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Molecular Docking Study on the interaction of κ-casein with Glucomannan

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A B S T R A C T

The purpose of this research were to investigate interaction between glucomannan and lactic acid in water solution, and interaction between κ-casein with glucomannan-lactic acid complex in water solution. The interaction between glucomannan and lactic acid in water solution at 90°C and 25°C, and interaction κ-casein with glucomannan-lactic acid complex at 90°C and 25°C was investigated using molecular docking calculations. Molecular docking to clearer visual about interaction and molecular changes of glucomannan and lactic acid in water solution at 90°C and 25°C, investigated interaction and molecular changes of glucomannan-lactic acid complex in water solution at 90°C and 25°C. Docking process using autodock vina program at PyRx 0.8. The result of docking continued to predict interaction between glucomannan-lactic acid complex with κ-casein using Patchdock dan fiberdock. The result of docking analyzed with simulation at 90^0C for 1000 ps using force field AMBER 03 at YASARA 13.4.21 program. Visualisation of the complex using Chimera 1.8. The results of molecular docking suggested that heating of glucomannan at 90°C caused hydrogen bonding among glucomannan molecules was broken**,** conformation changes of glucomannan and lactic acid, higher binding energy of lactic acid to glucomannan. Heating at 90°C formed complex of glucomannan-lactic acid and κ-casein with higher binding energy compared without heating. Conformation changes of glucomannan and lactic acid and the behavior of glucomannan solution was strongly dependent on lactic acid. The complex of glucomannan-lactic acid is more favorable to bind -κ-casein, dominated by hydrogen bond and hydrophobic interaction with hydrophobic core of κ-casein. Lactic acid have important role for increasing binding energy, lactic acid is important to mediate interaction between glucomannan and κ-casein. It concluded that lactic acid have important role on the behavior of glucomannan in water solution during heating at 90°C and have important role for increasing binding energy to mediate interaction between glucomannan and κ-casein.

Introduction

Glucomannan as neutral polysaccharide and milk protein thermodynamically was incompatible (Tolstoguzov, 2003), caused segregative phase separation, because there are segregative interaction among biopolymer (Abhyankar *et al.,* 2010; Abhyankar *et al.,* 2011). Glucomannan was major component of porang (*Amorphophallus onchophyllus*) flour produced from porang tuber.

Glucomannan consist of D- glucose and D-mannose with β –(1-4)glicosidic binding with molar ratio 1 : 1.6 and low rate acetyl group (approximately 1 acetyl group in each 17 residue) at C-6 position (Pang *et al.,* 2003). The structures of native konjac glucomannan (KGM) were primarily composed of the lamella structure units, which involve both granular crystalline and amorphous regions, and that the connection zones of such units contained both loose and tight aggregation regions. (Li *et al.,* 2009)

According to Li et al. (2009) that the swelling process of native KGM includes three steps i.e. the breakage of intermolecular hydrogen bonds of KGM, the re-establishment of hydrogen bonds with water molecules and hydrogen bonds among amorphous regions in lamellar structure units were broken by water. In swelling process, water can plasticize the natural polymer or form stable bridges through intermolecular hydrogen bonds (Li *et al.,* 2009). KGM molecules have opportunities to form intermolecular hydrogen bonds (Pan *et al.,* 2011). Water molecules can break intermolecular hydrogen bonds among cellulose chains to make the intermolecular distance when they were diffused into the amorphous region. Therefore, water absorbed can cause an increase in cellulose chain mobility by opening the intermolecular space and allowing more water molecules to influx and form hydrogen bonds with cellulose (Li *et al.,* 2009). At saturation, water absorption in the amorphous domains leads to the swelling and the formation of trapped water (Li *et al.,* 2009). Thermal properties of cellulose and water are markedly influenced through their interaction through intermolecular hydrogen bonds between water molecules with cellulose (Kennedy *et al.,* 1989; Hatakeyama and Hatakeyama, 1998; Hatakeyama *et al.,* 2000). Helical structure of KGM is mainly sustained by acetyl group, in water solution, hydrogen bond affects the helical arrangement of KGM. temperature exhibits a reversible destroying effect to some extent (Jian *et al.,* 2010)

Thermal and irradiation treatment could be combinated with lactic acid to modify physichochemichal properties of polysaccharide. Copolymers of corn starch grafted with poly (lactic acid) were directly prepared in aqueous media at 90°C (Gong *et al.,* 2006). In addition, it need to a treatment using combination of thermal or irradiation and lactic acid to produce modified glucomannan which compatible with casein.

Casein are primary colloid components in milk, casein consist of 4 types, i.e. αs1-(38%), αs2-(10%), β-(34%) dan κ-casein (15%) (Fox *et al.,* 2000). Casein are almost similar in molecular weight (αS1-casein 23.62, αS2-casein 25.50, β-casein 24.09 and κ-casein 19.00 kD) and net negative charge (Bourassa *et al.,* 2014).

