ISSN 2664-4142 (Print) & ISSN 2664-6749 (Online)
South Asian Research Journal of Pharmaceutical Sciences
Abbreviated Key Title: South Asian Res J Pharm Sci

| Volume-7 | Issue-1 | Jan-Feb 2025 | **DOI: https://doi.org/10.36346/sarjps.2025.v07i01.006**

Original Research Article

Mechanistic Underlying Anti-diabetic Potential of *Eclipta alba* Flavonoids against Aldose Reductase Inhibitory Action

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Article History
Received: 19.01.2025
Accepted: 24.02.2025
Published: 26.02.2025

Abstract: ***Background*:** One of the main factors contributing to morbidity and mortality in the world's population is diabetes mellitus. The primary symptoms of this condition are hyperglycemia, or high blood sugar, which is followed by polydipsia and polyuria. Damage to the retina, loss of kidney function, and nerve damage are examples of subsequent consequences. Moreover, diabetes mellitus will accelerate the development of cardiovascular disease. *Eclipta alba* (L.) Hassk. (Also known as *Eclipta prostrata* Roxb.) belongs to the Asteraceae family and is commonly known as false daisy in English and bhringoraj or bhringraj in Bangladesh and India. It is regarded as a weed of ethnomedicinal significance. Pharmacological activities of plant extracts and individual phytoconstituents have revealed anticancer, hepatoprotective, snake venom neutralizing, anti-inflammatory, and antimicrobial properties. ***Purpose*:** This study aimed to assess the antidiabetic activity of *Eclipta* alba leaf flavonoid through in-silico molecular docking. ***Method*:** Aldose reductase was chosen as the target proteins in the current investigation. The bond was found using the Auto Dock software using a grid-based docking method. Compounds' 2D structures were generated, converted to 3D, and subsequently energetically lowered up to an arms gradient of 0.01 using the Merck Molecular Force Field (MMFF). ***Result*:** Flavonoids of *E.alba* found to be effective anti-diabetic component and effectively binds to be target protein *Aldose reductase* with binding energy -8.96, -6.02 & -5.86 kcalmol^{-1} for apigenin, syringic acid & vanillic acid respectively. ***Conclusion*:** The finding of the *in-silico* molecular docking showed that both lead compound is effective binds & inhibitory action on target protein. The molecular docking of ligands like apigenin, syringic acid & vanillic acid with *Aldose reductase* receptor revealed that it has exhibited the chemical interaction with the amino acids in the active pockets.

Keywords: *E.Alba*, Molecular Docking, *Aldose Reductase* Enzyme, Apigenin, Syringic Acid & Vanillic Acid.

INTRODUCTION

Diabetes is a metabolic condition affecting proteins, lipids, and glucose, resulting from decreased insulin production or the development of insulin resistance. Chronic hyperglycemia resulting from diabetes leads to the glycation of body proteins, subsequently causing secondary complications that adversely affect the kidneys, eyes, nerves, and arteries [1]. Diabetes is associated with hyperglycemia, dyslipidemia, and both microvascular and macrovascular complications, which are the leading causes of morbidity and mortality in individuals with diabetes [2]. Management can be achieved through pharmaceutical agents, dietary modifications, and physical activity; however, these approaches may incur significant costs, produce undesirable effects, or impose further limitations [3, 4]. The pursuit of hypoglycemic agents that are both safer and more efficacious. A variety of diseases are collectively known as diabetes mellitus. The distinct aetiology and/or pathogenesis can characterize certain diabetic symptoms; nevertheless, overlapping phenotypes in numerous patients complicate etiological and pathogenetic classification [5]. Eclipta alba L. is a medicinal plant belonging to the Asteraceae family. This plant is commonly referred to as fake daisy and bhringaraj. This plant is employed in traditional medicine to treat several human ailments, including diabetes, coronary heart disease, gastrointestinal disorders, dermatological conditions, vitiligo, skin blemishes, respiratory infections, and hypertension. Furthermore, Eclipta alba has been extensively employed as a hair growth stimulant and dye. Eclipta alba comprises numerous active chemicals, including glycosides, triterpenoids, alkaloids, flavonoids, coumestans, and polyacetyl. This plant is purported to possess

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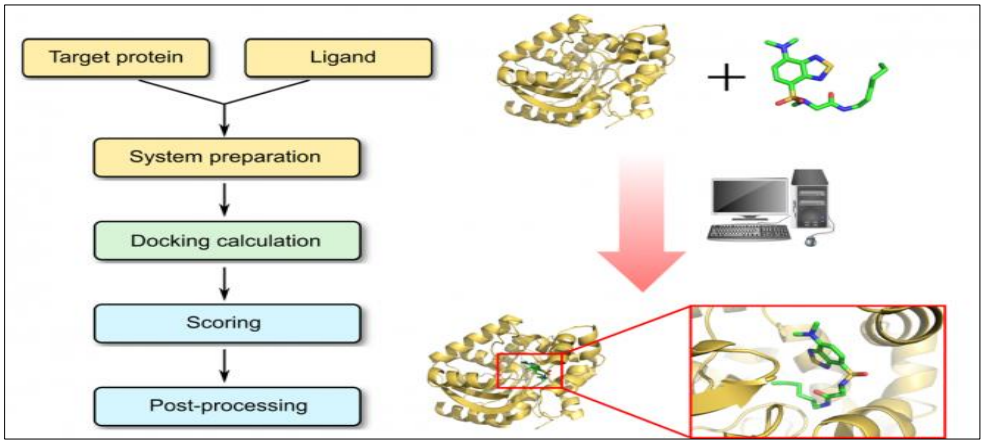
numerous pharmacological properties, including anthelmintic, neuroprotective, diuretic, antibacterial, antimalarial, antifungal, hepatoprotective, immunomodulatory, hypolipidemic, analgesic, anti-inflammatory, antidiabetic, antioxidant, anticancer, hair growth-promoting, memory-enhancing, and antivenom activities [6].

Eclipta alba

***In-Silico* Molecular Docking Study**

The study and development of novel chemicals with specific effects on humans is known as drug designing [7]. The growing number of disorders caused by microbes that are resistant to several drugs requires the development of a new class of antimicrobial drugs [8-11]. Consequently, the development of novel bioactive molecules that differ greatly from the chemical structures and modes of action of currently available prescription medications is imperative. The multidisciplinary, costly, and long process of finding new pharmaceuticals has been altered by recent developments in the development of novel medicinal molecules, such as. The cost of developing pharmaceuticals can be reduced by up to 50% with the use of CADD technology. The molecular docking technique [12] is used to comprehend the I drug-receptor interaction, II binding affinity, III orientation, and approach of drug molecules to the target site. Precise structural modelling and accurate activity forecasting are the main objectives of docking investigations. It offers the most hopeful view of how medications interact with receptors and offers a novel, reasoned strategy for drug development.



Conceptual work flow of *in-silico* molecular docking

Selection of Lead Bioactive Compound:

The extract value of the aqueous extract was found to be superior to that of the other extracts, and the phytochemical screening indicated the presence of flavonoids. The total flavonoid content was determined to be 51.2%. The aqueous extract was selected for subsequent assessment. The literature survey identifies numerous flavonoids, including Protocatechuic acid, 4-hydroxybenzoic acid, Apigenin, Luteolin, Quercetin, Kaempferol, Eriodictyol, Vanillic acid, Syringic acid, Chlorogenic acid, and 3'-O-methylorobol [13]. Apigenin, vanillic acid, and syringic acid were selected for an in-silico molecular docking investigation.

