ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

In Silico Strategy for Designing of Novel Chromene and Indole Derivatives To Combat Diabetes Mellitus.

Vishnu V, Saranya TS, and Asha Asokan Manakadan*.

Department of Pharmaceutical Chemistry & Analysis, Amrita School of Pharmacy, Kochi – 682041, Amrita Vishwa Vidyapeetham, Amrita University, AIMS Health Science Campus, Ponekkara P. O., Kerala, India.

ABSTRACT

Diabetes Mellitus is an assorted group of metabolic disorders due to the inability of pancreas to secrete insulin or the insensitivity of the cells to insulin. This work has been chosen considering the vital role of aldose reductase inhibitors in Diabetes Mellitus through the polyol pathway. Consequently an effective control is the key to tackle this abnormal condition. *In silico* analysis for the development of aldose reductase inhibitors were carried out using both phytochemicals and generation of new lead molecules as ligands. The phytochemicals selected for the study were Allicin, Galegine, Rhamnoside, Quercetin, Trigonelline and Ferulic Acid. The lead molecule nucleus finalized were that of chromenes and indole derivatives. The present study included the analysis of parameters relating to proteins such as primary and secondary structure analysis, subcellular location, analysis of cavities, ADME as well as docking results. Positive results were shown by Allicin, Galegine, Rhamnoside, Quercetin, Trigonelline and Ferulic Acid when compared with the standard drugs like Epalrest and Sorbinil. The lead molecules of chromeme derivative AR2,methyl2,2-dimethyl3-(4oxo-3-phenoxymethyl)-4H-chromrn-8-yl)propanoate and indole derivative AR7, methylidene({[1-(phenoxymethyl)-2,3-dihydro-1H-indol-5yl]oxy})amine screened displayed significant results over the phytochemicals and the standard drugs used. Further *in vitro* pharmacological activities might prove to be useful to substantiate the results.

Keywords: Aldose reductase, Diabetes Mellitus, Allicin, chromenes, indole derivatives

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Computational chemistry is a novel field with the application of computation in various aspects of chemistry. The stepping of computational chemistry in the pharmaceutical field has been of immense importance ever since. The added advantage of chemistry in assembly of innovative lead molecule is no doubt very essential in combating existing as well as newer disease condition emerging by time. The designing technique is made easier along with it being efficient and effective[1]. The computational drug designing assist in selecting newly generated lead molecules of good physicochemical properties for better pharmacological action in the body. Thus before moving into the synthesis of selected few molecules in hand, *in silico* analysis can be performed to obtain greater probability of more feasible molecules. This proves to be more cost and time effective process [2].

Diabetes Mellitus is a non-communicable disease and is a major cause of worry as it leads to progression of elevated levels of glucose in the body due to the insufficient concentration of required insulin hormone to combat glucose in the target cells or the inability of the utilization of adequate amount of normal insulin levels in the body due to resistance. It is a universal non-communicable disease with worldwide statistics of 422 million adults living with it as per the WHO estimates in 2014. According to WHO, more than 80% of people with diabetes live in least- and middle-income countries and this number is likely to be more than double by 2030 without intervention[3]. Diabetes Mellitus reflects the condition where the risk factor is the elevated glucose concentration in the body. Diabetes Mellitus is a condition which maintains the status of being a devastating and conflicting state of health with wide complications of its own along with the tendency to lead to other diseases such as Alzheimer's disease, blindness, atherosclerosis, Foot gangrene, Hyperhomocysteinemia, Myocardial infarction, Nephropathy, Neuropathy, Open angle glaucoma, Osteoporosis, Reduced bone mineral density and Retinopathy to name a few[4- 6].

