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Research Article

MULTI-ECLECTIC APPROACH TO SCUFFLE DIABETIC RETINOPATHY

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ABSTRACT

Bioinformatics is the amalgamation of biology computer science and information technology which has become an integral part of research and development in a variety of areas like functional genomics, proteomics, drug discovery and pharmacogenomics. By the analysis of phylogram, it is observed that proteins with minimum distance are cortistatin, VDR and somatostain. In this paper, diabetic retinopathy is a complex process in which several cytokines, growth factors, and free radicals play a vital role. Molecular docking play a key role in structure based drug designing process and docking of other inhibitory compound related to diabetic retinopathy is fruitful for designing new drugs for its therapeutic purpose. The present multiple alignment study propose that a close association exists between cortistatin, somatostain and vitamin-D receptor proteins in the pathogenesis of diabetic retinopathy, thus multi-eclectic approach is needed to fight diabetic retinopathy.

INTRODUCTION

Areas of bioinformatics and data mining are developing as interdisciplinary science. Bioinformatics uses advancements in the area of computer science, information technology and communication technology to solve complex problems in life sciences and biotechnology. Data capture, data warehousing and data mining have become major issues for biotechnologists and biological scientists because of the growth of data in biology in the form of, protein sequences, Protein 3D structures, metabolic pathways databases, genomes of a number of organisms and biodiversity related information. The advancements in information technology particularly the use of internet play a significant role in gathering and accessing the ever increasing information in biology and biotechnology. Bioinformatics is the combination of biology computer science and information technology which has become an integral part of research and development in a variety of areas like functional genomics, proteomics, drug discovery and pharmacogenomics. It is evident that bioinformatics has major role in a number of issues like biodiversity and environmental change, for instance, climate change is because of the release of unwanted carbon dioxide gases and various other greenhouse gases due to industrial revolution which have negative impact on earth's environment and in this case for reducing such toxic gases bioinformatics may help in sequencing microbial genome. Bioinformatics with its hold on various techniques and tools becomes common and in regular use in various research fields.

Diabetes mellitus is a chronic condition which is characterized by lack of insulin as well as hyperglycemia, dyslipidemia, and neurovascular damage. It can affect any organ of the body of patients suffering with diabetes mellitus and harm their quality of life. Diabetic retinopathy is a macro vascular complication of hyperglycemia which causes blindness. It is a common complication in type-1 and type-2 diabetes. Various molecular, clinical and biochemical factors contribute to the risk of diabetes retinopathy. Different protein biomarkers, novel and traditional can help in improving primary and secondary prevention strategies for diabetic retinopathy (1). Diabetic retinopathy can affect any individual irrespective of its racial and ethnic background. From different regions of the world, it has been reported that diabetic retinopathy in African/Afro-Caribbeans and South Asians compared to white Europeans is significantly more prevalent (2). Sequence mining is a data mining topic used to identify patterns of ordered events within a database. Its applications in medicine eventually manifested in diseases susceptibility prediction, readmission and pharmacovigilance (3). Sequence mining is commonly defined as finding the complete set of frequent subsequences in a set of sequences. Sequence mining discovers meaningful sequential

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patterns among a large quantity of data. Data mining is an area in which computer ethics play a major role where abundant data were gathered from various sources used to study patterns. Personal privacy leaks have become serious issue in data mining while extracting valuable data and also at the same time preventing personal information leaks, thus various techniques need to be developed to stop it (4). Molecular docking is highly used method to calculate protein-ligand interactions and AutoDock is computer software used globally for the same purpose (5). Docking of lead compounds into the binding site of aldose reductase protein and estimating binding affinity plays a significant role in structure based drug designing process. Multiple interlinked biochemical mechanisms have been postulated to be involved in diabetic retinopathy. The mechanisms mainly include: Increased aldose reductase activity that results in enhanced flux of glucose through the polyol pathway, formation of advanced glycationend product (AGEs), activation of protein kinase C (PKC), enhanced formation of reactive oxygen species (ROS), increased production of vascular endothelial growth factor (VEGF) and placental growth factor (P1GF), and reduced generation of endothelial nitric oxide (eNO) (6-13). Activation of VEGF leads to the destruction of the blood retinal barrier (BRB), the development of diabetic macular edema (DME) and neovascularization typical for Proliferative Diabetic Retinopathy (PDR). There are several growth factors related to diabetic retinopathy as a combination of angiogenic stimuli (14-15). Various techniques have been utilized to gauge blood flow in retina of individuals with diabetes. Despite some discrepancies between studies, in general individuals with a short duration of diabetes (less than 5 years) show a narrowing of the retinal arteries and retinal blood flow is reduced (16). Animal and cell culture model studies discloses that impaired growth factor support, enhanced oxidative/nitrosative stress, and its downstream effectors such as mitogen-activated protein kinase activation, inflammatory response, endothelin-1 over expression and impaired Ca^{2+} signaling also plays significant role in diabetic retinopathy pathogenesis.