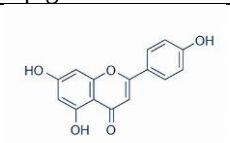
Apigenin obstructs tyrosine nitration of the insulin receptor kinase domain, resulting in the mitigation of insulin resistance. Multiple investigations indicated that apigenin diminishes the inhibition of α-amylase in Kunming mice, hence decreasing the digestion of dietary carbohydrates [14-15].

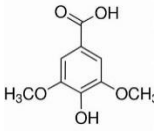
Vanillic acid: The beneficial effects of vanillic acid in diabetic nephropathic rats may be ascribed to its potent free radical scavenging ability, the down-regulation of NF-κB, TNF-α, and COX-2, as well as the up-regulation of Nrf-2 proteins in renal tissue [16].

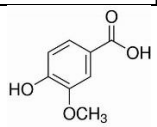
Syringic acid (SA) is a phenolic acid present in grapes, red wine, honey, acai palms, pumpkin, various dried fruits (such as olives and dates), spices, and other botanical sources. SA has been documented for its antidiabetic, antiglycating, antisteatosis, anti-inflammatory, antioxidant, antihypertensive, antibacterial, and antimicrobial effects. It possesses neuroprotective and hepatoprotective effects, and mitigates diabetes cataracts by inhibiting the aldose reductase enzyme. It possesses anticancer characteristics, serves as a component in dental cement, mitigates acute thrombosis and clot formation in mice, and enhances gastric acid secretion [17].

Selection of Target Molecule

Aldose reductase inhibitors are a category of pharmaceuticals that impede the degradation of glucose via the polyol pathway, potentially decelerating or reversing the advancement of neuropathy. Inhibiting aldose reductase to suppress glucose metabolism through the polyol route may prevent the aforementioned detrimental effects. Significant research over the past two decades has focused on evaluating the impact of aldose reductase inhibitors on human diabetic polyneuropathy [18].

Description of Apigenin [19]	
Synonym	Apigenin 5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one Versulin Apigenol
Chemical structure	
Molecular weight	270.24 g/mol
Molecular formula	$C_{15}H_{10}O_5$
Pharmacology	Antioxidant, anti-inflammatory, blood pressure reduction, and chemo-preventive. Apigenin has an effect in the downregulation of IL-1β and TNF-α; also, it shows anti-inflammatory properties by attenuating the expression of COX-2 and iNOS. At the cellular level, apigenin acts as an inhibitor of several protein-tyrosine and serine-kinases. Apigenin has many pharmacological roles as antiphlogistic, antispasmodic, and antibacterial agent, anti-asthmatic, anti-parkinsonism agent [20].

Description of Syringic acid [21]	
Synonym	4-Hydroxy-3,5-dimethoxybenzoic acid 3,5-Dimethoxy-4-hydroxybenzoic acid
Chemical structure	
Molecular weight	198.17 g/mol
Molecular formula	$C_9H_{10}O_5$
Pharmacology	Cardioprotective, Antidiabetic, Antiangiogenic, anti-inflammatory, Hepatoprotective & Neuroprotective [22-26].

Description of Vanillic acid [27]	
Synonym	Vanillic acid, 4-HYDROXY-3-METHOXYBENZOIC ACID Acide vanillique, p-Vanillic acid
Chemical structure	
Molecular weight	168.15 g/mol
Molecular formula	$C_8H_8O_4$
Pharmacology	Diverse bioactivity against cancer, diabetes, obesity, neurodegenerative, cardiovascular, and hepatic diseases by inhibition of the associated molecular pathways. Its derivatives also possess the therapeutic potential to treat autoimmune diseases as well as fungal and bacterial infections [28].

Molecular Docking Studies

Ligand Preparation

2D Structure of apigenin, syringic acid and vanillic acid were drawn using ChemSketch [29], the two-dimensional structure of the prepared ligand was converted into their 3-D structures optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligand were given below:

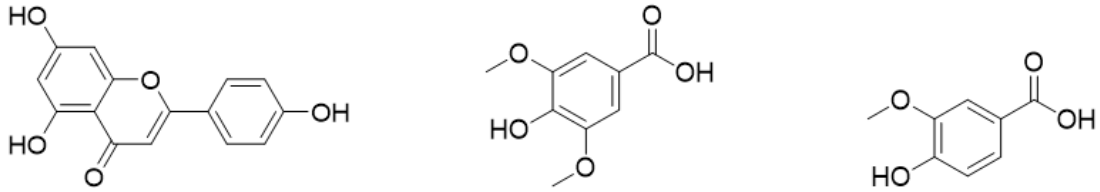


Figure 1: 2D structure of apigenin, syringic acid and vanillic acid

Preparation of the Grid File

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing and grid points for all the considered receptors in the current study are given in table 1 [30, 31].

Table 1: Grid parameters used in current docking analysis of Aldose reductase

S. No.	Receptor	x-axis	y-axis	z-axis	Spacing	x center	Y center	z center
1	Aldose reductase	40	40	40	0.392	-8.951	9.474	18.39

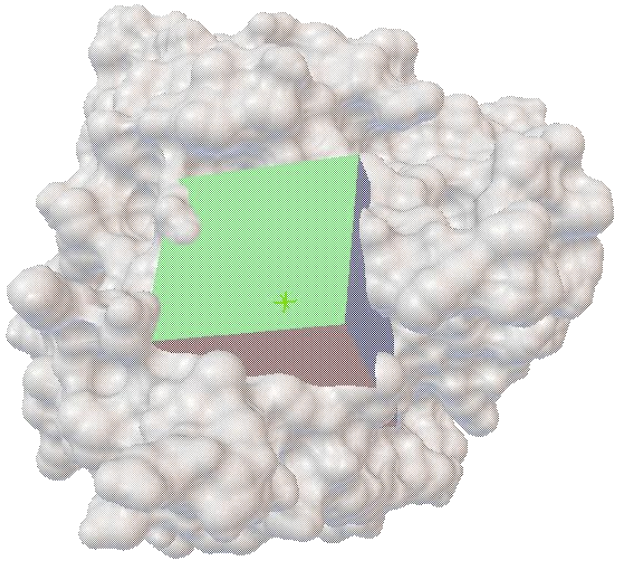


Figure 2: Grid box covering all active sites in aldosereductase receptor

Preparation of the Docking File

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [32-33].

Docking Study

Crystal structure

The crystal structure of the protein consisting of aldosereductase receptor is downloaded from the Protein Data Bank portal. All the primary information regarding all the receptor's structure was registered in the Protein data bank [34]. The complex ligand was separated by using Chimera software for all the target receptors.

