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Study in Silico:Interaction between AGE Compounds and Constituent Components of Vascular Endothelium Glycocalyx

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ABSTRACT

In vascular endothelial cells, there are glycocalyx on the luminal side and a basic membrane on the abluminal side. In the condition of diabetes and hyperglycemia, the formation of AGE compounds will be accompanied by a decrease in the thickness of the glycocalyx in vascular endothelial cells. This study aimed to analyze the possiblity of interaction between several AGE compounds and glucose compounds with the components of the glycocalyx. The analysis was performed in silico by the docking method used Hex 8.0 software. Docking was carried out between several AGE-glycocalyx compounds, and also glucose-glycocalyx. The AGE compounds analyzed included 3-deoxyglucosone, glyoxal, methylglyoxal, CML, pentosidine, and pyrraline. Subsequent analysis was carried out to see the interactions formed using LigPlus + software and Discovery Studio 4.1. The results of this study reported that the estimated amount of bond energy needed for the interaction process between the glycosaminoglycan chain and AGE will determine whether the glycosaminoglycan chain would be released from the glycocalyx structure or not. Another result obtained was that only a few AGE compounds were known to be able to interact with the core protein, so it is suspected that the presence of AGE will not sufficiently affect the structure and function of the core protein. Further analysis is needed to strengthen the results obtained from this study.

Keywords: AGE, endothelial, diabetes, glycocalyx, hyperglycemia, vascular.

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BACKGROUND

Endothelial glycocalyx is a carbohydrate-rich layer that lines the vascular endothelium. The glycocalyx is connected to the endothelium through several 'backbone' molecules, which are mainly proteoglycans and glycoproteins. More towards the luminal part, glycocalyx is formed by dissolved plasma components which are connected to each other either directly or through proteoglycans and or dissolved glycosaminoglycans. The composition of proteoglycans, glycoproteins, and membrane bound glycosaminoglycans cannot be seen as a static image. The whole layer - also known as the endothelial surface layer - is very dynamic, with membrane bound molecules that are constantly being replaced[1].

Proteoglycans are known to be the backbone molecules of glycocalyx which have the most important functions. Proteoglycans are composed of core proteins with one or more linked glycosaminoglycan chains. The syndecan and glypican core protein groups have strong bonds with cell membranes[2], while other proteoglycans such as mimecan, perlecan, and biglycan will be secreted after modification of their glycosaminoglycan chains[3]. There are five types of glycosaminoglycan chains, including: heparin, chondroitin sulfate, sulfate dermat, sulfate bondage, and hyaluronic acid. These compounds are polymers of disaccharides which are modified through sulfation and (de) acetylation.

In the vascular system, sulfate-like proteoglycans represent 50-90% of the total amount of proteoglycans present in glycocalyx[1]. The second most common glycosaminoglycan found in endothelial cell glycocalyx is chondroitin sulfate / dermat sulfate. The presence of sulfate and chondroitin sulfate is reported to have a 4: 1 ratio in vascular endothelium[4]. Another glycosaminoglycan that has an important function in glycocalyx is hyaluronic acid. This long polymeric molecule is different from other glycosaminoglycans, which are hyaluronic acids which are not connected to core proteins. The exact relationship with cell membranes is unknown, but this compound can bind to the CD44 receptor[5].

In addition to proteoglycans, some glycoproteins are also backbone molecules, which connect glycocalyx with endothelial cell membranes. Cell adhesion molecules are glycoproteins which have an important role in cell recruitment from the bloodstream and in cell signaling. Three families of cell adhesion molecules found in endothelial glycocalyx include the selectin family, the integrin family, and the immunoglobulin superfamily. The glycoproteins of the selectin family found in vascular endothelium are E-selectin and P-selectin, both of which are involved in interactions between leukocyte cells and endothelial cells[6]. E-selectin is not stored in granules, but requires the synthesis of mRNA and de novo proteins to be expressed on the cell surface. Endothelial cell stimulation by cytokines such as interleukin-1, TNF-α, and lipopolysaccharides are known to increase E-selectin expression[7]. Integrins are heterodimer molecules composed of α and β subunits. Integrin is found in various

cell types, including endothelial cells, leukocytes, and platelets. In its luminal membrane, endothelial cells express the αvβ3 integrin, which is an important mediator for interactions between platelets and endothelial cells[8].