MATERIALS AND METHODS

The phytochemicals were taken as ligands to signify the importance of lead molecules from the natural source. The phytochemicals related to Diabetes Mellitus as aldose reductase inhibitor were selected to determine the interactions with the targets selected. The phytoconstituents studied were Allicin, Galegine, Rhamnoside, Quercetin, Trigonelline and Ferulic Acid**.** The genes and proteins associated with aldose reductase were taken for the designing of an inhibitor for the aldose reductase involved in the polyol pathway. The analysis was made by carrying out interactional studies of all the mentioned phytochemicals with the gene AKR1B1 and associated protein 1MAR. The target proteins linked with activity of aldose reductase was identified from the RSCB Protein data bank repository. The structures of the various phytochemicals have been generated using Chemsketch. The available aldose reductase inhibitors are Epalrestat, Fidarestat, Fidaresтst Stereoisomer, Ranirestat, Sorbinil and Zopolrestat; out of which Epalrestat and Sorbinil were engaged for the interactional studies. Docking studies were executed using Argus lab, which is a software that utilizes principles of molecular dynamics simulation and docking. Since Molecular dynamics simulation is incorporated, both ligand and the target can be treated in a flexible manner [7] .The primary and secondary analysis of protein structure was done using the tools ProtParam and SOPMA respectively [8, 9]. The molecular properties predictions were calculated using Molsoft and bioactivity scores were considered using Molinspiration[10, 11].

RESULTS AND DISCUSSION

The preliminary characterization was carried out by determining the target properties. The analysis of primary structure was carried out using ProtParam for the determination of halflife, instability index, aliphatic index and Grand average of hydropathicity of the target proteins 1MAR. The number of amino acids involved in aldose reductase protein 1MAR was 315. The molecular weight was found to be 35722.2 and the theoretical pI 6.55. The total number of atoms was computed to be 5052. The extinction coefficient was found to be 49765 at absorbance 0.1% (=1g/l) 1.383. The N-terminal of the sequence is considered as A (ala). The estimated half-life was calculated as 4.4 hours (the mammalian reticulocytes, in vitro), >20 hours (yeast, in vivo) and >10 hours (Escherichia coli, in vivo). The instability index was 36.27, which helped to classify the protein as stable. The aliphatic index was found to be 93.43, therefore the protein will demonstrate considerable thermostability whereas the Grand Average of Hydropathicity was found to be -0.260. . The protein analysis results showed the proteins to be stable and hydrophilic in nature. The secondary structure analysis was carried out using SOPMA to determine the arrangement of amino acids in alpha helix, beta strand and random coils. The results of

ISSN: 0975-8585

secondary structure analysis illustrate the alpha helix in the range of 35- 38% and random coil to be in the range of 38- 49% [12, 13]. The secondary structure analysis of proteins displayed a stable character of the proteins. The proteins were subjected to cavity or pocket analysis using CASTp and predicted about 3 pockets for 1MAR. The maximum pocket size area of 5920 (Å) was found for the protein 1MAR [14]. The subcellular location of the proteins was found out using WoLFPSORT [15]. The protein was located in the subcellular portion of the cytoplasm.

Phytochemicals with aldose reductase inhibitory activity were listed in **Table 1**. The designed ligands AR1, AR2, AR3, AR4, AR5 and AR6 chromenes derivatives as aldose reductase inhibitor is shown in **Fig. 1.** and AR7, AR8, AR9 and AR10 indole derivatives is revealed in **Fig. 2.**

Table 1: Phytochemicals Used As Aldose Reductase Inhibitors

S No.	Phytochemicals	Family	Phytoconstituent	Part Of Phytochemical Used
1	*Allium cepa L.*	Liliaceae	Allicin	Onion, Shallot; found in Bulb
2	*Camellia sinensis (L.) KUNTZE*	Theaceae	Galegine	Tea; found in Leaf
3	*Tagetes erecta L.*	Asteraceae	Rhamnoside	Aztec Marigold; found in Leaf
4	*Abelmoschus esculentus (L.) MOENCH*	Malvaceae	Quercetin	Okra; found in Flower
5	*Achillea millefolium L.*	Asteraceae	Trigonelline	Milfoil, Yarrow; found in Plant
6	*Ajuga iva (L.) SCHREBER*	Lamiaceae	Ferulic Acid	Ivy Bugle; found in Shoot