The structural differences show a different affinity for α-, β- and κ-caseins toward hydrophilic and hydrophobic interactions (Bourassa *et al.,* 2014). κ-CN located at the micelle surface and consist of two different region, in which N terminal (para-κ-CN)

interaction hydrophobicly with others casein in inner region, and hydrophilic group at outer surface from C-terminal (caseinomacropeptide, CMP), formed electrostatic force among micelle (Dalgleish and Corredig, 2012). The κ-casein monomer has a MW of 19 kDa and a radius of 3−4 nm, κ-casein micelle have diameter 13-18 nm (Ossowski *et al.*, 2012).

Molecular docking and molecular dynamic simulation method have been widely used in the study of macromolecule conformation and the interaction with their complexes (Pang *et al.*, 2005; Pang *et al.*, 2006; Pang *et al.*, 2009). Many previous studies have evaluated the rheological properties of KGM in aqueous solutions, most of these have been carried out at neutral pH and room temperature (Jin *et al.*, 2014; Xu *et al.*, 2007). The characteristicsof KGM in acidic pH conditions and at higher temperatures are important for their applications in these conditions (Jian et al, 2015).

A molecular docking study has been done on the system for clearer visualing glucomannan molecular changes using lactic acid and thermal in water solution and visualing interaction between glucomannan-lactic acid complex with κ-casein.

Materials and Methods

Molecular Modelling

κ-casein protein sequence from the result of homology modeling (SWISSMODEL) with 1ZRS template. 3D structure model of glucomannan and lactic acid was downloaded from Pubchem (pubchem.ncbi. nlm.nih.gov) with CID:24892726 and CID:612 respestively.

Molecular Docking

Docking process has done for prediction of interaction between glucomannan and lactic acid at before and after heating. Docking process using program autodock vina at PyRx 0.8. The complex from docking to be continued to predict interaction with κ-casein using docking service online i.e. Patchdock and fiberdock. Docking result analysed any more.

Molecular Dynamics Simulation

Simulation of molecule dynamic has done at complex between glucomannan and lactic acid. Simulation process at 90 ^{0}C for 1000 ps using force field AMBER 03 at YASARA 13.4.21 program. The result of docking continued to predict interaction between glucomannan-lactic acid complex with κ-casein using Patchdock dan fiberdock. The result of docking analyzed with simulation at 90^{0}C for 1000 ps using force field AMBER 03 at YASARA 13.4.21 program.

Molecular Interaction

Molecular interaction has done to find out active group that involved in the interaction, using LigandScout 2.0 program.

Molecular Visualization

Complex Visualisation has done using Chimera 1.8

Results and Discussion

Molecular Docking Glucomannan-lactic Acid Complex

Much attention has been paid to the chain structure of KGM in water (Jian *et al.*, 2010; Pang *et al.*, 2003), but the complex conformation of glucomannan with lactic acid molecules and glucomannan-lactic acid complex with κ-casein at high temperature has not been studied. To investigate the rule of temperature on the complex conformation

and molecular dynamic simulation at different temperatures were carried out on KGM–lactic acid and KGM–lactic acid with κ-casein complex in water solution.

The result showed that glucomannan and lactic acid in water solution at 25°C have binding energy -1.8, however at 90°C have binding energy -2.4 as shown at Table 1. After heating in water solution at 90°C, binding energy between glucomannan and lactic acid increased. This result indicated there are conformation changes of glucomannan and lactic acid as shown at Figure 1. Heating glucomannan and lactic acid at 90^0C in water solution caused hydrogen bonding of glucomannan was broken. Heating caused conformation changes of glucomannan and lactic acid. According to Jian et al. (2011) that at low temperature, KGM chain exhibited helical structure, and with the increase of temperature, the helical structure was preserved, temperature had little effect on the helical conformation of the complex, however, the hydrogen bond site changed as temperature increased, the total number of hydrogen bond changed slightly. At acidic condition (pH 4) using HCl and 20°C, KGM in the colloidal solution-to-gel transition state, at 80°C formed weakening of inter- and intra-molecular attraction forces rapidly, the influence of temperature on the behavior of KGM solution was strongly dependent on the pH (Jian *et al.*, 2015).