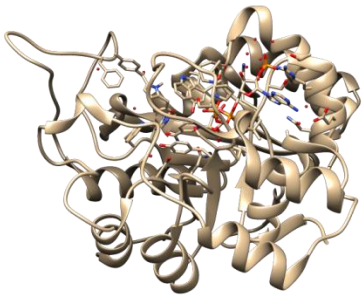


Figure 3: Crystal structure of aldose reductase receptor (PDB ID-3s3g)

Processing of Protein

All the downloaded receptor proteins are having only one chains, i.e. chain A, which has been selected for experimental purpose and complex ligand was removed from it. The bound ligand was separated from the macromolecular complex by using software Chimera [35, 36].

Molecular Docking Simulation Studies

Docking of ligands like apigenin, syringic acid and vanillic acid against aldose reductase receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [37-39].

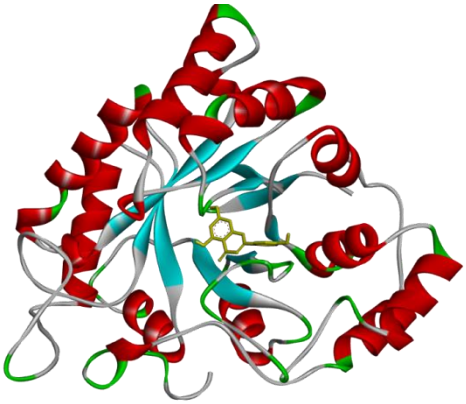


Figure 4: Binding mode of apigenin within the active site of aldose reductase receptor

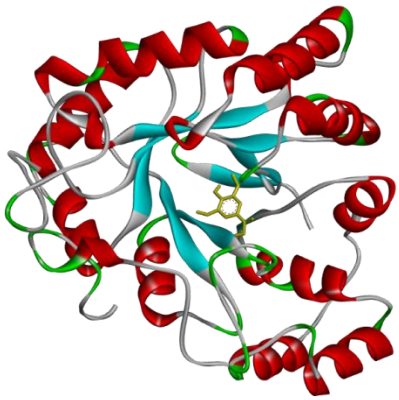


Figure 5: Binding mode of syringic acid within the active site of aldose reductase receptor

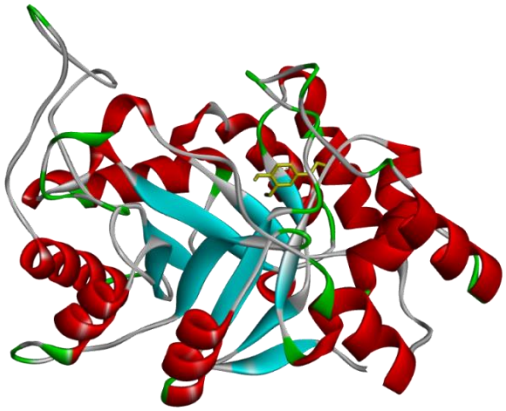


Figure 6: Binding mode of vanillic acid within the active site of aldose reductase receptor

Toxicity & ADME-T Studies

The ligand molecules viz. apigenin, syringic acid and vanillic acid were studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [40].

RESULT AND DISCUSSION

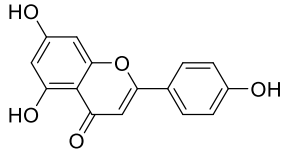
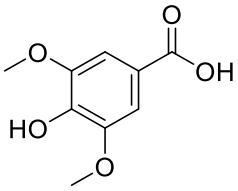
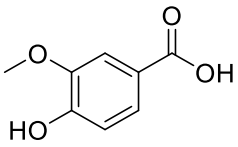
Diabetes mellitus (DM) is a long-term metabolic disease of the carbohydrates that causes abnormal glucose homeostasis and elevated blood glucose levels. Diabetes mellitus (DM) is recognized as one of the most dangerous diseases of the twenty-first century on a global basis. Numerous oral hypoglycemic drugs have been utilized in clinical settings to treat this illness. These drugs, which are divided into several types, include -glucosidase inhibitors, biguanides, sulfonylureas, thiazolidinediones (TZD), meglitinides, and dipeptidyl peptidase (IV) inhibitors. Every class targets a particular kind of organ and operates in a unique way. In actuality, several anti-diabetic drug combinations are commonly used to increase the treatment's efficacy. Though these medications have many advantages, they also have long-term side effects that might arise from long-term use, such as cardiovascular disease, lactic acidosis, hypoglycemia, gastrointestinal issues, and others. To date, by searching for these natural chemicals as novel anti-diabetic medications with little to no side effects over the long term, molecular docking studies have been performed to predict the potential inhibitor that has been compared with marketed anti-diabetic drugs. An essential computational technique for forecasting potential drug-protein interactions is molecular docking, which involves choosing a ligand that represents a bioactive molecule found in medicinal plants. Flavonoids are polyphenolic chemicals found in a wide range of plant species. They are mostly used as a source of starting material in the pharmaceutical and food industries, and they exhibit a variety of biological activities of interest, such as antioxidant capacity, anti-inflammatory activity, wound healing properties, and immune system activation. Regulating postprandial plasma glucose levels is crucial for the initial management of diabetes mellitus. A therapy option for reducing postprandial hyperglycemia is the suppression of enzymes that metabolize carbs. Natural substances offer a more secure method of inhibition compared to manmade pharmaceuticals. Key enzymes that hydrolysed carbohydrates and facilitate glucose absorption into the bloodstream are α-amylase and α-glucosidase. Synthetic medications that inhibit α-amylase and α-glucosidase include acarbose, miglitol, and voglibose. These drugs possess distinct downsides, as they are nonspecific and may induce significant adverse effects such as gastrointestinal tract irritation and exacerbation of diabetes complications. *E. alba* has long been utilized in the treatment of hypertension, coronary heart disease, vitiligo, diabetes, dermatological conditions, gastrointestinal disorders, respiratory ailments, and for the management of cuts and wounds. It is a member of the Asteraceae family. Plant-derived substances are referred to as herbal drugs, botanical drugs, botanicals, phytomedicines, traditional medicines, herbal medicines, traditional Chinese medicines (TCMs), traditional herbal medicinal products, natural health products, or plant food supplements. This plant possesses multiple therapeutic applications, such as bhringraj oil, which is renowned as a hair tonic for preserving black hair and reversing baldness. Flavonoids are polyphenolic compounds present in various plant species. They primarily serve as a foundational resource in the pharmaceutical and food sectors, demonstrating several biologically relevant actions, including antioxidant efficacy, anti-inflammatory qualities, wound healing capabilities, and immune system stimulation. The antidiabetic effects of dietary flavonoids and their molecular mechanisms on specific pathways: glucose transporter, hepatic enzymes, tyrosine kinase inhibitor, AMPK, PPAR, and NF-κB. Flavonoids enhance the etiology of diabetes and its consequences via regulating glucose metabolism, hepatic enzyme activity, and lipid profiles. Numerous studies demonstrate a beneficial effect of some dietary flavonoids on diabetes; however, the mechanisms of action and potential adverse effects require more elucidation