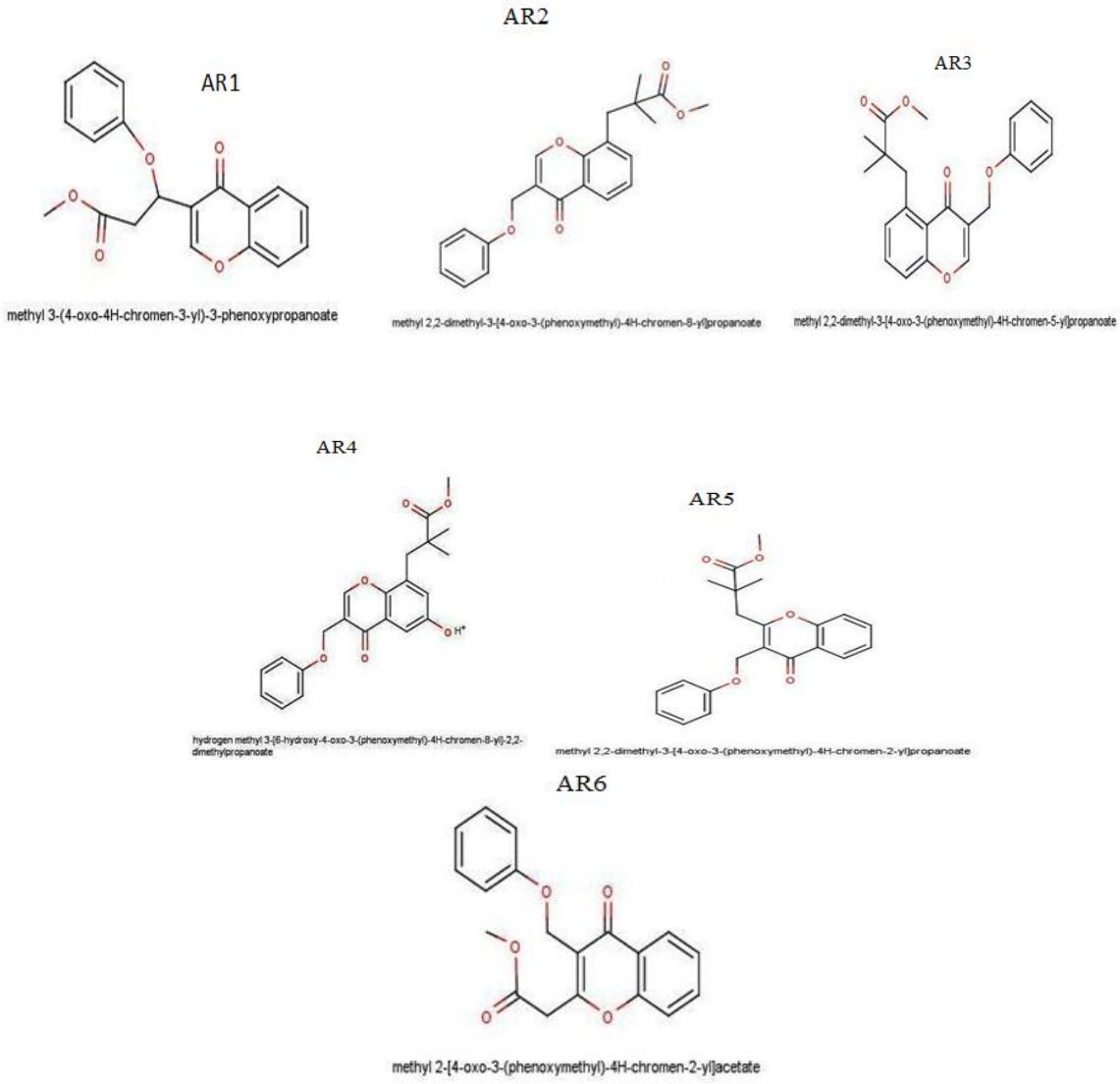

FIG. 1. AR1, AR2, AR3, AR4, AR5 AND AR6 chromenes derivatives as aldose reductase inhibitor

