular parts of RAGE. Here, we provide basic characterization of the oligomerization patterns of full-length RAGE (including

the transmembrane (TM. This study showed that argypirimidine, pentosidine, pyrralline, and imidazole could interact with RAGE in the V and C domain. Previous study also reported that the four AGEs bound to the C domain of RAGE (6)cardiovascular disease, stroke, neuropathy, and nephropathy. Different studies have been done to employ AGEs as drug targets for the diseases therapy. In previous study, we have found bioactive peptide from Ethawah goat milk for anti-diabetic that may work through inhibition of AGE receptor function. However, the mechanism of bioactive peptides inhibits AGE- AGE receptor (RAGE. The V domain is a ligand-binding domain that has a role in the extracellular and intracellular signal transduction. The C domain plays an important as a mediator that supports the function of V domain (19,20)amyloid fibrils, amphoterins and S100/calgranulins. The overlapping distribution of these ligands and cells overexpressing RAGE results in sustained receptor expression which is magnified via the apparent capacity of ligands to upregulate the receptor. We hypothesize that RAGE-ligand interaction is a propagation factor in a range of chronic disorders, based on the enhanced accumulation of the ligands in diseased tissues. For example, increased levels of AGEs in diabetes and renal insufficiency, amyloid fibrils in Alzheimer's disease brain, amphoterin in tumors and S100/calgranulins at sites of inflammation have been identified. The engagement of RAGE by its ligands can be considered the 'first hit' in a two-stage model, in which the second phase of cellular perturbation is mediated by superimposed accumulation of modified lipoproteins (in atherosclerosis.