[41]. A recent proteomic study on aldose reductase has revealed that AR is significantly expressed in human platelets, and that epalrestat, an AR inhibitor, reduces platelet aggregation, suggesting that AR is essential for platelet aggregation. The findings are corroborated by the observation that suppressing AR reduces hyperglycemia-induced platelet hyperaggregation in human platelets by diminishing oxidative stress. According to the results, AR is crucial for platelet aggregation, particularly at elevated blood sugar levels. Platelet hyperaggregation associated with diabetes is likely primarily induced by oxidative stress resulting from the AR-dependent polyol pathway. Mammalian tissues possess substantial quantities of aldose reductase, also referred to as aldoketo reductase. Aldose reductase is the enzyme that commences the polyol pathway by turning glucose into sorbitol, which is subsequently oxidized to fructose. Aldose reductase exhibits selectivity for a diverse array of substrates, including galactose and glucose. Aldose reductase generally functions at moderate catalytic velocities and exhibits a low affinity for glucose. Elevated glucose levels and saturated hexokinase result in increased activity. Under these conditions, sorbitol is produced and accumulates within the cell, resulting in osmotic effects and subsequent tissue hydration. Some complications of diabetes may be partially attributable to this underlying cause. Aldose reductase is associated with the onset of diabetic neuropathy (DN) and facilitates the transformation of glucose into sorbitol within the polyol pathway. The results of molecular docking of the lead molecule against various selected receptors indicated that apigenin, syringic acid, and vanillic acid have strong affinity for aldose reductase, with binding energies of -8.96, -6.02, and -5.86 kcal mol^{-1}, respectively (Table 2).The IC 50 values of syringic acid and vanillic acid demonstrated significant results. The 2D and 3D binding interactions of the lead bioactive against the designated receptor are illustrated in Figures 7-12. The binding interaction of the selected molecule with the molecular target is demonstrated as follows:

Lead molecule	**Vander waal's**	**Conventional hydrogen**	**C-H bounding**	**π-cation**	**π-Alkyl**	**π- π**
Apigenin	His110, Lys77, Cys44, Pro261, Pro211, Leu228, Ser214, Asp216, Tyr209	Asp43, Thr19	Trp20, Gly18	Cys21	Leu212, Pro215, ILE260	----
Syringic acid	His110, GLN 183, ILE260, Gly18, Lys262	Tyr48, Ser210, Lys21, Asp43, Tyr48	Lys77	Trp20		Trp20
Vanillic acid	Leu212, Pro261, Pro211, Gly18, Tyr209, Trp209, Lys21, Ser214, Pro215	Lys262, Ser210	-------	ILE 260	------	-----

The pharmacokinetic profiling of the apigenin, syringic acid and vanillic acid ligand had revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like mutagenic, reproductive effects, irritant effect, and tumorogenic properties. The pharmacokinetic and toxicity profiling results of apigenin, syringic acid and vanillic acid were shown in figure 13-15 & table 3-5. Theoretically, all the ligand molecules have shown encouraging docking score. All compound followed Lipinski rule and showed all most similar drug likeness score.

Table 2: Results of docking of ligands like apigenin, syringic acid and vanillic acid against aldose reductase receptor

S. No.	**Compound Name**	**Structure**	**B.E**	**Ki**	**IC50**
1	***Apigenin***		-8.96	15.24	0.069
2	***Syringic acid***		-6.02	10.16	0.10
3	***Vanillic acid***		-5.86	9.89	0.10

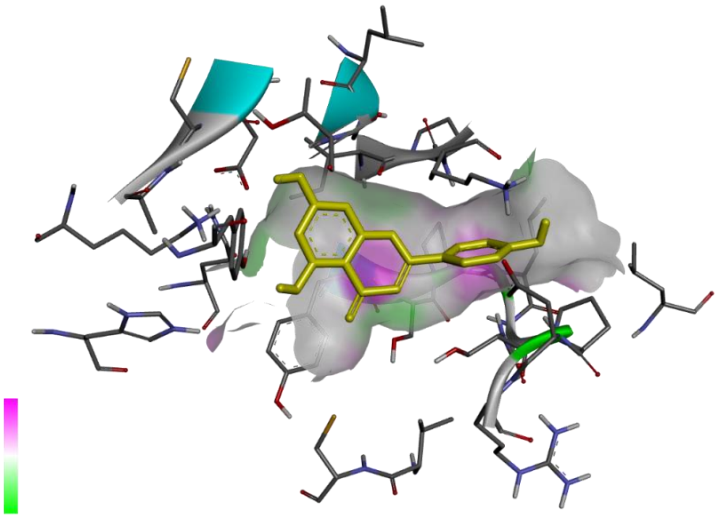


Figure 7: Three-dimensional binding mode of apigenin within the active site of aldose reductase receptor

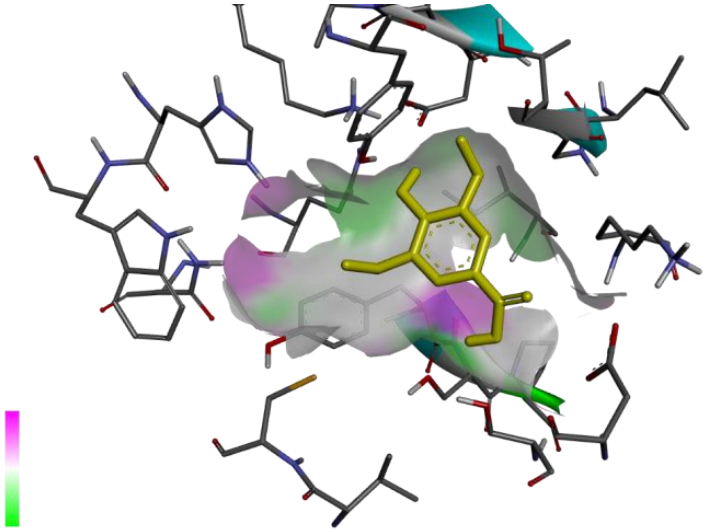


Figure 8: Three-dimensional binding mode of syringic acid within the active site of aldose reductase receptor

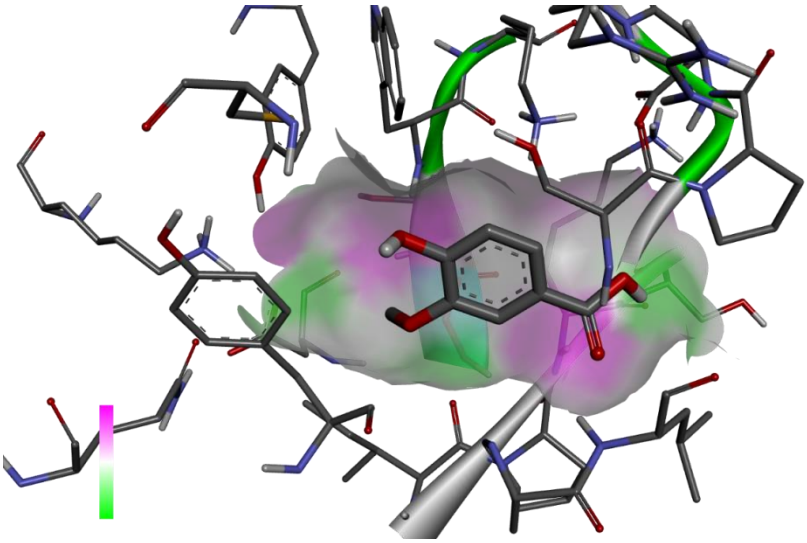


Figure 9: Three-dimensional binding mode of vanillic acid within the active site of aldose reductase receptor