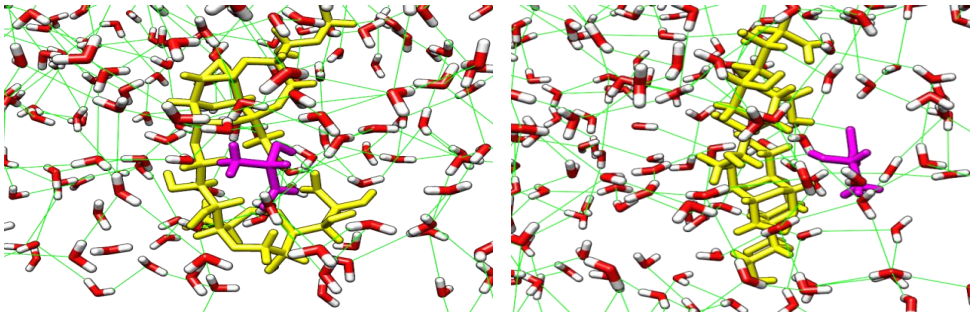
Table.1 Binding Energy between Glucomannan and Lactic Acid

Receptor	Ligand	Binding Energy (Kcal/mol)
Glucomannan (90°C)	Lactic acid (90°C)	-2.4
Glucomannan	Lactic acid (25°C)	-1.8

Table.2 Binding Energy between Glucomannan-Lactic Acid and □-Casein

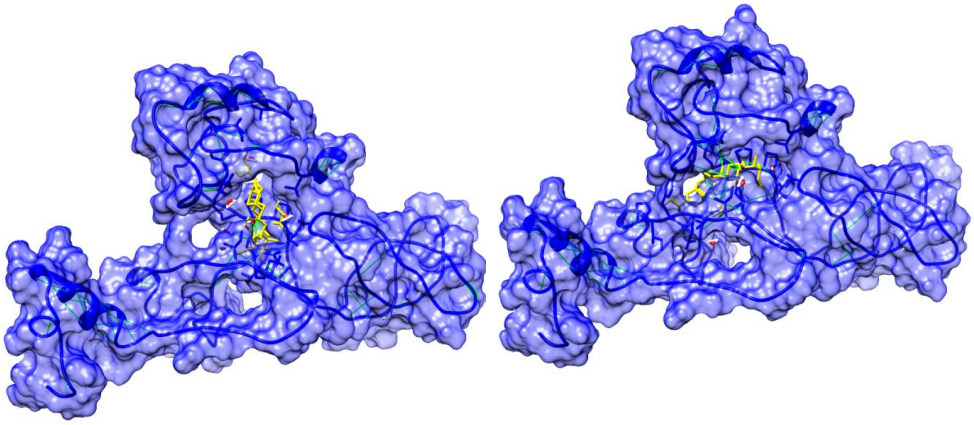
Receptor	Ligand	Binding Energy
κ-casein	Glucomannan-lactic acid complex,90°C	-50.16
κ-casein	Glucomannan-lactic acid complex,25°C	-45.73

Fig.1 Interaction between Glucomannan (Yellow) and Lactic Laktat Acid (Grey) in Water Solution (A) Interaction between Glucomannan-Lactic Acid After Heating at 90°C (B) Interaction between Glucomannan-Lactic Acid at 25°C



(a) (b)

Fig.2 Interaction between Glucomannan-lactic acid-κ-Casein. (a) Glucomannan-lactic Acid after Heating at 90°c (b) Glucomannan-lactic Acid at 25°c



(a) (b)

Fig.3 Surface Representation of κ-Casein Bind to Glucomannan in the Binding Pocket

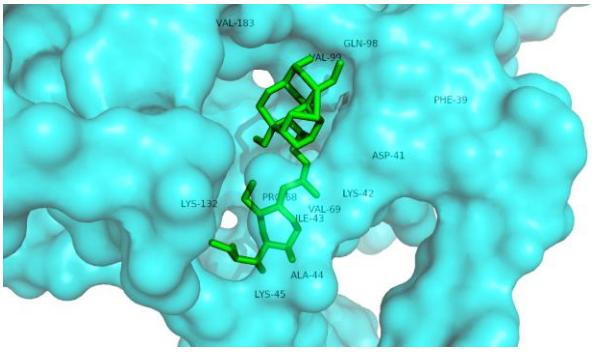


Fig.4 Binding Pose of Glucomannan in κ-Casein

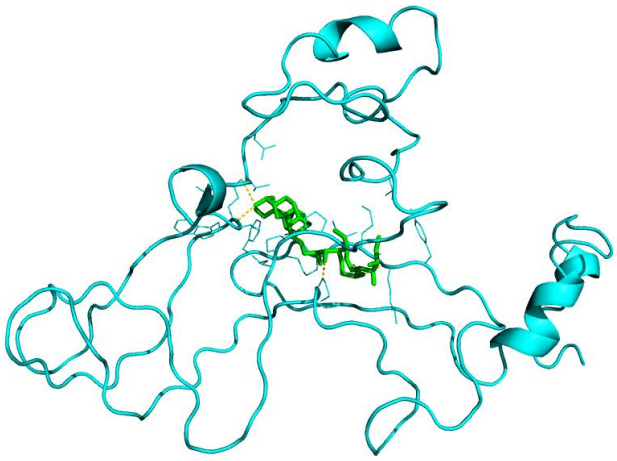


Fig.5 Surface Representation of κ-Casein Bind to Glucomannan-Lactic Complex Acid in the Binding Pocket