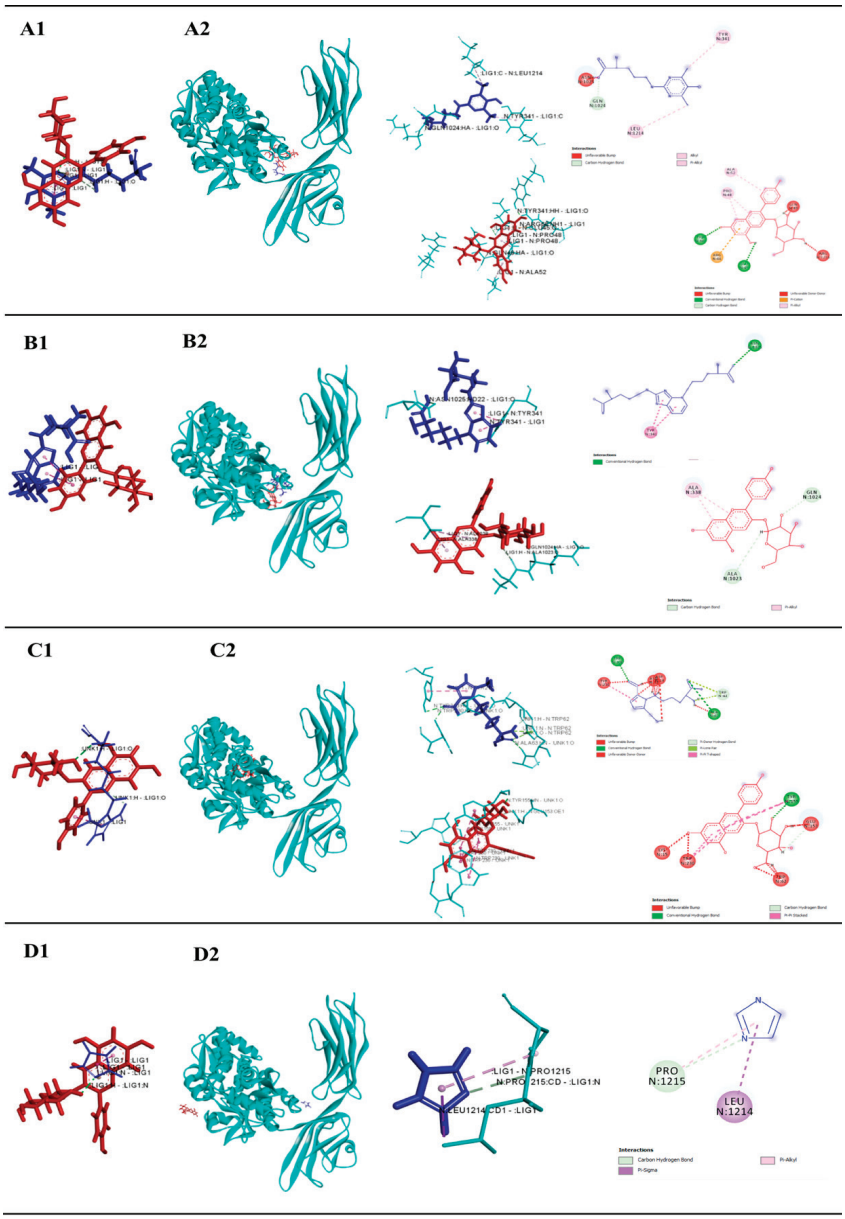

Figure 3. The molecular docking visualization of AGEs-Cyanidin-3-O-glucoside complex and RAGE. AGEs-Cyanidin-3-O-glucoside complex is in the left side (A1-D1) and AGE-Cyanidin-3-O-glucoside-RAGE complex is in the right side (A2-D2).

RAGE is activated through the binding with AGEs that cause the stimulation of signal transduction and the activation of NF-kB. NF-κB activates transcription genes to secrete pro-inflammatory cytokines, such as TNF-α, IL-1α, and IL-6. It also causes the increase of vascular cell adhesiveness and oxidative stress that can cause vascular complications of diabetes (9). The binding of AGEs (argypirimidine, pentosidine, pyrralline, and imidazole) with RAGE can modulate the complex cellular signaling cascade leading to inflammation and oxidative stress which trigger the development of the pathogenesis of diabetes, cardiovascular, atherosclerosis, stroke, and cancer (21–23)the products of nonenzymatic glycoxidation of proteins and lipids. The finding that AGEs stimulate signal transduction cascades through the multiligand receptor RAGE unveiled novel insights into diabetes and its complications. Inextricably woven into AGE-RAGE interactions in diabetes is the engagement of the innate and adaptive immune responses. Although glucose may be the triggering stimulus to draw RAGE into diabetes pathology, consequent cellular stress results in release of proinflammatory RAGE ligands S100/calgranulins and HMGB1. We predict that once RAGE is engaged in the diabetic tissue, a vicious cycle of ligand-RAGE perturbation ensues, leading to chronic tissue injury and suppression of repair mechanisms. Targeting RAGE may be a beneficial strategy in diabetes, its complications, and untoward inflammatory responses. Receptor for AGE (RAGE. The interaction of the four AGEs with RAGE is stabilized by hydrogen and hydrophobic bonds. When the hydrogen atoms of a molecule bind to other molecules that are more electronegative, the hydrogen bonds are created (24). These bonds play a role to stabilize the