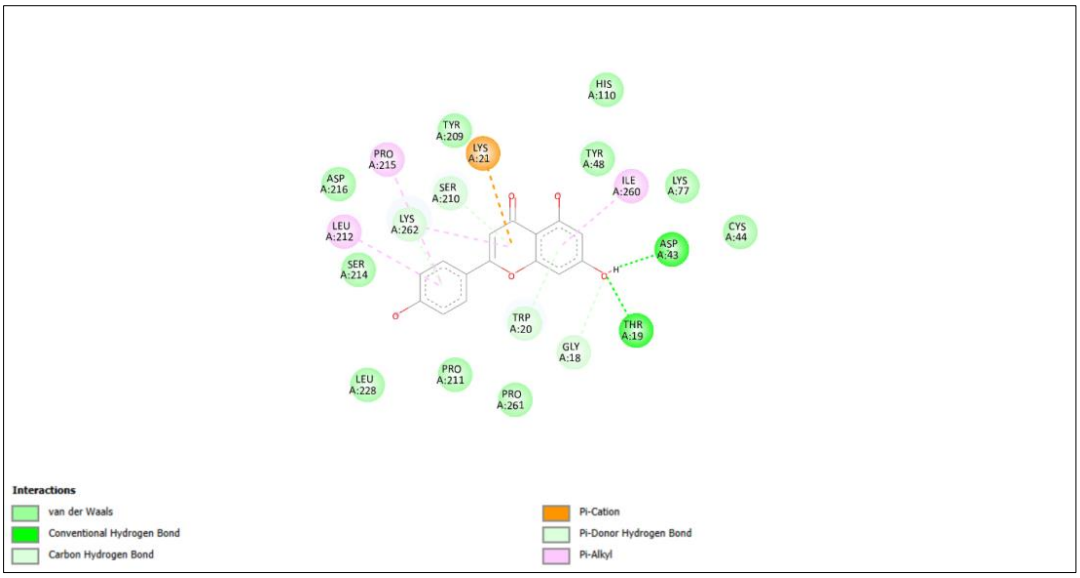


Figure 10: Two-dimensional binding mode of apigenin within the active site of aldose reductase receptor

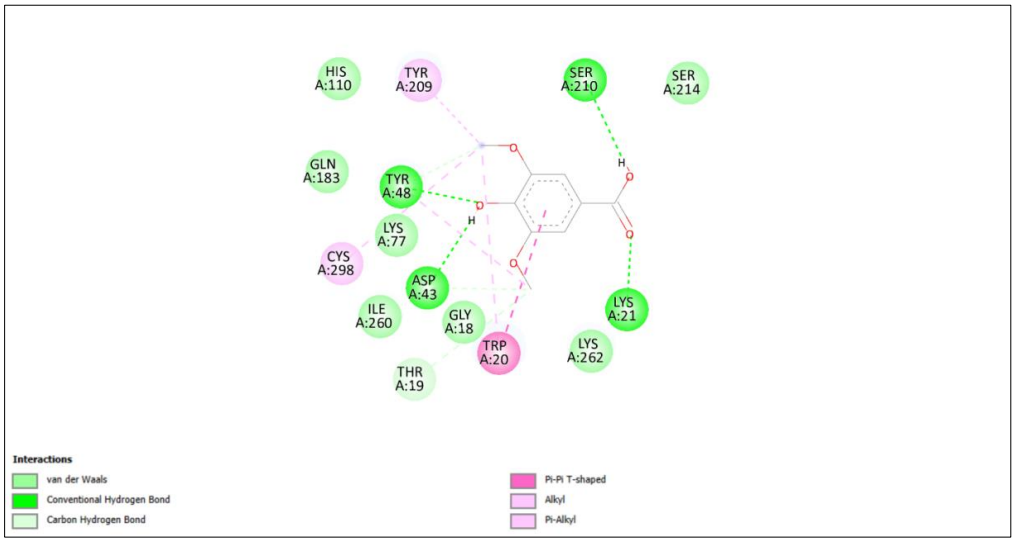


Figure 11: Two-dimensional binding mode of syringic acid within the active site of aldose reductase receptor

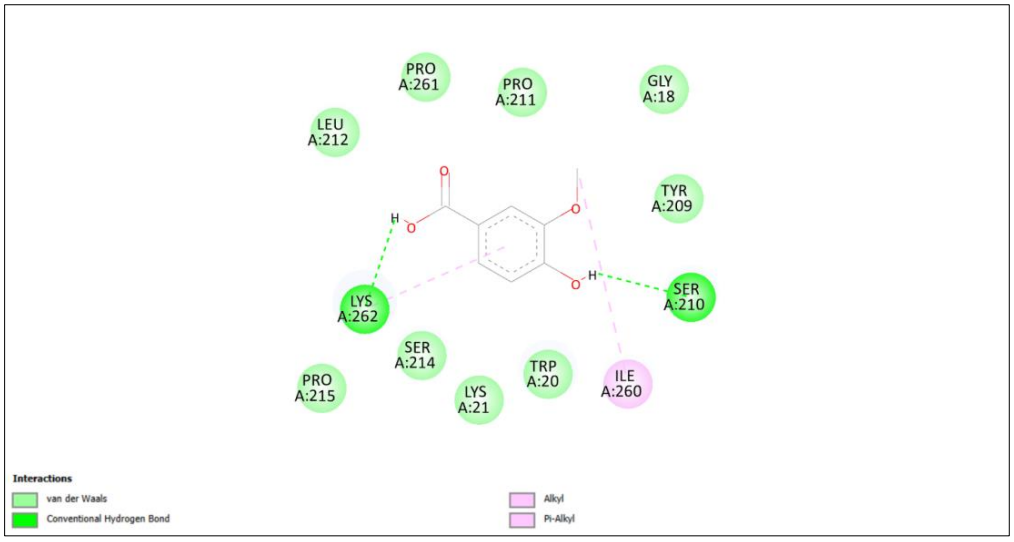


Figure 12: Two-dimensional binding mode of vanillic acid within the active site of aldose reductase receptor