ISSN: 0975-8585

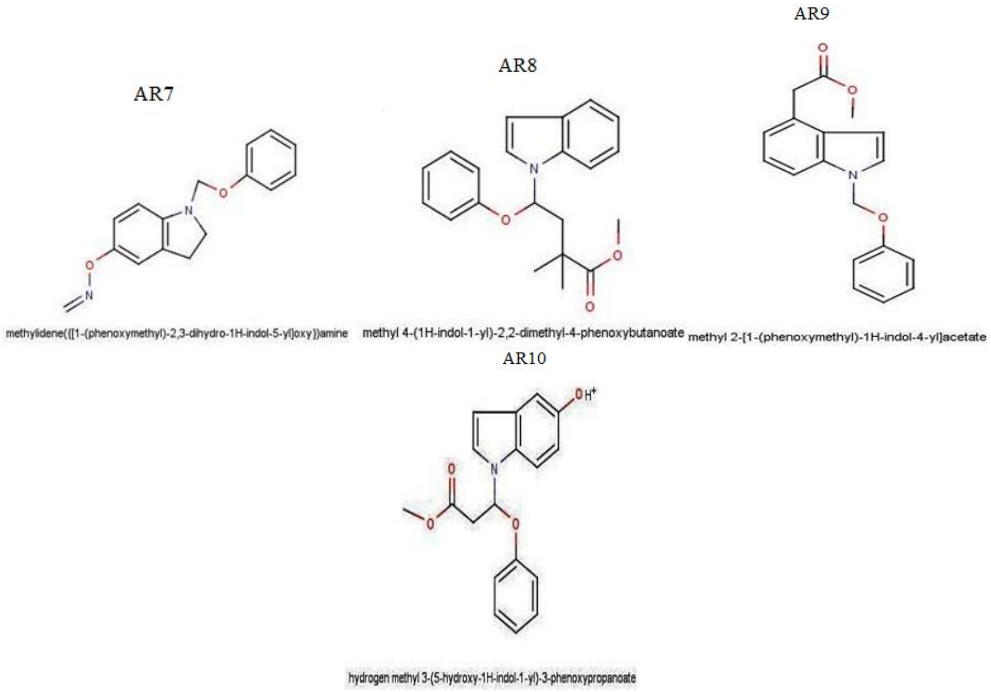

FIG. 2. AR7, AR8, AR9 AND AR10 indole derivatives as aldose reductase inhibitor

The ligands were then subjected to molecular property calculation and the parameters molecular weight, number of hydrogen bond acceptors (nHBA), number of hydrogen bond donors (n HBD), mollogP, mollogS, molPSA, molecular volume, number of stereoisomers and drug likeness model score were studied. **Table 2** and **3** gives the molecular properties and bioactive scores of the individual ligands respectively.

TABLE 2: Calculation of molecular properties of phytoconstituents and designed ligands

Sl no:-	Phytoconstituents	Molecular formula	Molecular Weight	Number of HBA	Number of HBD	MolLogP	MolLogS	MolPSA	MolVol	Number Of stereo centres	Drug likeness model score
1	Allicin	C6 H11 O S2	163.03	3	1	2.31	-1.19 (in Log(moles/L)) 10488.53 (in mg/L)	13.72 A^2	161.58 A^3	0	-1.18
2	Galegine	C6 H13 N3	127.11	1	4	0.91	-2.16 (in Log(moles/L)) 874.55 (in mg/L)	49.94 A^2	145.92 A^3	0	-0.74
3	Rhamnoside	C6 H12 O5	164.07	5	4	-2.01	-0.03 (in Log(moles/L)) 154658.34 (in mg/L)	72.58 A^2	133.08 A^3	5	-1.07
4	Quercetin	C15 H10 O7	302.04	7	5	2.11	-3.87 (in Log(moles/L)) 40.95 (in mg/L)	102.61 A^2	281.71 A^3	0	0.93
5	Trigonelline	C7 H8 N O2	138.06	2	1	0.57	-0.75 (in Log(moles/L)) 24432.43 (in mg/L)	31.91 A^2	127.93 A^3	0	0.26
6	Ferulic acid	C10 H10 O4	194.06	4	2	2.04	-2.44 (in Log(moles/L)) 701.54 (in mg/L)	52.80 A^2	194.88 A^3	0	-0.44
7	AR1	C19 H16 O5	324.1	5	0	3.38	-4.41 (in Log(moles/L)) 12.64 (in mg/L)	48.11 A^2	329.95 A^3	1	0.22
8	AR2	C21 H20 O5	352.13	5	1	4.21	-4.51 (in Log(moles/L)) 10.80 (in mg/L)	56.45 A^2	373.38 A^3	0	-0.05
9	AR3	C22 H22 O5	366.15	5	0	4.56	-5.49 (in Log(moles/L)) 1.19 (in mg/L)	49.53 A^2	397.32 A^3	0	0.15
10	AR4	C22 H22 O5	366.15	5	0	4.56	-5.02 (in	49.22 A^2	397.87 A^3	0	-0.25