Interaction		Point interaction	Donor atom	Acceptor atom	Type	Chemistry bond	Energy binding (kcal/mol)
A. Interaction of Advanced Glycation End Products (AGEs)-receptor (RAGE)							
Argypirimidine-RAGE		N:ARG1218:HH11 - :LIG1:OXT	N:ARG1218:HH11	:LIG1:OXT	Conventional Hydrogen Bond	Hydrogen Bond	-247
		:LIG1:H - N:GLY1213:O	:LIG1:H	N:GLY1213:O	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:GLY1213:O	:LIG1:H	N:GLY1213:O	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1:C - N:LEU1214	:LIG1:C	N:LEU1214	Alkyl	Hydrophobic	
		:LIG1:C - N:LYS42	:LIG1:C	N:LYS42	Alkyl	Hydrophobic	
		:LIG1:C - N:LYS46	:LIG1:C	N:LYS46	Alkyl	Hydrophobic	
		:LIG1 - N:LYS46	:LIG1	N:LYS46	Pi-Alkyl	Hydrophobic	
Pentosidine-RAGE		N:ASN1025:HD21 - :LIG1:O	N:ASN1025:HD21	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	-350,4
		:LIG1 - N:ALA52	:LIG1	N:ALA52	Pi-Alkyl	Hydrophobic	
		:LIG1 - N:PRO1215	:LIG1	N:PRO1215	Pi-Alkyl	Hydrophobic	
		:LIG1 - N:ALA52	:LIG1	N:ALA52	Pi-Alkyl	Hydrophobic	
Pyrralline-RAGE		N:LEU262:HN - :LIG1:O	N:LEU262:HN	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	-591,1
		:LIG1:H - N:LEU299:O	:LIG1:H	N:LEU299:O	Conventional Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:TRP230	:LIG1:H	N:TRP230	Pi-Sigma	Hydrophobic	
		:LIG1 - N:TRP62	:LIG1	N:TRP62	Pi-Pi T-shaped	Hydrophobic	
		:LIG1 - N:TRP230	:LIG1	N:TRP230	Pi-Pi T-shaped	Hydrophobic	
		:LIG1 - N:ALA63	:LIG1	N:ALA63	Pi-Alkyl	Hydrophobic	
Imidazole-RAGE		:LIG1:H - N:ASP65:OD1	:LIG1:H	N:ASP65:OD1	Conventional Hydrogen Bond	Hydrogen Bond	-100,4
		:LIG1:H - N:ASP65:OD2	:LIG1:H	N:ASP65:OD2	Carbon Hydrogen Bond	Hydrogen Bond	
		N:MET330:CE - :LIG1	N:MET330:CE	:LIG1	Pi-Sigma	Hydrophobic	
		N:MET330:SD - :LIG1	N:MET330:SD	:LIG1	Pi-Sulfur	Other	
		N:TRP340 - :LIG1	N:TRP340	:LIG1	Pi-Pi Stacked	Hydrophobic	
		:LIG1 - N:TRP340	:LIG1	N:TRP340	Pi-Pi Stacked	Hydrophobic	
		:LIG1 - N:ALA63	:LIG1	N:ALA63	Pi-Alkyl	Hydrophobic	
B. Interaction of AGEs-RAGE Complex with Cyanidin-3-O-glucoside							
Argpirimidine-RAGE-Cyanidin-3-O-glucoside	Argypirimidine-RAGE	N:ARG1218:HH11 - N:LIG1:OXT	N:ARG1218:HH11	N:LIG1:OXT	Conventional Hydrogen Bond	Hydrogen Bond	-301,4
		N:LIG1:H - N:GLY1213:O	N:LIG1:H	N:GLY1213:O	Carbon Hydrogen Bond	Hydrogen Bond	
		N:LIG1:H - N:GLY1213:O	N:LIG1:H	N:GLY1213:O	Carbon Hydrogen Bond	Hydrogen Bond	
		N:LIG1:C - N:LEU1214	N:LIG1:C	N:LEU1214	Alkyl	Hydrophobic	
		N:LIG1:C - N:LYS42	N:LIG1:C	N:LYS42	Alkyl	Hydrophobic	
		N:LIG1:C - N:LYS46	N:LIG1:C	N:LYS46	Alkyl	Hydrophobic	
		N:LIG1 - N:LYS46	N:LIG1	N:LYS46	Pi-Alkyl	Hydrophobic	
	RAGE-Cyanidin-3-O-glucoside	N:LYS15:HZ3 - :LIG1:O	N:LYS15:HZ3	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	
		N:TRP62:HE1 - :LIG1:O	N:TRP62:HE1	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:ASP14:OD2	:LIG1:H	N:ASP14:OD2	Conventional Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:ASP14:OD2	:LIG1:H	N:ASP14:OD2	Carbon Hydrogen Bond	Hydrogen Bond	
		N:GLU153:OE1 - :LIG1	N:GLU153:OE1	:LIG1	Pi-Anion	Electrostatic	
		N:TRP62 - :LIG1	N:TRP62	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:TRP62 - :LIG1	N:TRP62	:LIG1	Pi-Pi Stacked	Hydrophobic	
		:LIG1 - N:PRO154	:LIG1	N:PRO154	Pi-Alkyl	Hydrophobic	
		:LIG1 - N:ALA63	:LIG1	N:ALA63	Pi-Alkyl	Hydrophobic	
Pentosidine-RAGE-Cyanidine-3-glucoside	Pentosidine-RAGE	N:ASN1025:HD21 - N:LIG1:O	N:ASN1025:HD21	N:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	-307,2
		N:LIG1 - N:ALA52	N:LIG1	N:ALA52	Pi-Alkyl	Hydrophobic	
		N:LIG1 - N:PRO1215	N:LIG1	N:PRO1215	Pi-Alkyl	Hydrophobic	
		N:LIG1 - N:ALA52	N:LIG1	N:ALA52	Pi-Alkyl	Hydrophobic	
	RAGE-Cyanidin-3-O-glucoside	N:ALA63:HN - :LIG1:O	N:ALA63:HN	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:GLU111:OE1	:LIG1:H	N:GLU111:OE1	Conventional Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:GLU111:OE1	:LIG1:H	N:GLU111:OE1	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:GLU111:OE1	:LIG1:H	N:GLU111:OE1	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:GLU111:OE1	:LIG1:H	N:GLU111:OE1	Carbon Hydrogen Bond	Hydrogen Bond	
		N:ASP14:OD2 - :LIG1	N:ASP14:OD2	:LIG1	Pi-Anion	Electrostatic	
		N:GLU153:OE1 - :LIG1	N:GLU153:OE1	:LIG1	Pi-Anion	Electrostatic	
		N:GLU153:OE1 - :LIG1	N:GLU153:OE1	:LIG1	Pi-Anion	Electrostatic	
		:LIG1:O - N:TRP62	:LIG1:O	N:TRP62	Pi-Lone Pair	Other	
		N:TYR155 - :LIG1	N:TYR155	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:PHE156 - :LIG1	N:PHE156	:LIG1	Pi-Pi T-shaped	Hydrophobic	
		N:TRP340 - :LIG1	N:TRP340	:LIG1	Pi-Pi T-shaped	Hydrophobic	
		N:TRP340 - :LIG1	N:TRP340	:LIG1	Pi-Pi T-shaped	Hydrophobic	
		:LIG1 - N:PRO154	:LIG1	N:PRO154	Pi-Alkyl	Hydrophobic	