Diabetes and its complications are one of the most significant causes of death in the world[9]. The effect of an increase in glucose levels in blood plasma that occurs continuously in each part of the body is different according to the type of cells that make it up. Cells that express high levels of glucose transporter 1 (GLUT 1) such as vascular endothelial cells will not be able to regulate their intracellular glucose concentrations, and will be more susceptible to damage due to hyperglycemia induction[10]. One of the cascade complexes that directs cellular dysfunction in response to high blood glucose levels is due to the formation of advanced glycation end products (AGEs)[11]. Increased glucose levels will cause the formation of covalent compounds with plasma proteins through a non-enzymatic process known as glycation. Protein glycation reactions that cause AGE formation are thought to be a major cause of diabetic complications[12]. High glucose levels will induce plasma proteins and collagen. Non-enzymatic modification of plasma proteins such as albumin, fibrinogen, and globulin can interfere with several cellular effects including changes in the binding of drug compounds in plasma, platelet activation, free radical formation, fibrinolysis damage and immune system regulation disorders. It was reported that exposure to exogenous AGE in high levels can cause renal and vascular complications[13]. In this study will be studied related to the interaction between several AGE compounds and glucose with vascular endothelial glycocalcone making molecules in silico, so it is expected to provide information related to the relationship between AGE and vascular complications.

METHOD

Searching for amino acid sequences and structure of active compounds

The amino acid sequences making up syndecan proteins (GI: 207141), glypican (GI: 204425), mimecan (157824206), integrins (GI: 30088879), E-selectin (GI: 40924), and L-selectin (GI: 400181) of Rattus norvegicus was obtained from the National Center for Biotechnology Information (NCBI) database, United States National Library of Medicine (NLM), National Institute of Health (NIH) (http://www.ncbi.nlm.nih.gov). 3D structure of glucose compounds (CID: 53782692), fructose (CID: 53782691), pyrraline (CID: 122228), glyoxal (CID: 7860), methylglyoxal (CID: 880), 3-deoxyglucosone (3-DG) (CID: 114839)), pentosidine (CID 119593), carboxymethyl lysine (CML) (CID 123800), heparin sulfate (CID:53477714), chondroitin sulfate (CID: 24766), and hyaluronic acid (CID: 24728612) obtained from the PubChem Open Chemistry Database. The 3D structure of these compounds is obtained in the form of * .sdf file format, which will then be converted to a * .pdb file using OpenBabel software[14].

3D Protein Structure Modeling

The 3D structure modeling of syndecan, glypican, mimecan, integrin, E-selectin, and L-selectin proteins was predicted used the SWISS-MODEL webserver[15;16] used the homology modeling method. The 3D structure of the protein was then validated used Ramachandran plot analysis.

Docking and Visualization Between Proteins – Ligands

Docking simulations were performed using HEX 8.0 software[17]. The docking protocol consists of three stages of visualization, namely rigid-body energy minimization, semi-flexible repairs, and finishing refinement in explicit solvents. The docking results were then visualized with PyMOL software and Discovery Studio 4.1.

Analysis of Bonding Interactions between Proteins and Ligands

The results of the docking analysis would be visualized using Discovery Studio 4.1, LigPlot + software[18] and LigandScout 3.1[19]. Analysis of interactions between proteins and ligands were done to see the number and type of bonds that are formed, such as hydrogen bonds, hydrophobic bonds, and van der waals bonds. Pharmacophore analysis was also carried out to see the residues directly involved in the interaction process, as well as energy minimization analysis to improve the structure and shape of the molecules at the time of interaction.

RESULTS

Interaction between glycosaminoglican chains with AGE and Glucose Compounds

In silico analysis to see possible interactions between glycosaminoglycan chains including sulfur, chondroitin sulfate and hyaluronic acid with several AGE compounds and glucose compounds shows that glucose and fructose can bind to glycosaminoglycan chains with less energy than the energy needed by glyoxal and methylglyoxal (Table 1). It was also reported that other AGE compounds such as 3-DG, CML, pentosidine, and pyrraline all require less energy to interact with the glycosaminoglycan chains than glucose and fructose compounds. Among all the AGE compounds analyzed, it is known that pentosidine has the smallest binding energy compared to other AGE compounds.