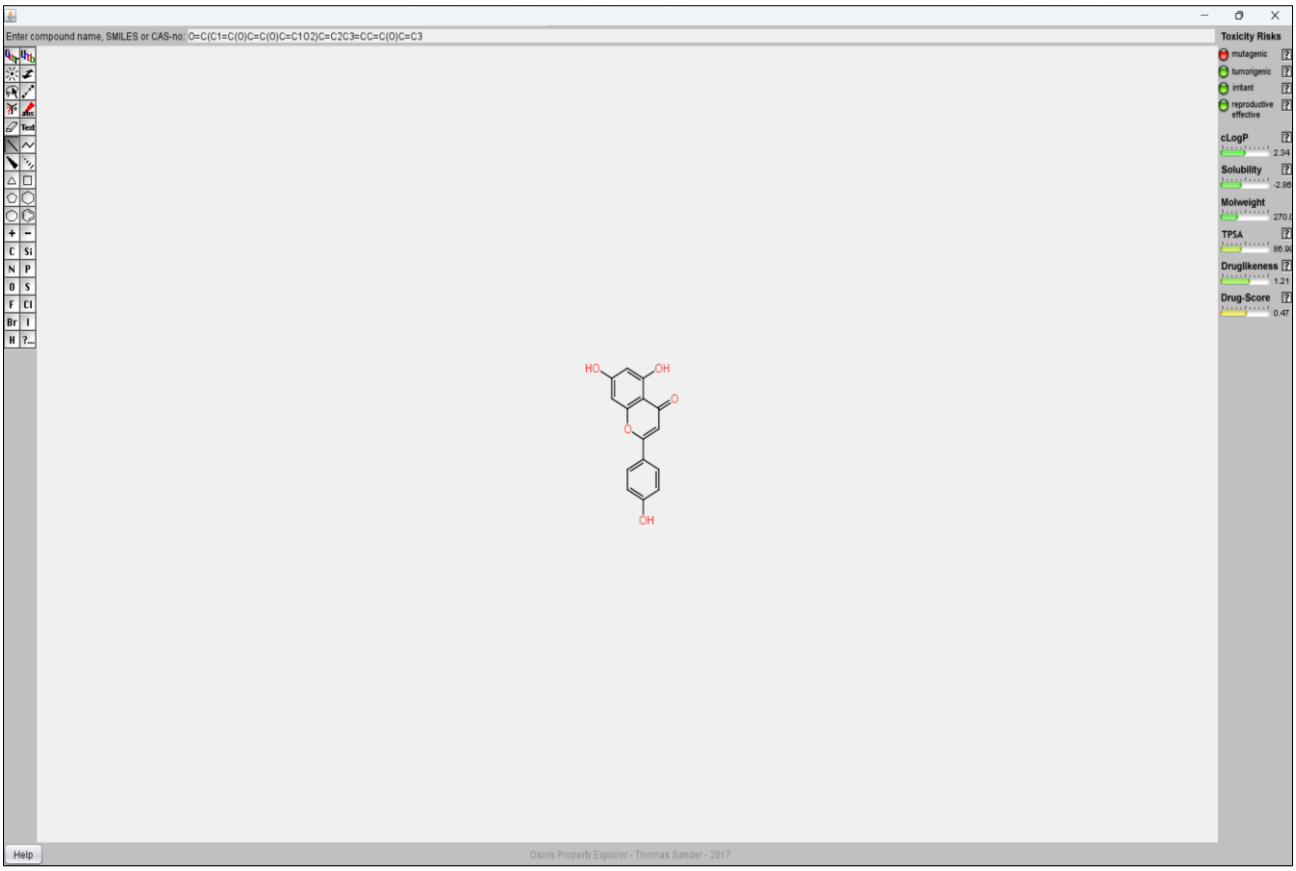


Figure 13: Pharmacokinetic and toxicity profiling of apigenin

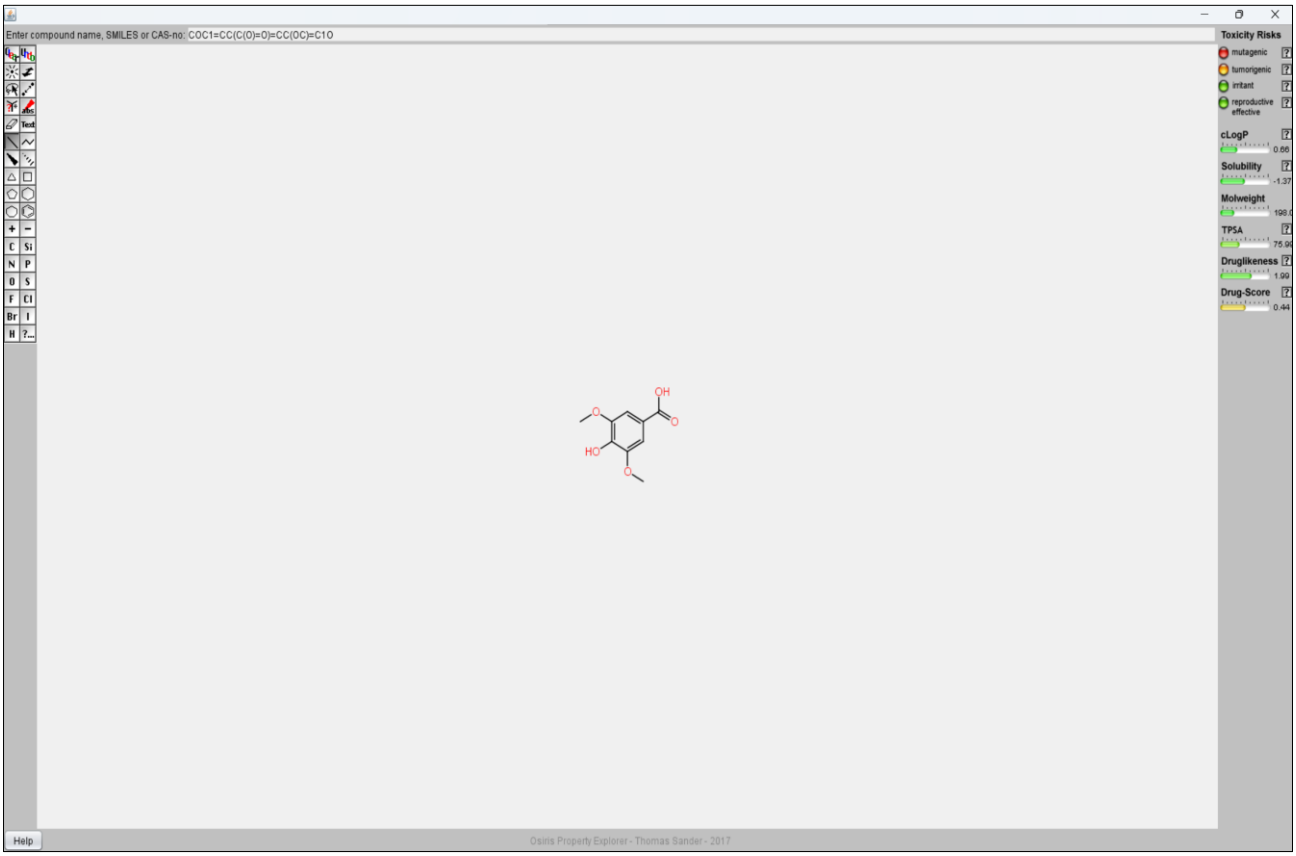


Figure 14: Pharmacokinetic and toxicity profiling of syringic acid.