ISSN: 0975-8585

							Log(moles/L)) 3.46 (in mg/L)				
11	AR5	C22 H22 O5	366.15	5	0	4.50	-5.70 (in Log(moles/L)) 0.72 (in mg/L)	49.19 A^2	405.28 A^3	0	0.46
12	AR6	C19 H16 O5	324.10	5	0	3.31	-4.51 (in Log(moles/L)) 9.96 (in mg/L)	48.60 A^2	340.18 A^3	0	0.39
13	AR7	C16 H16 N2 O2	268.12	4	0	3.01	-4.04 (in Log(moles/L)) 24.37 (in mg/L)	31.87 A^2	267.30 A^3	0	-0.63
14	AR8	C21 H23 N O3	337.17	3	0	5.04 (> 5)	-5.71 (in Log(moles/L)) 0.65 (in mg/L)	28.96 A^2	349.04 A^3	1	0.00
15	AR9	C18 H17 N O3	295.12	3	0	3.66	-4.00 (in Log(moles/L)) 29.46 (in mg/L)	30.63 A^2	291.37 A^3	0	-0.05
16	AR10	C18 H17 N O4	311.12	4	1	3.54	-4.34 (in Log(moles/L)) 14.18 (in mg/L)	45.98 A^2	295.45 A^3	1	-0.03
17	Epalrestat	C15 H13 N O3 S2	319.03	5	1	3.22	-4.78 (in Log(moles/L)) 5.33 (in mg/L)	45.10 A^2	335.10 A^3	0	-0.43
18	Sorbinil	C11 H9 F N2 O3	236.06	3	2	1.54	-3.23 (in Log(moles/L)) 140.11 (in mg/L)	58.32 A^2	229.93 A^3	1	-0.09

TABLE 3: Calculation of bioactive score of phytoconstituents and designed ligands

Sl No:	Phytoconstituents	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Allicin	-2.51	-2.26	-2.95	-2.66	-1.40	-1.52
2	Galegine	-1.83	-1.07	-2.58	-2.70	-1.68	-1.15
3	Rhamnoside	-1.09	-0.42	-1.15	-0.92	-0.70	-0.13
4	Quercetin	-0.06	-0.19	0.28	0.36	-0.25	0.28
5	Trigonelline	-0.78	0.41	-1.85	-3.06	-1.01	0.03
6	Ferulic acid	-0.47	-0.30	-0.72	-0.14	-0.81	-0.12
7	AR1	-0.05	-0.56	-0.31	0.06	-0.24	-0.24
8	AR2	-0.13	-0.51	-0.45	0.11	-0.40	-0.02
9	AR3	-0.10	-0.34	-0.36	0.22	-0.24	0.12
10	AR4	0.02	-0.40	-0.26	0.32	-0.30	0.14
11	AR5	-0.19	-0.35	-0.32	0.07	-0.09	0.05
12	AR6	-0.18	-0.36	-0.35	-0.03	-0.01	-0.03
13	AR7	-0.17	-0.53	-0.27	-0.36	-0.13	-0.27
14	AR8	0.21	0.00	0.04	0.14	0.02	0.25
15	AR9	0.06	-0.13	0.21	0.09	-0.17	0.12
16	AR10	0.18	0.03	0.15	0.20	-0.02	0.21
17	Epalrestat	-0.98	-1.60	-1.15	-0.65	-0.64	-0.14
18	Sorbinil	-0.59	-0.17	-1.01	-0.91	-0.32	-0.04