Interaction between core proteins with AGE compounds and glucose

Glypican

Analysis of possible interactions between glypican proteins with AGE and glucose compounds shows that of the 8 compounds analyzed, which include 3-deoxyglucosone (3-DG), CML, fructose, glucose, glyoxal, methylglyoxal, pentosidine, and pyrraline, only four compounds can interact with glypican, which is 3-DG, fructose, glucose, and pyrraline. Each of these compounds interacts with glypican only by passing one hydrogen bond, 3-DG on Lys383; fructose and glucose in Asp295; and pyrraline in Gln390 (Table 2.)

The site of interaction between each of these compounds with glypican is on an adjacent site, but it is not possible to occur competitive binding because the amino acids involved for interaction with each of these compounds are different, except for glucose and fructose compounds which have a site of interaction that is the same, thus

enabling the occurrence of competitive binding between the two compounds (Figure 1). Based on the analysis of the energy needed for the interaction process, pyrraline is the easiest compound to interact with glypican compared to 3 other compounds. This can be seen based on the low energy needed for interactions, which is -202.13 kJ / mol, compared to the energy needed by other compounds to bind to glypican.

Syndecan

Syndecan is a single transmembrane domain protein that is thought to function as a co-receptor, specifically for protein-coupled G receptors. Analysis of interactions between several AGE compounds with glucose shows that among the 8 compounds analyzed, only five were known to be able to interact with syndecan, these compounds including 3-DG, CML, fructose, glucose, and pyrraline (Table. 2). The 3-DG compound interacts with syndecan through 3 hydrogen bonds in the amino acid residues Lys284, Lys295, Glu292; CML compounds interact through 4 hydrogen bonds in the amino acid Lys295, Met281, Lys282; fructose and glucose compounds interact only through one hydrogen bond, namely the amino acid Glu292; and pyrraline compounds also interact through only one hydrogen bond, namely the amino acid residue Arg280.

Competitive binding is thought to occur between fructose, glucose and 3-DG compounds, in which all three of these compounds require the amino acid Glu292 to be able to interact with syndecan. However, based on binding energy analysis, it appears that the amount of energy needed to bind to each of these compounds is almost the same (3-DG requires -155.75 kJ / mol to interact with syndecan, while fructose and glucose each need -153.39 kJ / mol). Although the energy required by 3-DG is slightly smaller than glucose and fructose, this small difference will not sufficiently influence the competitive binding process. It is assumed that competitive binding in this case will be influenced by the concentration level of each compound, so which compounds will bind to the syndecan in advance.

Mimecan

Based on the results of the docking analysis, it appeared that of the 8 compounds analyzed, none of these compounds can interact with Mimecan.

Interaction between cell adhesion molecules with AGE and glucose

Integrin is a transmemberan receptor that bridges interactions between cells and interactions between cells and the extracellular matrix. Based on the results of the docking analysis, it appears that out of the 8 compounds analyzed, only four of them can interact with integrins. CML compounds interact through three hydrogen bonds in the amino acid residues Val52 and Phe15; fructose and glucose compounds interact through a hydrogen bond to the amino acid Asn80; while the pyrraline compound also interacts through a hydrogen bond in the amino acid residue Ala51 (Table 3).

One of the four compounds that can interact with integrins above, pyrraline compounds are the compounds that most easily bind to integrins. That is because the energy needed by pyrraline to bind to integrins is lower (-205.19 kJ / mol) compared to the energy needed by other compounds to interact with integrin (CML -188.11 kJ / mol; fructose and glucose -154.09 kJ / mol) . Meanwhile, when compared between CML with fructose and glucose, CML will more easily interact with integrins when compared with glucose and fructose. Based on the analysis of amino acids involved in the interaction process, it is thought that there is no competitive binding between the 4 compounds above, except for fructose and glucose compounds which have the same site of interaction with integrins.

Interaction between E-selectin with AGE and glucose

Compounds known to interact with E-selectin include: 3-DG, CML, fructose, glucose, glyoxal, and pentosidine. The 3-DG compound interacts with E-selectin via a hydrogen bond to the amino acid Asn203; CML compounds interact through three hydrogen bonds in Thr179, Leu170, and Asp175; fructose and glucose compounds interact through a hydrogen bond in the amino acid residue Thr179; Glyoxal compounds interact through four hydrogen bonds in amino acid residues Lys173, Cys174, Asp175, Gln176; and pentosidine compounds interact with E-selectin through a hydrogen bond in the amino acid residue Trp231 (Table 3).