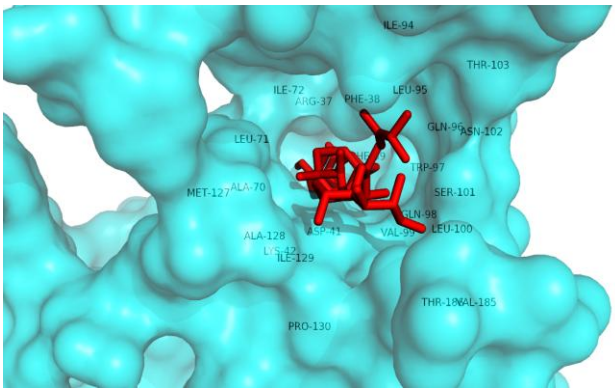
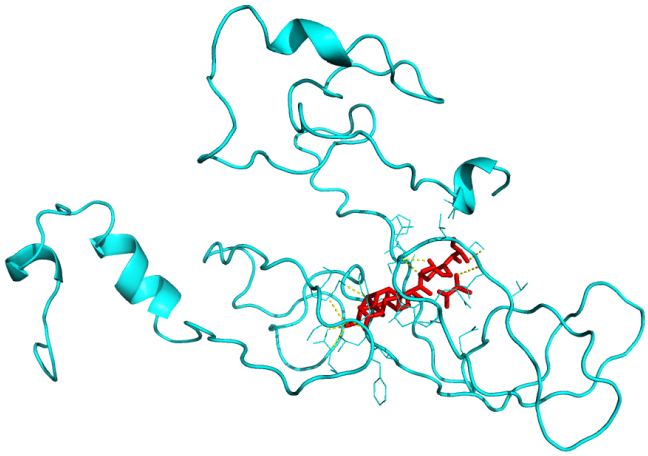


Fig.6 Binding Pose of Glucomannan-Lactic Acid Complex in κ-Casein



Molecular Docking κ-casein-Glucomannan-lactic Acid Complex

Glucomannan-lactic acid complex which produced from heating at 90°C gave higher binding energy (-50.16) to κ-casein than Glucomannan-lactic acid which produced without heating (-45.73) as shown at Table 2. It indicated that lactic acid have important role in binding of glucomannan which heated at 90°C on κ-casein.

Docking study as shown at Figure 2, showed that binding between glucomannan-lactic acid complex and κ-casein indicated at hydrophobic core of κ-casein. Docking study showed binding site and conformation of binding glucomannan-lactic acid complex to κ-casein. The result of docking study indicated that binding glucomannan molecule to κ-casein dominated by hydrogen binding and hydrophobic group contact with hydrophobic core of κ-casein. Binding energy between glucomannan-lactic acid complex which heated at 90°C and κ-casein higher than glucomannan-lactic acid in water solution without heating, this result attributed with higher hydrogen binding capacity formed.

It similar with previous research that binding some substances to casein predominantly

occurred through hydrophobic contacts in the hydrophobic core of protein via formation of hydrogen bonds (Mehranfar *et al.*, 2013; Mehranfar *et al.*, 2015).

Binding Site Glucomannan-lactic Acid Complex in κ-casein

Molecular docking analysis at Fig 3, Fig4, Fig 5 and Fig 6 showed that the complex glucomannan-lactic acid is more favorable to bind κ-casein than glucomannan only, it means the glucomannan and lactic acid can make complex easily than glucomannan only. Glucomannan bind to κ-casein use hidrogen bond and hydrophobic interaction for stabilizing the complex such as Val183, Gln98, Phe39, Asp41, Lys42, Val69, Ile43, Ala44, Lys45, Lys132, Pro68, Val99. The interaction is different when lactic acid include in the complex. Glucomannan-lactic acid complex bind to κ-casein and the complex was stabilized by hydrogen bond and hydrophobic interaction such as Ile94, Leu95, Thr103, Gln96, Asn102, Trp97,Ser101, Leu100, Gln98, Val99, Thr186, Val185, pro130, Ile129, Lys42, Ala128, Asp41, Met127, Ala70, Leu71, Arg37, Phe38. Our result showed that lactic acid have role for increasing binding energy. Lactic acid is important to mediate interaction between glucomannan and κ-casein.

It concluded that lactic acid have a important role on the behavior of glucomannan in water solution during heating at 90°C. Lactic acid have important role for increasing binding to mediate interaction between glucomannan and κ-casein.

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