According to Lipinski rule of five, mollog P value should not be greater than five [16]. The ligand structures AR3, AR4, AR5 and AR8 showed slight variation whereas all other compounds values were satisfactory with values less than 5, which points out good or moderate permeability across cell-membrane. The molecular weight should not exceed 500 daltons as per the rule, and all the compounds values were satisfactory with values less than 500 daltons. If the molPSA is less than $160A^0$, then it would bind to receptor easily, in this case, all the compounds were satisfactory with their molPSA values. The number of hydrogen bond acceptors should be < or=10, all the compounds were suitable with their values which were less than 10. The number of hydrogen bond donors should be < or =5, all the compounds had reasonable values. The molecular properties were compared to standard drugs Epalrestat and Sorbinil. All the phytochemicals and ligands were subjected to energy minimization and docked with the proteins. The results of the interaction energies of the docked ligands and the standard drug to the target proteins used were summarized in **Table 4.**

TABLE 4: Docking analysis of 1MAR target protein with ligands

Ligands/Standard drug	1MAR Interaction Energy (kcal/Mol)
AR 1	-3.8892
AR 2	-4.18535
AR 4	-3.93535
AR 5	-3.59134
AR 6	-3.83666
AR 7	-4.27317
AR 9	-4.10346
AR 10	-4.02029
Epalrestat	-4.17308
Sorbinil	-4.38607

Of the various phytochemicals tested as aldose reductase inhibitors to combat complications of diabetes, positive results were shown by Allicin, Galegine, Trigonelline, Quercetin, Rhamnoside and Ferulic Acid. Allicin reported average interaction energy of -3.73811kcal/mol, Galegin displayed average interaction energy of -3.98812kcal/mol, Trigonelline showed average interaction energy -4.04874kcal/mol, Quercetin reported average interaction energy of -4.08645, Rhamnoside portrayed average interaction energy of-3.57662 kcal/mol whereas Ferulic Acid reported average interaction energy of -3.98681 kcal/mol. Here, we see Allicin with lower average interaction energy, offers greater interactions. All the lead molecules showed positive results especially AR2, AR7, AR9, AR9 and AR10 screened dsignificant results over the phytochemicals and the standard drugs used. The lead molecules of chromene derivative AR2,methyl2,2-dimethyl3-(4oxo-3-phenoxymethyl)-4H-chromrn-8-yl)propanoate reports average interaction energy of -4.18535kcal/mol, indole derivative AR7, methylidene({[1-(phenoxymethyl)-2,3-dihydro-1H-indol-5yl]oxy})amine reports average interaction energy of -4.27317 kcal/mol as shown in **Fig. 3.** and **4**. The ADMETox results show that all the designed lead molecules have significant results without toxicity.

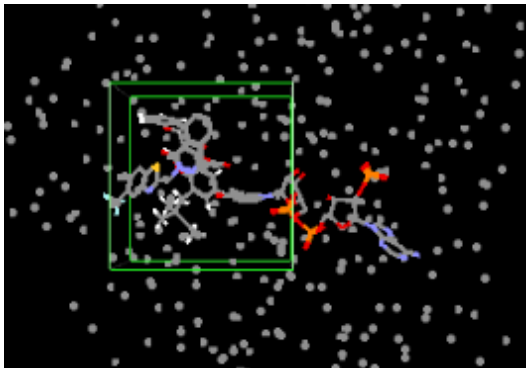

FIG. 3. AR2 chromenes derivative methyl2,2-dimethyl3-(4oxo-3-phenoxymethyl)-4H-chromrn-8-yl)propanoate as aldose reductase inhibitor