From the six compounds which able to interact with E-selectin above, several competitive bindings occur between one compound and another. CML compounds have competitive binding with fructose and glucose in the amino acid residue of Thr179, but because CML binding energy is lower (-147.84 kJ / mol) compared to fructose and glucose (-143.37 kJ / mol), it is suspected that CML will be easier to binds to E-selectin. Another competitive binding occurs between CML and glyoxal, which both of these compounds require Asp175 amino acids to bind to E-selectin, but because the energy required by CML is lower than glyoxal, it is suspected that CML will also be easier to bind with E-selectin compared to glyoxal. Compared with all the other compounds, pentosidine has a lower binding energy (-205.98 kJ / mol), so it is suspected that pentosidine is the most easily bound to E-selectin compared to other compounds.

DISCUSSION

Some of diabetes complications include retinopathy, nephropathy, and an increased risk of cardiovascular atherothrombotics. One marker of diabetes is the absence or resistance of insulin, which can then lead to hyperglycemia, impaired protective capacity of blood vessel walls[20], thereby causing an increase in vascular permeability and impaired NO synthase function[21]. One study reported that the systemic glycocalyx volume of normal volunteers would be reduced by half after 6 hours of induction of acute hyperglycemia[22]. Another study also reported that the volume of systemic glycocalyx in type 1 diabetics was about half the amount of glycocalyx in healthy controls, which would be even less in diabetes with microalbuminuria[23]. Both studies also report that acute and chronic hyperglycemia are associated with decreased glycocalyx dimensions, which in turn will contribute to endothelial dysfunction[24].

High glucose levels can cause the formation of extracellular AGE, which AGE is also known to induce inflammatory activation in endothelial cells[25]. In this study, some of the AGE compounds analyzed were known to be able to interact with sulfate chains of sulfur, chondroitin sulfate and hyaluronic acid interactions with low energy requirements. Interactions between these AGE compounds are thought to be involved in the process of synthesis and release of glycosaminoglycan chains from glycocalyx. The binding energy needed by 3-DG, methylglyoxal, CML, pentosidine, and pyrraline to interact with sulfur and hyaluronic acid is lower than the energy needed to interact with chondroitin sulfate. It is suspected that the size of the binding energy is related to the possibility of synthesis and release of the glycosaminoglycan chain.

Chondroitin sulfate proteinoglycans can increase accompanied by a decrease in sulfate liver proteoglycans in diabetic conditions[26], which will cause the thickness of the glycocalyx, which contains large amounts of sulfate, will also decrease[22]. Another in vitro study reported that in environments with high glucose levels, causing release of sulfur and hyaluronic acid release components into the culture media[27], in which decreases in sulfate levels caused by hyperglycemia are known to be associated with functional disorders endothelial cells[28]. Some of these studies are in line with the results of the analysis in this study, namely that different glycosaminoglycan chains have responses that may also differ in their interactions with AGE.

From this study it was also reported that some AGE and glucose compounds can interact with syndecan and glypican core proteins, but it can not interact with Mimecan. Some AGEs that can interact with syndecan and glypican include 3-DG, pyrraline, and CML (only on syndecan). Because only a small portion of AGE compounds can interact with core proteins, it is thought that this amount will not sufficiently affect the function and structure of core proteins. Studies conducted by Morrison & Lowe-Krentz[29] reported that the syndecan-1 and glypican-1 core proteins are not affected by high glucose levels, so it is suspected that agents that it can enhance sulfate liver synthesis will be able to restore the effects for structural improvement glycocalyx.

In hyperglycemia and diabetes, reduced glycocalyx volume causes vascular abnormalities, which include adhesion of mononuclear cells and platelets on the endothelial surface, affecting the availability of NO, and causes an increase in macromolecular leakage through the endothelium[30]. Hyperglycemia can stimulate cross-interaction and modification of matrix proteins through the glyco-oxidation process, and AGE compounds produced from these processes, which are reported that the process will affect the synthesis of matrix proteins[31].