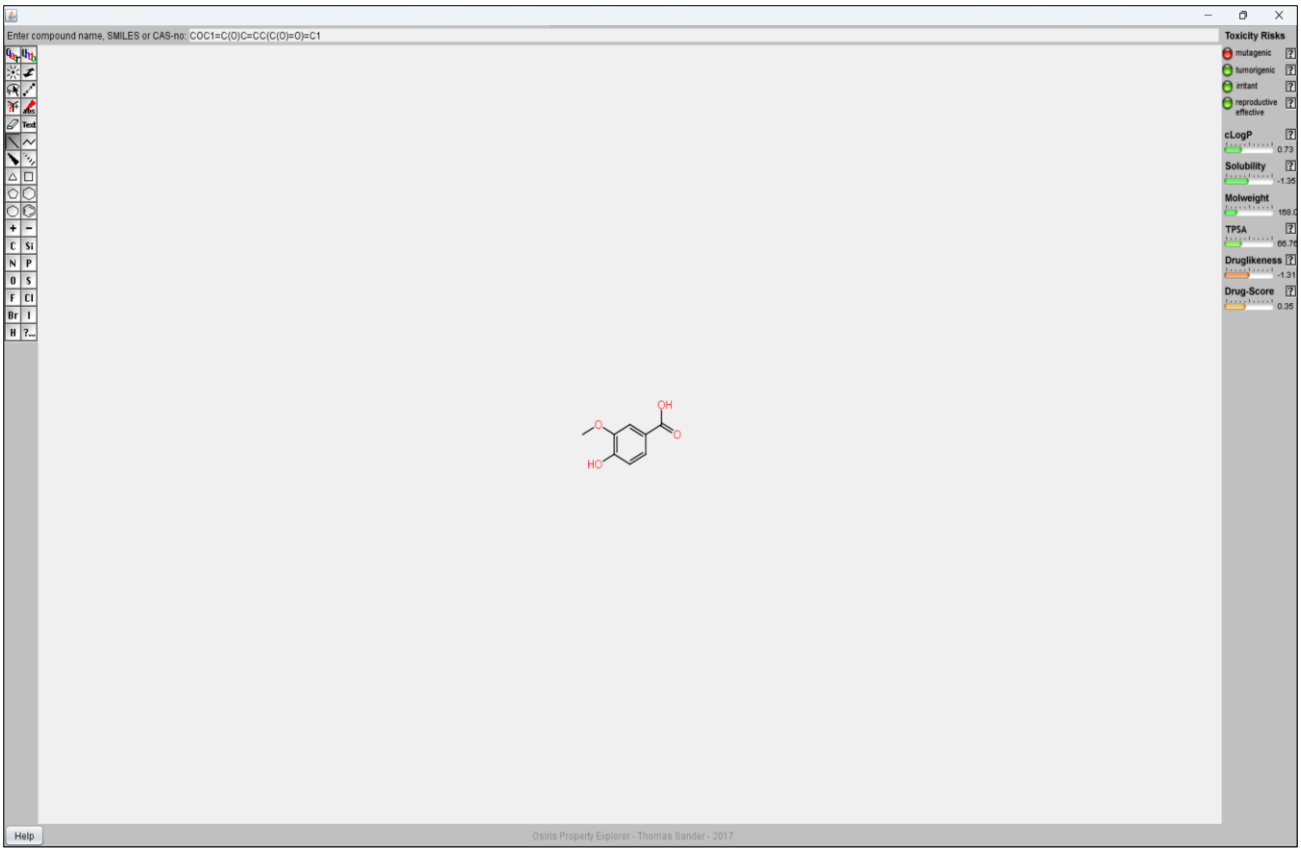


Figure 15: Pharmacokinetic and toxicity profiling of vanillic acid

Table 3: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	**Tumorigenic**	**Irritant**	**Reproductive effectivity**
Apigenin	NO	NO	Yes	NO
Syringic acid	NO	NO	NO	No
Vanillic acid	NO	NO	NO	No

Table 4: Lipinski Properties of lead molecules

Compound	*cLogP*	Solubility	Mol.wt.	TPSA	Drug likeness	Drug score
Apigenin	2.34	-2.08	270	0.1	1.25	0.47
Syringic acid	0.56	-1.37	198	0.95	1.00	0.44
Vanillic acid	0.73	-1.38	168	0.71	1.01	0.56

Table 5: Drug likeness of lead molecules

Compound	Lipinski rule of five	H bond donar(<5)	H bond acceptor (<10)
Apigenin	Yes	3	5
Syringic acid	Yes	2	5
Vanillic acid	Yes	2	4

CONCLUSION

Computer based predicative validation of current investigation was designed by molecular docking of lead compound (Apigenin, syringic acid and vanillic acid) with aldose reductase receptor protein. The finding of the *in-silico* molecular docking showed that selected lead compound was effective binds & inhibitory action on target protein. The molecular docking of selected flavonoids with aldose reductase receptor revealed that it has exhibited the chemical interaction with the amino acids in the active pockets. Theoretically, all the ligand molecules have shown encouraging docking score. In the aqueous leaf extract from *E.alba*, flavonoids combine synergistically to induce anti-diabetic activity.