Pyrralline-RAGE-Cyanidin-3-O-glucoside	Pyrralline-RAGE	N:LEU262:HN - N:LIG1:O	N:LEU262:HN	N:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	-294
		N:LIG1:H - N:LEU299:O	N:LIG1:H	N:LEU299:O	Conventional Hydrogen Bond	Hydrogen Bond	
		N:LIG1:H - N:TRP230	N:LIG1:H	N:TRP230	Pi-Sigma	Hydrophobic	
		N:LIG1 - N:TRP62	N:LIG1	N:TRP62	Pi-Pi T-shaped	Hydrophobic	
		N:LIG1 - N:TRP230	N:LIG1	N:TRP230	Pi-Pi T-shaped	Hydrophobic	
		N:LIG1 - N:ALA63	N:LIG1	N:ALA63	Pi-Alkyl	Hydrophobic	
	RAGE-Cyanidin-3-O-glucoside	:LIG1:H - N:ASN332:OD1	:LIG1:H	N:ASN332:OD1	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:GLY174:O	:LIG1:H	N:GLY174:O	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1 - N:ILE329	:LIG1	N:ILE329	Pi-Alkyl	Hydrophobic	
		:LIG1 - N:ARG98	:LIG1	N:ARG98	Pi-Alkyl	Hydrophobic	
Imidazole-RAGE-Cyanidin-3-O-glucoside	Imidazole-RAGE	N:LIG1:H - N:ASP65:OD1	N:LIG1:H	N:ASP65:OD1	Conventional Hydrogen Bond	Hydrogen Bond	-299,9
		N:LIG1:H - N:ASP65:OD2	N:LIG1:H	N:ASP65:OD2	Carbon Hydrogen Bond	Hydrogen Bond	
		N:MET330:CE - N:LIG1	N:MET330:CE	N:LIG1	Pi-Sigma	Hydrophobic	
		N:MET330:SD - N:LIG1	N:MET330:SD	N:LIG1	Pi-Sulfur	Other	
		N:TRP340 - N:LIG1	N:TRP340	N:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:LIG1 - N:TRP340	N:LIG1	N:TRP340	Pi-Pi Stacked	Hydrophobic	
		N:LIG1 - :LIG1	N:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:LIG1 - :LIG1	N:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:LIG1 - N:ALA63	N:LIG1	N:ALA63	Pi-Alkyl	Hydrophobic	
	RAGE-Cyanidin-3-O-glucoside	:LIG1:H - N:ASP14:OD2	:LIG1:H	N:ASP14:OD2	Conventional Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:ASP14:OD2	:LIG1:H	N:ASP14:OD2	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:ASP14:OD2	:LIG1:H	N:ASP14:OD2	Carbon Hydrogen Bond	Hydrogen Bond	
		N:GLU153:OE1 - :LIG1	N:GLU153:OE1	:LIG1	Pi-Anion	Electrostatic	
		N:TRP62 - :LIG1	N:TRP62	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:TRP62 - :LIG1	N:TRP62	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:LIG1 - :LIG1	N:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:LIG1 - :LIG1	N:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
		:LIG1 - N:PRO154	:LIG1	N:PRO154	Pi-Alkyl	Hydrophobic	
		:LIG1 - N:ALA63	:LIG1	N:ALA63	Pi-Alkyl	Hydrophobic	