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TABLES AND FIGURES

Table 1. Binding energy for interactions between glycosaminoglycan chains with AGE and glucose compounds.

	Heparin Sulfate	Chondroitin sulfate	Hyaluronic acid
Glucose	-110.77 kJ/mol	-106.46 kJ/mol	-112.35 kJ/mol
Fructose	-110.77 kJ/mol	-106.46 kJ/mol	-112.35 kJ/mol
3-deoxyglucosone	-119.35 kJ/mol	-103.50 kJ/mol	-125.71 kJ/mol
Glyoxal	-72.08 kJ/mol	-64.38 kJ/mol	-62.88 kJ/mol
Methylglyoxal	-82.22 kJ/mol	-68.51 kJ/mol	-74.16 kJ/mol
CML	-113.74 kJ/mol	-113.20 kJ/mol	-124.76 kJ/mol
Pentosidine	-160.99 kJ/mol	-134.87 kJ/mol	-166.42 kJ/mol
Pyrraline	-137.48 kJ/mol	-129.48 kJ/mol	-162.11 kJ/mol

Table 2. Possible interactions between core proteins with AGE and glucose

Molecule	Point interaction	Category	Distance (Å)	Donor atom	Acceptor atom	Binding energy
Glypican-3-DG	3-DG:O - LYS383:O	Hydrogen bond	2,3607	O	O	**-145.82 kJ/mol**
Glypican - fructose	Fructose:O - ASP295:O	Hydrogen bond	2,9658	O	O	**-152.64 kJ/mol**
Glypican - glucose	Glucose:O - ASP295:O	Hydrogen bond	2,9658	O	O	**-152.64 kJ/mol**
Glypican - pyrraline	Pyrraline:O - GLN390:OE1	Hydrogen bond	2,9046	O	OE1	**-202.13 kJ/mol**
Syndecan - 3-DG	LYS284:H - Syndecan:O	Hydrogen bond	2,3467	H	O	**-155.75 kJ/mol**
	LYS295:HZ2 - Syndecan:O	Hydrogen bond	2,4829	HZ2	O	
	Syndecan:O - GLU292:O	Hydrogen bond	3,0259	O	O	
Syndecan - CML	LYS295:HZ2 - Syndecan:O	Hydrogen bond	2,1123	HZ2	O	**-167.59 kJ/mol**
	Syndecan:O - MET281:O	Hydrogen bond	2,5206	O	O	
	Syndecan:O - LYS282:O	Hydrogen bond	2,3775	O	O	

	Syndecan:H - LYS282:O	Hydrogen bond	2,3775	H	O	
Syndecan - fructose	Fructose:O - GLU292:O	Hydrogen bond	3,2049	O	O	**-153.39 kJ/mol**
Syndecan - glucose	Glucose:O - GLU292:O	Hydrogen bond	3,2049	O	O	**-153.39 kJ/mol**
Syndecan - pyrraline	ARG280:HE - pyrraline:O	Hydrogen bond	2,4866	HE	O	**-192.51 kJ/mol**

Table 3. Possible interactions between Integrin and AGE and Glucose

Molecule	Point interaction	Category	Distance (Å)	Donor atom	Acceptor atom	Binding energy
Integrin - CML	VAL52:H - CML:O	Hydrogen bond	2,4478	H	O	**-188.11 kJ/mol**
	CML:O - PHE15:O	Hydrogen bond	1,8581	O	O	
	CML:H - PHE15:O	Hydrogen bond	1,8581	H	O	
Integrin - fructose	ASN80:HD21 - fructose:O	Hydrogen bond	2,4887	HD21	O	**-154.09 kJ/mol**
Integrin - glucose	ASN80:HD21 - glucose:O	Hydrogen bond	2,4887	HD21	O	**-154.09 kJ/mol**
Integrin - pyrraline	ALA51:H - pyrraline:O	Hydrogen bond	1,5994	H	O	**-205.19 kJ/mol**
E-selectin - 3-DG	ASN203:HD21 - 3-DG:O	Hydrogen bond	2,1131	HD21	O	**-141.63 kJ/mol**
E-selectin - CML	THR179:H - CML:O	Hydrogen bond	1,3577	H	O	**-147.84 kJ/mol**
	CML:O - LEU170:O	Hydrogen bond	3,0530	O	O	
	CML:O - ASP175:OD1	Hydrogen bond	2,6437	O	OD1	
E-selectin - fructose	THR179:H - fructose:O	Hydrogen bond	1,7418	H	O	**-143.37 kJ/mol**
E-selectin - glucose	THR179:H - glucose:O	Hydrogen bond	1,7418	H	O	**-143.37 kJ/mol**
L-selectin - glyoxal	LYS173:H - glyoxal:O	Hydrogen bond	1,5234	H	O	**-79.99 kJ/mol**
	CYS174:H - glyoxal:O	Hydrogen bond	2,367	H	O	
	ASP175:H - glyoxal:O	Hydrogen bond	2,1068	H	O	
	GLN176:H - glyoxal:O	Hydrogen bond	2,4895	H	O	
E-selectin - pentosidine	TRP231:H - pentosidine:O	Hydrogen bond	2,4007	H	O	**-205.98 kJ/mol**