Diabetic retinopathy*:* It is a vascular disease characterized by changes in retinal capillary bed. Most of the capillary changes occur in the inner nuclear and outer plexiform layers. Selective loss of pericytes, the retinal capillary cells that contain abundant smooth-muscle actin and have a contractile function, thus, regulating retinal capillary blood flow, is a characteristic lesion that occurs early in the histopathology of diabetic retinopathy (18). Aldose reductase is the first and rate-limiting enzyme of the polyol pathway that converts glucose to fructose which plays a major role in diabetic retinopathy by inducing retinal lesions including blood retinal barrier beak down, loss of pericytes, neuroretinal apoptosis and glial reactivation and neovascularization-events that are associated with diabetic retinopathy. In different animal studies it has been reported that rats administered with aldose reductase inhibitors prevented basement membrane thickening pericyte loss, and development of micro aneurysms in the retinal capillaries (19). However, results came from clinical trials showed that modification in concentrations and activities of some other protein and enzymes also has role in diabetic retinopathy pathogenesis. In some studies it appears that vitamin-D inhibit vascular smooth muscle cell growth *in vivo* because of its ant proliferative activity and its inadequacy leads to retinopathy in patients with type-1 and type-2 diabetes. Vitamin-D receptor is an active form of vitamin-D and it is highly expressed in human tissues which includes retina, thus it is regarded as the candidate gene associated with diabetic retinopathy **(20)**. Cortistatin (CORT) is a neuropeptide which is structurally similar to somatostain. It is reported that the concentration of somatostain (SST) in vitreous fluid is higher than in plasma in non-diabetic patients and lower intravitreous concentration of SST has been detected in PDR patients and patients with diabetic macular edema. These results suggest that SST could be a natural angiogenic inhibitor present in the vitreous fluid and shortage of intravitreal SST could be associated with retinal neovascularization (21).

Table 1 28 genes obtained from NCBI which are in close association with diabetic retinopathy with amino acid length and accession numbers (23).

S. No.	Gene	Protein	Length	Accession
1	ACE	Angiotensin-converting enzyme	739 aa	AAH36375
2	ADIPOQ	Adiponectin	244 aa	AAH96310
3	AGER	Advanced glycosylation end product-specific receptor	404 aa	AAH20669
4	AKR1B1	Aldo-ketoreductase family 1, member B1 (aldose reductase)	316 aa	AAH00260
5	ALDRL2	aldehyde reductase	325 aa	AAB92369.1
6	ANGPT2	Angiopoietin 2	496 aa	AAI26203.1
7	AOC3	Amine oxidase, copper containing 3 (vascular adhesion protein 1)	763 aa	AAH50549.1
8	CORT	CORT protein, partial	122 aa	AAH40034.1
9	CRP	C-reactive protein isoform 1 precursor	224 aa	NP_000558.2
10	CTGF	Connective tissue growth factor	349 aa	AAH87839.1
11	GCNT1	Glucosaminyl (N-acetyl) transferase 1, core 2 (beta-1,6-N-acetylglucosaminyltransferase)	428 aa	AAI09103.1
12	HGF	Hepatocyte growth factor (hepapoietin A; scatter factor)	728 aa	AAI30285.1
13	IGF1	insulin-like growth factor I isoform 4 preproprotein	153 aa	NP_000609.1
14	ITGA2	integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)	1181 aa	AAM34795.1
15	MTHFR	MTHFR protein	73 aa	AAH18766.1
16	NFKB1	NFKB1 protein, partial	550 aa	AAH33210.1
17	NOS2A	Nitric oxide synthase 2, inducible	1153 aa	AAI30284.1
18	NOS3	Nitric oxide synthase 3 (endothelial cell)	1203 aa	AAH63294.1
19	PGF	Placental growth factor	170 aa	AAH01422.1
20	PRKCB1	Protein kinase C, beta	673 aa	AAH36472.1
21	RAGE	RAGE protein	231 aa	AAH53536.1
22	SST	Somatostatin	116 aa	AAH32625.1
23	TGFA	transforming growth factor alpha	160 aa	AAA61159.1
24	TIMP2	TIMP metallopeptidase inhibitor 2	220 aa	AAH71586.1
25	TNC	tenascin C	2201 aa	CAI15110.1
26	TNF	tumor necrosis factor (TNF superfamily, member 2)	233 aa	BAE78639.1
27	VDR	VDR protein	473 aa	AAH33465.1
28	VEGF	vascular endothelial growth factor	191 aa	CAI19965.1