REFERENCE

1. Rao, B. K., Kesavulu, M. M., Giri, R., & Rao, C. A. (1999). Antidiabetic and hypolipidemic effects of Momordica cymbalaria Hook. fruit powder in alloxan-diabetic rats. *Journal of ethnopharmacology*, *67*(1), 103-109.
2. Lopes-Virella, M. F., & Virella, G. (2003). The role of immune and inflammatory processes in the development of macrovascular disease in diabetes. *Front Biosci*, *8*(Suppl), 750-768.
3. Nagappa, A. N., Thakurdesai, P. A., Rao, N. V., & Singh, J. (2003). Antidiabetic activity of Terminalia catappa Linn fruits. *Journal of ethnopharmacology*, *88*(1), 45-50.
4. Krishna, B., Na, mmi., S., Kota, M. K., & Krishna, Rao, R. V. (2004). Evaluation ofhypoglycaemic and antihyperg lycemic effects of Datura metel Linn seeds in norm aland alloxan-induced diabetic rats. *J. of Ethnopharmacol*, *9*, 95-98.
5. Leslie, R. D. G. (1977). (ed): Molecular Pathogenesis of Diabetes mellitus. Front Hormone Res. Basel, Karger, 1-22.
6. Chung, I. M., Rajakumar, G., Lee, J. H., Kim, S. H., & Thiruvengadam, M. (2017). Ethnopharmacological uses, phytochemistry, biological activities, and biotechnological applications of Eclipta prostrata. *Applied microbiology and biotechnology*, *101*, 5247-5257.
7. Taft, C. A., & Da Silva, V. B. (2008). Current topics in computer-aided drug design. *Journal of pharmaceutical sciences*, *97*(3), 1089-1098.
8. Kakkar, S., Kumar, S., Narasimhan, B., Lim, S. M., Ramasamy, K., Mani, V., & Shah, S. A. A. (2018). Design, synthesis and biological potential of heterocyclic benzoxazole scaffolds as promising antimicrobial and anticancer agents. *Chemistry Central Journal*, *12*, 1-11.
9. Rani, J., Saini, M., Kumar, S., & Verma, P. K. (2017). Design, synthesis and biological potentials of novel tetrahydroimidazo [1, 2-a] pyrimidine derivatives. *Chemistry Central Journal*, *11*, 1-11.
10. Hu, Y., & Fu, L. (2012). Targeting cancer stem cells: a new therapy to cure cancer patients. *American journal of cancer research*, *2*(3), 340.
11. Kassab, A. E., & Gedawy, E. M. (2013). Synthesis and anticancer activity of novel 2-pyridyl hexahyrocyclooctathieno [2, 3-d] pyrimidine derivatives. *European Journal of Medicinal Chemistry*, *63*, 224-230.
12. Kumar, S., Lim, S. M., Ramasamy, K., Vasudevan, M., Shah, S. A. A., Selvaraj, M., & Narasimhan, B. (2017). Synthesis, molecular docking and biological evaluation of bis-pyrimidine Schiff base derivatives. *Chemistry Central Journal*, *11*, 1-16.
13. Feng, L., Zhai, Y. Y., Xu, J., Yao, W. F., Cao, Y. D., Cheng, F. F., ... & Zhang, L. (2019). A review on traditional uses, phytochemistry and pharmacology of Eclipta prostrata (L.) L. *Journal of ethnopharmacology*, *245*, 112109.
14. Charbonneau, A., & Marette, A. (2010). Inducible nitric oxide synthase induction underlies lipid-induced hepatic insulin resistance in mice: potential role of tyrosine nitration of insulin signaling proteins. *Diabetes*, *59*(4), 861-871.
15. Zhang, B. W., Li, X., Sun, W. L., Xing, Y., Xiu, Z. L., Zhuang, C. L., & Dong, Y. S. (2017). Dietary flavonoids and acarbose synergistically inhibit α-glucosidase and lower postprandial blood glucose. *Journal of agricultural and food chemistry*, *65*(38), 8319-8330.
16. Singh, B., Kumar, A., Singh, H., Kaur, S., Arora, S., & Singh, B. (2022). Protective effect of vanillic acid against diabetes and diabetic nephropathy by attenuating oxidative stress and upregulation of NF-κB, TNF-α and COX-2 proteins in rats. *Phytotherapy Research*, *36*(3), 1338-1352.
17. Mirza, A. C., Panchal, S. S., Allam, A. A., Othman, S. I., Satia, M., & Mandhane, S. N. (2022). Syringic acid ameliorates cardiac, hepatic, renal and neuronal damage induced by chronic hyperglycaemia in Wistar rats: a behavioural, biochemical and histological analysis. *Molecules*, *27*(19), 6722.
18. Chalk, C., Benstead, T. J., & Moore, F. (2007). Aldose reductase inhibitors for the treatment of diabetic polyneuropathy. *Cochrane database of systematic reviews*, (4).
19. https://pubchem.ncbi.nlm.nih.gov/compound/apigenin.
20. Kumar, V., & Kundu, S. (2022). Studies on apigenin and its biological and pharmacological activity in brain disorders. *Advanced Pharmaceutical Bulletin*, *12*(4), 645.
21. https://pubchem.ncbi.nlm.nih.gov/compound/Syringic-acid.
22. Srinivasulu, C., Ramgopal, M., Ramanjaneyulu, G., Anuradha, C. M., & Kumar, C. S. (2018). Syringic acid (SA)–a review of its occurrence, biosynthesis, pharmacological and industrial importance. *Biomedicine & Pharmacotherapy*, *108*, 547-557.
23. Cao, Y., Zhang, L., Sun, S., Yi, Z., Jiang, X., & Jia, D. (2016). Neuroprotective effects of syringic acid against OGD/R-induced injury in cultured hippocampal neuronal cells. *International journal of molecular medicine*, *38*(2), 567-573.
24. Ding, S. K., Wang, L. X., Guo, L. S., Luo, P., Du, J. J., Zhao, Z. L., & Wang, G. G. (2017). Syringic acid inhibits apoptosis pathways via downregulation of p38MAPK and JNK signaling pathways in H9c2 cardiomyocytes following hypoxia/reoxygenation injury. *Molecular Medicine Reports*, *16*(2), 2290-2294.
25. Sancak, E. B., Akbas, A., Silan, C., Cakir, D. U., Turkon, H., & Ozkanli, S. S. (2016). Protective effect of syringic acid on kidney ischemia-reperfusion injury. *Renal failure*, *38*(4), 629-635.
26. Fang, W., Zhu, S., Niu, Z., & Yin, Y. (2019). The protective effect of syringic acid on dextran sulfate sodium-induced experimental colitis in BALB/c mice. *Drug Development Research*, *80*(6), 731-740.
27. https://pubchem.ncbi.nlm.nih.gov/compound/Vanillic-acid.

28. Kaur, J., Gulati, M., Singh, S. K., Kuppusamy, G., Kapoor, B., Mishra, V., ... & Corrie, L. (2022). Discovering multifaceted role of vanillic acid beyond flavours: Nutraceutical and therapeutic potential. *Trends in Food Science & Technology*, *122*, 187-200.
29. ACD/Structure Elucidator, version 2018.1, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, 2019.
30. Soni, H., Mishra, S., Mishra, R. K., & Mishra, S. R. (2022). Silibin as potent inhibitor of COVID-19 main protease: in-silico docking approach. *Journal of Molecular Pharmaceuticals and Regulatory Affairs*, *4*(1), 1-7.
31. Malik, J. K., Soni, H., Sharma, S., & Sarankar, S. (2020). Hydroxychloroquine as potent inhibitor of COVID-19 main protease: Grid based docking approach. *Eurasian Journal of Medicine and Oncology*, *4*(3), 219-226.
32. Soni, H., Gautam, D., Sharma, S., & Malik, J. (2020). Rifampicin as potent inhibitor of COVID-19 main protease: In-silico docking approach. *Saudi Journal of Medical and Pharmaceutical Sciences*, *6*(9), 588-593.
33. Malik, J., Jhariya, D., Ahirwar, P., Sharma, S., Upadhyay, S., & Soni, H. (2024). Mechanistic insight anti-arthritis efficacy of bio-actives of Moringa oleifera: In-silico molecular docking. *Journal of Pharmacognosy and Phytochemistry*, *13*(1), 44-48.
34. Himesh, S. (2011). 2D-Qsar Study Of 4-(4-Alkoxylphenyl)-3-Ethyl-4h-1,2,4-Triazoles As Open-Chain Analogues Of 7-Alkoxyl-4,5-Dihydro[1,2,4]Triazolo[4,3-A]Quinolines. *Journal of Pharmacy Research*, *4*(5).
35. Soni, H. (2014). In-silico analysis to access the antibacterial effect of Rutin on E. coli: molecular docking approach. *UJP*, *3*(06), 23-29.
36. Sander, T., Freyss, J., von Korff, M., Reich, J. R., & Rufener, C. (2009). OSIRIS, an entirely in-house developed drug discovery informatics system. *Journal of chemical information and modeling*, *49*(2), 232-246.
37. Kciuk, M., Gielecińska, A., Mujwar, S., Mojzych, M., & Kontek, R. (2022). Cyclin-dependent kinase synthetic lethality partners in DNA damage response. *International Journal of Molecular Sciences*, *23*(7), 3555.
38. Kciuk, M., Mujwar, S., Rani, I., Munjal, K., Gielecińska, A., Kontek, R., & Shah, K. (2022). Computational bioprospecting guggulsterone against ADP ribose phosphatase of SARS-CoV-2. *Molecules*, *27*(23), 8287.
39. Himesh, S. (2024). Computational Modeling for Designing of Syringic acid against mTOR1: *As Potent Anticancer Agents Journal of Pharmacognosy and Phytochemistry*, *13*(5), 359-363.
40. Thomas Sander, Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, 4123 Allschwil, Switzerland, Email: thomas.sanderidorsia.com.
41. Al-Ishaq, R. K., Abotaleb, M., Kubatka, P., Kajo, K., & Büsselberg, D. (2019). Flavonoids and their anti-diabetic effects: Cellular mechanisms and effects to improve blood sugar levels. *Biomolecules*, *9*(9), 430.