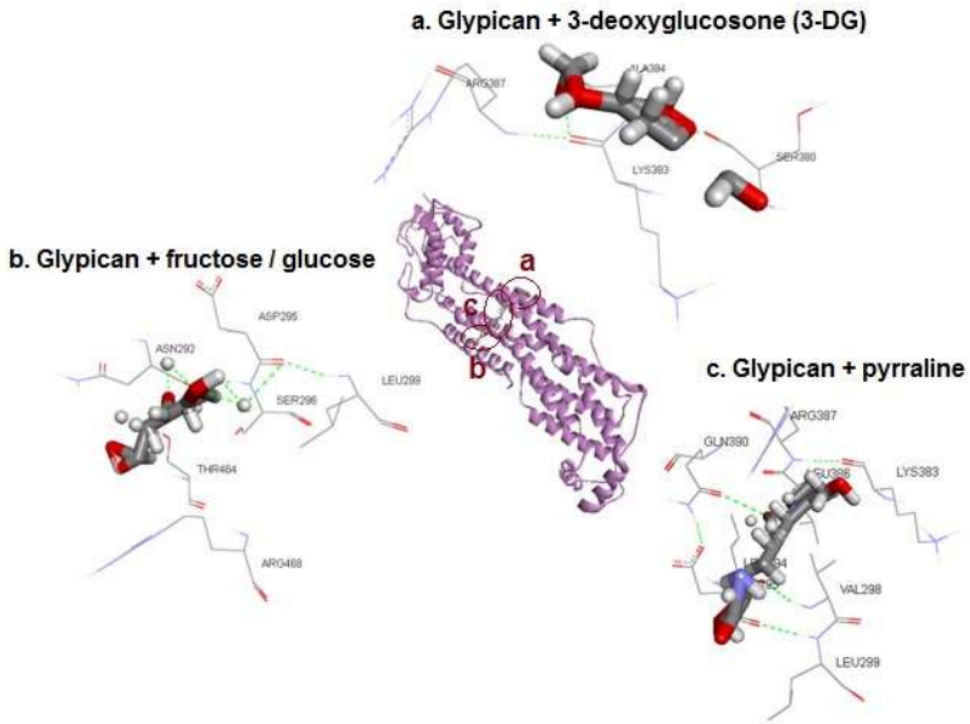

Figure 1. Interactions between glypican and 3-DG (a), fructose/glucose (b) and pyrraline (c) compounds.