Table 1. Interaction of Advanced Glycation End Products (AGEs)-receptor (RAGE) and Cyanidin-3-O-glucoside

structure or strengthen protein-ligand interactions up to 40 kJ/mol (25)protein structure and molecular recognition. The core of most protein structures is composed of secondary structures such as α helix and β sheet. This satisfies the hydrogen-bonding potential between main chain carbonyl oxygen and amide nitrogen buried in the hydrophobic core of the protein. Hydrogen bonding between a protein and its ligands (protein, nucleic acid, substrate, effector or inhibitor. Hydrophobic bonds are non-covalent interactions with long carbon chains and can not bind to water (26). This study reported that the pyrralline-RAGE interaction required the lowest energy of -591.1 kcal/mol, while Imidazole-RAGE had the highest energy of -100.4 kcal/mol. A molecule requires energy, called binding energy (binding affinity), to form chemical bonds with the other molecules. The smaller the binding affinity indicates the less energy needed between molecules to interact. Therefore, they can interact with each other easily (27).

A compound is a competitive inhibitor when it can compete with the substrate to bind to the active site of the enzyme. The interaction between the inhibitor and the enzyme will prevent the bonding between the enzyme and the substrate (28). One of the factors that influence a competitive inhibitor in inhibiting the interaction between two proteins efficiently is the binding affinity of inhibitors (29). This research found that cyanidin-3-O-glucoside can compete with imidazole through binding the ALA63 of RAGE in the complex of imidazole-RAGE with Cyanidin-3-O-glucoside. Therefore, imidazole-RAGE interaction might be inhibited. The binding affinity of the imidazole-RAGE-cyanidin-3-O-glucoside complex was also smaller than that of the imidazole-RAGE complex, which was -299 kcal/mol. Previous study, reported that that the interaction and position between ligand-receptors after binding to the bioactive compound affected the binding energy (6)cardiovascular disease, stroke, neuropathy, and nephropathy. Different studies have been done to employ AGEs as drug targets for the diseases therapy. In previous study, we have found bioactive peptide from Ethawah goat milk for anti-diabetic that may work through inhibition of AGE receptor function. However, the mechanism of bioactive peptides inhibits AGE- AGE receptor (RAGE. The binding of cyanidin-3-O-glucoside to AGEs-RAGE complex also influenced the binding energy in the AGEs-RAGE-cyanidin-3-O-glucoside complex in this study. However, cyanidin-3-O-glucose complexes with imidazole could not bind to RAGE. It might be inferred that the cyanidin-3-O-glucose could inhibit the imidazole-RAGE interaction more effectively by the establishment of imidazole-RAGE-cyanidin-3-O-glucoside complex than in the imidazole-cyanidin-3-O-glucoside-RAGE complex.

This study reported that argypirimidine and cyanidin-3-O-glucoside could establish the interactions with ALA52 and TYR341 of RAGE showed in the argypirimidine-cyanidin-3-O-glucoside-RAGE complex. Cyanidin-3-O-glucoside was also capable of binding the TRP230 of RAGE, which was the residue bound to pyrralline, in the pyrralline-cyanidin-3-O-glucoside-RAGE complex. Our results showed that cyanidin-3-O-glucoside might have a biological function as a competitive inhibitor of both AGEs in binding to RAGE. The binding