EXPERIMENTAL RESULTS

Various proteins which are involved in diabetic retinopathy disease pathogenesis were analyzed using multiple sequence alignment and we have constructed a score table (see table 1) of different proteins which are closely related to diabetic retinopathy. From Clustal Omega, we have obtained a polygenetic tree using the gathered data (FASTA sequences of proteins) and it revealed that VDR, CORT and SST are the three proteins with minimum distance suggesting a dominant role of them in diabetic retinopathy when compared to other 25 proteins studied. This phylogenic tree indicated that cortistatin, somatostain and vitamin-D receptor proteins has close relation

(Figure-1) and plays a significant role in pathogenesis of diabetic retinopathy. It is evident that proteomics study in combination with the sequence mining and multiple alignment tools are useful for accurate prediction of biomarkers as new therapeutic targets which are associated with diabetic retinopathy. The natural compounds selected for molecular docking have some collective structural features. All the lead compounds showed good binding energy and also exhibited interactions and better lower free energy values, indicating more thermodynamically favored interaction. The compounds melicitrin and quercetin exhibited binding energies of -10.52 Kcal/mol and -9.45 Kcal/mol respectively with melicitrin interacting Arg17, Arg268 and NAP1318 and for quercetin Leu212. Compound kaempferol interacts with Arg217, Glu229 and Leu212 with binding energy of -8.86 Kcal/mol and naringenin interacts with Gly213 with binding energy of -8.76 Kcal/mol. This study indicates all the four natural compounds interact with ALR2.

Table 2 Experimental activities and predicted values by Lamarckian Genetic Algorithm dockings of the four compounds.

Test compounds	Interacting amino acids	Binding energy, ΔG (Kcal/mol)	Dissociation constant (kI) (nM)
Quercetin	Leu212(2)	-9.45	117.72
Kaempferol	Arg217, Glu229, Leu212	-8.86	317.8
Naringenin	Gly213	-8.76	381.94
Melicitrin	Arg217, Arg268(2), NAP1318	-10.88	10.52

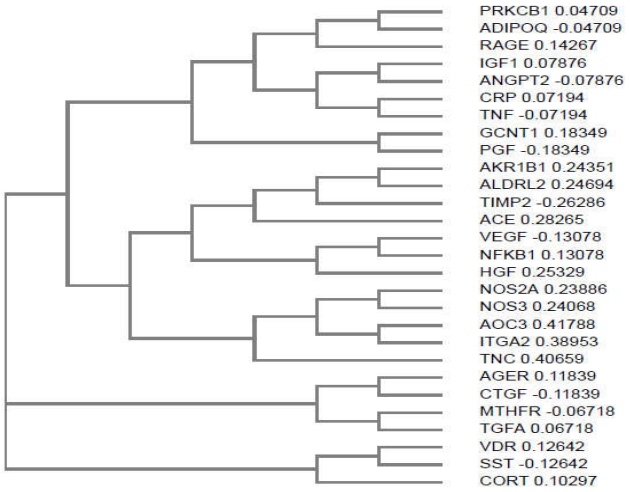
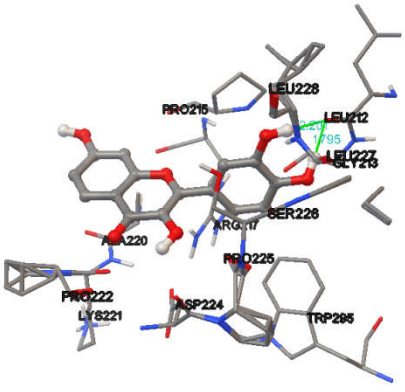
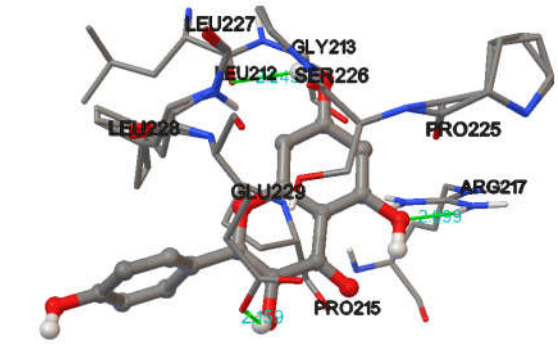