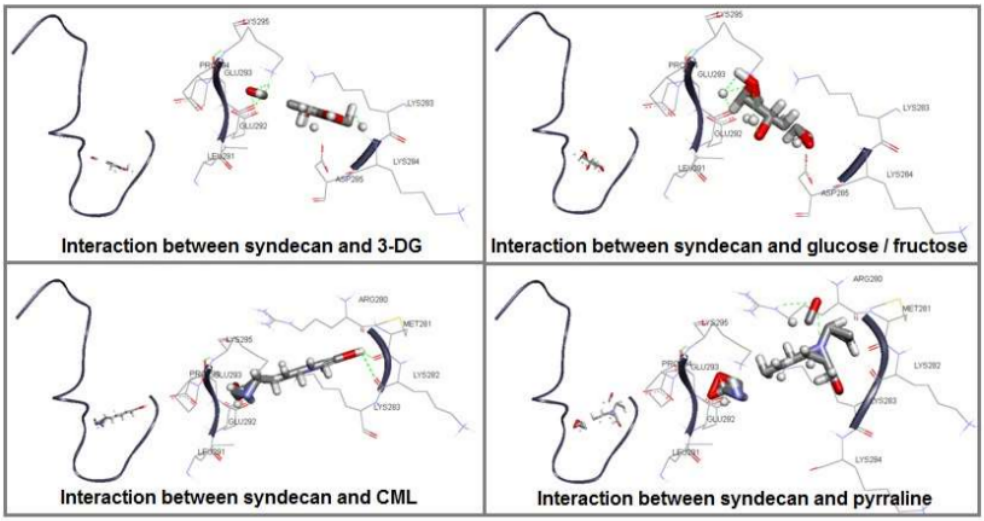

Figure 2. Interactions between syndecan and 3-DG, glucose, fructose, CML, and pyrraline.

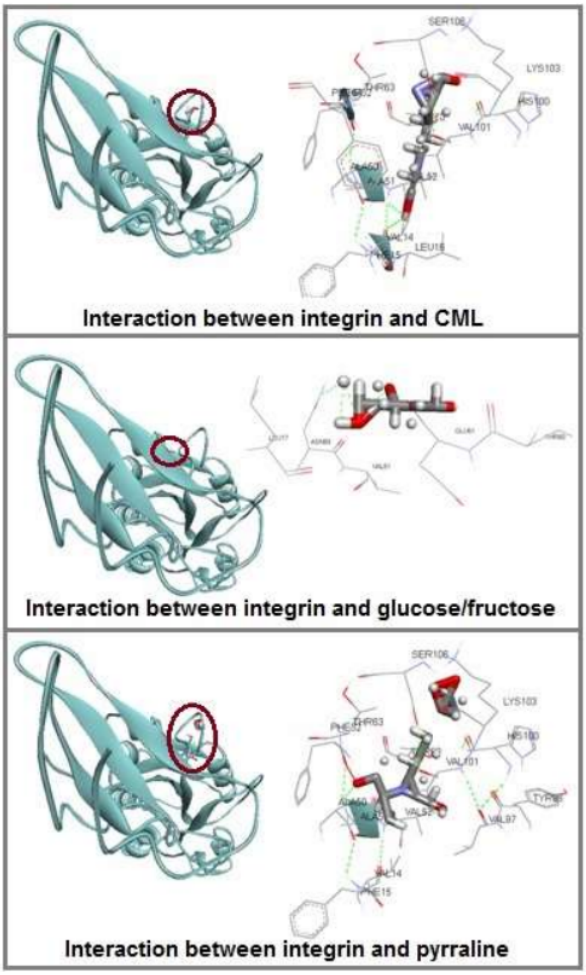

Figure 3. Interactions between integrins with CML, fructose, glucose, and pyrraline.

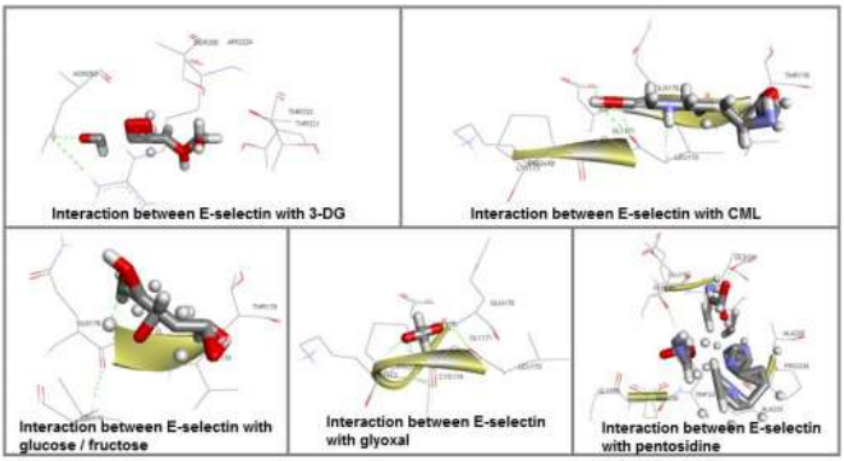

Figure 4. Interaction between E-selectin and 3-DG, CML, fructose, glucose, glyoxal, and pentosidine.

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