Interaction		Point interaction	Donor atom	Acceptor atom	Type	Chemistry bond	Energy binding (kcal/mol)
A. Interaction of AGEs and Cyanidin-3-O-glucoside							
Argypirimidine-Cyanidin-3-O-glucoside		:LIG1:H - :LIG1:N	:LIG1:H	:LIG1:N	Conventional Hydrogen Bond	Hydrogen Bond	-164
		:LIG1:H - :LIG1:O	:LIG1:H	:LIG1:O	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1:N - :LIG1	:LIG1:N	:LIG1	Pi-Lone Pair	Other	
		:LIG1 - :LIG1	:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
		:LIG1 - :LIG1	:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
Pentosidine-Cyanidin-3-O-glucoside		:LIG1 - :LIG1	:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	-163,2
		:LIG1 - :LIG1	:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
Pyrralline - Cyanidin-3-glucoside		:LIG1:H - :LIG1:O	:LIG1:H	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	-150,3
		:LIG1:H - :LIG1:O	:LIG1:H	:LIG1:O	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1 - :LIG1	:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
Imidazole-Cyanidin-3-O-glucoside		:LIG1:H - :LIG1:N	:LIG1:H	:LIG1:N	Conventional Hydrogen Bond	Hydrogen Bond	-95,7
		:LIG1:N - :LIG1	:LIG1:N	:LIG1	Pi-Lone Pair	Other	
		:LIG1 - :LIG1	:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
		:LIG1 - :LIG1	:LIG1	:LIG1	Pi-Pi Stacked	Hydrophobic	
B. Interaction of AGEs-Cyanidin-3-O-glucoside Complex with RAGE							
Argypirimidine-Cyanidin-3-O-glucoside-RAGE	Argypirimidine-RAGE	N:GLN1024:HA - :LIG1:O	N:GLN1024:HA	:LIG1:O	Carbon Hydrogen Bond	Hydrogen Bond	-411,8
		:LIG1:C - N:LEU1214	:LIG1:C	N:LEU1214	Alkyl	Hydrophobic	
		N:TYR341 - :LIG1:C	N:TYR341	:LIG1:C	Pi-Alkyl	Hydrophobic	
		:LIG1 - N:ALA52	:LIG1	N:ALA52	Pi-Alkyl	Hydrophobic	
	RAGE-Cyanidin-3-O-glucoside	Hydrogen Bond	Hydrogen Bond	Hydrogen Bond	Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:GLU45:O	:LIG1:H	N:GLU45:O	Conventional Hydrogen Bond	Hydrogen Bond	
		N:GLN49:HA - :LIG1:O	N:GLN49:HA	:LIG1:O	Carbon Hydrogen Bond	Hydrogen Bond	
		N:ARG66:NH1 - :LIG1	N:ARG66:NH1	:LIG1	Pi-Cation;Pi-Donor Hydrogen Bond	Hydrogen Bond;Electrostatic	
		:LIG1 - N:PRO48	:LIG1	N:PRO48	Pi-Alkyl	Hydrophobic	
		:LIG1 - N:PRO48	:LIG1	N:PRO48	Pi-Alkyl	Hydrophobic	
		:LIG1 - N:ALA52	:LIG1	N:ALA52	Pi-Alkyl	Hydrophobic	
Pentosidin-Cyanidin-3-O-glucoside_RAGE	Pentosidine-RAGE	N:ASN1025:HD22 - :LIG1:O	N:ASN1025:HD22	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	-462,2
		N:TYR341 - :LIG1	N:TYR341	:LIG1	Pi-Pi T-shaped	Hydrophobic	
		:LIG1 - N:TYR341	:LIG1	N:TYR341	Pi-Pi T-shaped	Hydrophobic	
	RAGE-Cyanidin-3-O-glucoside	N:GLN1024:HA - :LIG1:O	N:GLN1024:HA	:LIG1:O	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:ALA1023:O	:LIG1:H	N:ALA1023:O	Carbon Hydrogen Bond	Hydrogen Bond	
		:LIG1 - N:ALA338	:LIG1	N:ALA338	Pi-Alkyl	Hydrophobic	
		:LIG1 - N:ALA338	:LIG1	N:ALA338	Pi-Alkyl	Hydrophobic	
Pyrralline-Cyanidin-3-O-glucoside_RAGE	Pyrralline-RAGE	N:ALA63:HN - :LIG1:O	N:ALA63:HN	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	-1304,9
		N:TYR210:HH - :LIG1:O	N:TYR210:HH	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	
		N:TRP230:HE1 - :LIG1:O	N:TRP230:HE1	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:TRP62	:LIG1:H	N:TRP62	Pi-Donor Hydrogen Bond	Hydrogen Bond	
		:LIG1:O - N:TRP62	:LIG1:O	N:TRP62	Pi-Lone Pair	Other	
		:LIG1:N - N:TRP62	:LIG1:N	N:TRP62	Pi-Lone Pair	Other	
		:LIG1 - N:TYR210	:LIG1	N:TYR210	Pi-Pi T-shaped	Hydrophobic	
	RAGE-Cyanidin-3-O-glucoside	N:TYR155:HN - :LIG1:O	N:TYR155:HN	:LIG1:O	Conventional Hydrogen Bond	Hydrogen Bond	
		:LIG1:H - N:GLU153:OE1	:LIG1:H	N:GLU153:OE1	Carbon Hydrogen Bond	Hydrogen Bond	
		N:TYR155 - :LIG1	N:TYR155	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:TYR155 - :LIG1	N:TYR155	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:TRP230 - :LIG1	N:TRP230	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:TRP230 - :LIG1	N:TRP230	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:TRP230 - :LIG1	N:TRP230	:LIG1	Pi-Pi Stacked	Hydrophobic	
		N:TRP230 - :LIG1	N:TRP230	:LIG1	Pi-Pi Stacked	Hydrophobic	
Imidazole-Cyanidin-3-O-glucoside_RAGE	Imidazole-RAGE	N:PRO1215:CD - :LIG1:N	N:PRO1215:CD	:LIG1:N	Carbon Hydrogen Bond	Hydrogen Bond	-108,4
		N:LEU1214:CD1 - :LIG1	N:LEU1214:CD1	:LIG1	Pi-Sigma	Hydrophobic	
		:LIG1 - N:PRO1215	:LIG1	N:PRO1215	Pi-Alkyl	Hydrophobic	