ISSN: 0975-8585

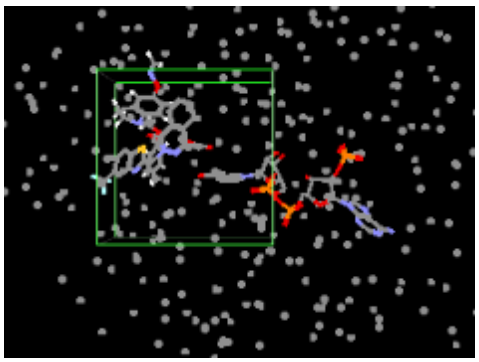

FIG. 4. AR7 indole derivative methylidene({[1-(phenoxymethyl)-2,3-dihydro-1H-indol-5yl]oxy})amine as aldose reductase inhibitor

CONCLUSION

Computational drug designing techniques have proved advantageous for identifying novel aldose reductase inhibitor ligand molecules which could prove beneficial for combating complications of diabetes mellitus relating to polyol pathway. Both phytochemicals as well as lead molecules generated were tested for their interactional energies. The analysis included the study of various parameters relating to proteins such as primary and secondary structure analysis, subcellular location, and analysis of the various cavities present in the protein. The ADME as well as docking results were included in the present study. The target proteins were stable in nature. Phytochemicals showed better docking results compared to the standard drugs like Epalrestat and Sorbinil. Allicin proved to be better than the other phytochemicals. The lead molecule of chromene derivative AR2, methyl 2,2-dimethyl 3-(4oxo-3-phenoxymethyl)-4H-chromrn-8-yl)propanoate and indole derivative AR7, methylidene({[1-(phenoxymethyl)-2,3-dihydro-1H-indol-5yl]oxy}) amine generated displayed significant results compared to the phytochemicals and standard drugs thus showing considerable activity as aldose reductase inhibitors. The lead molecules can be subjected to further studies for the use as aldose reductase inhibitor.

ACKNOWLEDGEMENTS

We are thankful to Dr. Sabitha M., Principal, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Amrita University, for providing necessary facilities for carrying out the research work.

REFERENCES

[1] Finn PW, Kavraki LE. Algorithmica 1999; 25: 347-71.
[2] Tami JM, James MB and Andrew JM. Annual Review of Pharmacology and Toxicology 1997; 37: 71–90.
[3] http://www.who.int/diabetes/en/
[4] Michael JF. Clinical Diabetes 2008; 26(2): 77-82.
[5] Bailes BK. AORN J. 2002; 76(2): 266-76, 278-82, quiz 283-6.
[6] Brajendra KT, Arvind KS. Medical science monitor 2006; 12(7): 130-147.
[7] Mark A. thompson planaria software LLC, Seatle,WA,USA, http://www.arguslab.com
[8] Gasteiger E, Hoogland C, Gattiker A, Duvaud S, Wilkins MR, Appel RD, Bairoch A. Protein Identification and Analysis Tools on the ExPASy Server. (In) John M. Walker (ed): The Proteomics Protocols Handbook, Humana Press 2005: 571-607.
[9] Geourjon C, Deleage G. Computer Applications in the Biosciences 1995; 11: 681-684.
[10] Fernandez-Recio J., Totrov M., Abagyan R. Pac Symp Biocomput. 2002; 552-63.
[11] JME Molecule Editor [http://www.molinspiration.com/jme/index.html]
[12] MS Susmi, RS Kumar, V Sreelakshmi, SV Menon, S Mohan, TS Saranya, Sathianarayanan, AA Manakadan. Research J. Pharm. and Tech. 2015; 8(9): 1199-1204.
[13] Gayathri S. G., Vishnu V., Shigil Shibu, Saranya T. S, Asha Asokan Manakadan. Journal of Chemical and Pharmaceutical Research 2015; 7(11): 170-176.

[14] Joe D, Zheng O, Jeffery T, Andrew B, Yaron T, Jie L. Nucleic Acids Research 2006; 34: 116-118.
[15] Paul H, Keun JP, Takeshi O, Naoya F, Hajime H, Adams CCJ, Kenta N. Nucleic Acids Research 2007; 35: 585–587.
[16] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Advanced Drug Delivery Reviews 2001; 46: 3–26.