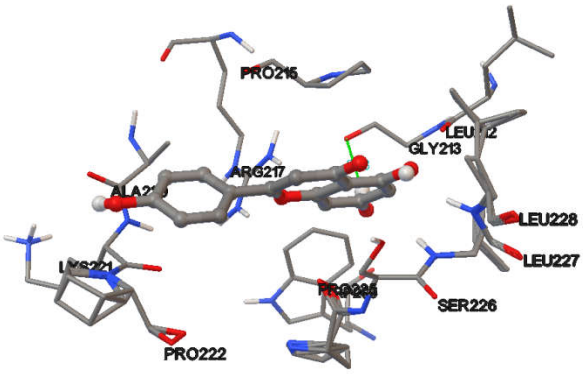
Figure 1 Phylogram constructed using Neighbor-Joining Algorithm with Clustal Omega.



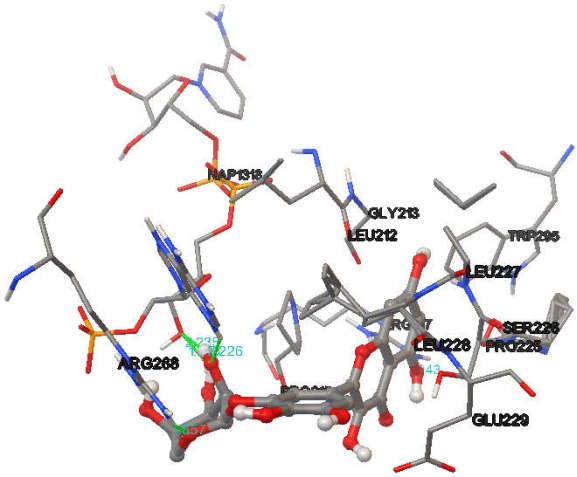
Quercetin



Kaempferol



Naringenin



Melicitrin

Figure 2 3D structures of Quercetin, Kaempferol, Naringenin and Melicitrin.

CONCLUSION

From the literature study, it can be concluded that diabetic retinopathy is a complex process in which several cytokines, growth factors, and free radicals play a vital role. By the analysis of phylogram, it is observed that proteins with minimum distance are cortistatin, VDR and somatostain. Researcher have found that cortistatin mRNA has significant role in immune tissues like monocytes, macrophages and dendritic cells and it has been reported that insulin secretion was inhibited by cortistatin and does not effects glucose levels during physiological processes. According to Hernandez C, et al., patients suffering with PDR showed lower cortistatinintravitreous levels when compared to non-diabetic patients and levels of cortistatin were higher in vitreous fluid

than in the plasma and non-existence of relationship between plasma and vitreous cortistatin concentrations which suggest that it has possible role in retinal homeostasis (24). Generally increase in hyperglycemia increases the activity of aldose reductase which in turns set off a series of events which causes enhanced iNOS, VEGF, PIGF, and free radicals expression. Several clinical trials were carried out by different scientists but the results were diverged whereas isolation of vascular endothelial growth factors (VEGF) and its angiogenic activity that its expression was increased in hypoxia made it a supreme candidate. But VEGF antagonists showed limited beneficial actions suggesting that changes in the concentrations and activities of other proteins and enzymes for instance, endothelial nitric oxide synthase (eNOS) and various growth factors likewise assume a noteworthy part in the pathogenesis of diabetic retinopathy. Molecular docking is widely used method for calculating protein-ligand interactions. AutoDock 4.2 uses binding free energy assessment to assign the best binding conformation and docking studies are commonly performed for predicting binding modes to proteins and their binding energies of ligands. Molecular docking play a key role in structure based drug designing process and docking of other inhibitory compound related to diabetic retinopathy is fruitful for designing new drugs for its therapeutic purpose. The current multiple alignment study propose that a close association exists between cortistatin, somatostain and vitamin-D receptor proteins in the pathogenesis of diabetic retinopathy, thus multi eclectic approach is needed to fight diabetic retinopathy. This study strongly suggests further research on these proteins related to diabetic retinopathy and various other genes closely associated with diabetes and molecular docking studies can be helpful in treatment and prevention of diabetic retinopathy by designing new drugs to counterattack it.

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