Table 2. Interaction of AGEs-Cyanidin-3-O-glucoside and receptor AGEs

energy of the argypirimidine-cyanidin-3-O-glucoside-RAGE complex was -411.8 kcal/mol, lower than the argypirimidine-RAGE complex. The pyrralline-cyanidin-3-O-glucoside-RAGE complex also had the binding energy of -1305 kcal/mol. It was lower than the binding energy of the pyrralline-RAGE complex. Moreover, the binding sites of the four AGEs and RAGE were changed in the presence of cyanidin-3-O-glucoside showed in the AGE-cyanidin-3-O-glucoside-RAGE complex. This result implied that cyanidin-3-O-glucoside might interfere with the AGEs so that they could not bind to certain sites of RAGE. Ligand binding, hydrogen bonding, and hy-

drophobic effects may change the overall fold or protein conformation, leading to a nonfunctional protein (30). In this case, the AGEs-RAGE signaling might be impeded by cyanidin-3-O-glucoside.

Cyanidin-3-O-glucoside is an anthocyanin that can be found in pigmented rice, including red rice. It has two hydroxyls on the B ring and hydrogen donor or acceptor in its structure so that it has the potential to have strong antioxidant activity (31–34)different brans of Thai rice cultivars which were divided into 3 groups: white color (Hom mali 105, Supan, Saohai, Hom chaiya and Hom jun. The heating process in food contributes to the accumulation of AGEs. Frying and roasting can increase AGEs content higher than steaming and boiling. Consuming foods with proper processing, such as whole grains that are rich in vitamins and antioxidants, can inhibit the formation of AGEs (35). This study indicated that cyanidin-3-O-glucoside might act as a competitive inhibitor of AGEs (argypirimidine, pentosidine, and pyrralline), leading to the potential ability in inhibiting the interaction of AGEs and RAGE through the establishment of AGEs-Cyanidin-3-O-glucoside-RAGE complex.

5. CONCLUSION

Cyanidin-3-O-glucoside in red rice may have a potential compound as an inhibitor of AGEs-RAGE signaling. This was shown from the stable complex formed of AGEs-cyanidin-3-O-glucoside-RAGE.

- **Acknowledgement:** This research funded by Professor Grants Brawijaya University 2019-2020 and DIKTI (Directorate General of Higher Education) Grant for Magister Program 2020. We thank Hazna Noor Meidinna for assisting the completion of this research.
- **Author's contribution:** All authors were included in all steps of preparation this article. Final proof reading was made by the first author.
- **Conflict of interest:** None declared.
- **Financial support and sponsorship:** Nil.

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