Research Article

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IN SILICO IDENTIFICATION OF NOVEL BIOACTIVE COMPOUNDS FROM MEDICINAL PLANTS AGAINST DIABETIC FOOT ULCER

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ABSTRACT

Diabetes mellitus is a chronic lifestyle disease with imbalanced insulin levels in patients, resulting in adverse conditions like renal failure, blindness, heart attack and stroke. Diabetic foot ulcers are the most dangerous complication characterised by a pathological triad of infection and vascular disease in the foot. The lower leg of a diabetic patient is more susceptible to infection, resulting in foot ulcers, which, when kept untreated, necessitates leg amputation. Human fibroblast collagenase is a key protein often required in small quantities for wound healing. However, they are imbalanced in diabetic foot ulcers, causing deterioration and inability to heal. Although drugs are available, higher dosages promote gastrointestinal issues with nausea, diarrhoea and stomach pain. The current study fully anticipates identifying a prominent herbal drug to treat diabetic foot ulcers using Bioinformatic tools. The study revealed that phytocompounds from *Ficus carica* exhibited excellent binding with the target, suggesting their well-known ability to treat diabetic foot ulcers.

Keywords: Diabetes mellitus, Diabetic foot ulcer, Human fibroblasts collagenase, phytocompounds, *Ficus carica*, Amino acid residues.

INTRODUCTION

Diabetes, a pervasive metabolic condition that affects people of all ages with excessive blood sugar levels and impaired insulin sensitivity. According to the World Health Organization (WHO) report, globally, about 422 million individuals had type 2 diabetes mellitus (T2DM) with a mortality rate of 1.5 million, among which 48% of deaths occurred in patients under the age of 70 [1]. In order to comprehend the dangers and complications related to diabetes, the epidemiology of type 1 diabetes mellitus (T1D) and its patterns were depicted by taking into account biological and geographical factors in human populations [2]. Studies suggest that the major causative agents for this condition are high-sugar diets with heavy calories, lack of exercise, genetic predisposition, and lifestyle changes. One of the most debilitating effects of diabetes is a diabetic foot, characterised by the formation of an ulcerated foot in a diabetic patient already suffering from neuropathy or peripheral vascular disease in their lower limb. Human fibroblast collagenase performs three vital roles in wound healing: breaking down the capillary basement membrane during the inflammatory phase, clearing the damaged extracellular matrix, and finally, aiding in the fibroblast migration during the proliferation stage [3]. Treating diabetic foot ulcers (DFUs) still poses a substantial therapeutic challenge to the medical field owing to the need for novel clinically effective therapies in an economically friendly manner [4]. The significant effect of prolonged treatment with drugs for DFU found in 48 patients under observation for about four weeks was the formation of body ulcers [3]. Secondary metabolites in plants are the essential substances responsible for the medicinal properties in plants secreted as a defence mechanism against predators, which can be assessed with phytochemical screening [5]. Plants are used in traditional medicine to treat several conditions, including cardiovascular disorders, respiratory conditions and gastrointestinal conditions [6].

Ethnopharmacological studies suggest that the plant *Ficus carica* has been traditionally applied for 40 illnesses worldwide. Phytochemical research has led to the identification of plant pigments as well as numerous primary and secondary metabolites capable of various biological activities [7]. They exhibit pharmacological activity against ailments like ulcers, leprosy, cancer, diabetes, skin diseases, liver diseases, paralysis, asthma, and anaemia [8]. Thus, it is a promising candidate for developing novel therapeutics in pharmaceutical research by exhibiting antibacterial, antiprotozoal, antiviral, astringent, and antidiarrheal activities [9].

The biological activity of the plant varies with different parts, where its delicate branches were used as a toothbrush, its fruits were considered diuretics, and the seeds were applied as antidotes [10,11]. Ayurveda recommends numerous medicinal plants for the treatment of diabetes. One among them is the Caesalpiniaceae family member *Cassia auriculata* (CA) Linn, often called Tanner's Cassia, possessing anti-hyperglycemic and antioxidant activity [12]. Polyphenols are the active components of CA, and thus, various technologies have been incorporated to increase the yield of polyphenols [13]. *Cassia auriculata* Linn is found throughout the deciduous woods of India, whose leaves, petals, and fruits are highly utilised to treat anthelmintic problems [14]. In addition to this, they have various pharmacological effects like antidiabetic, antioxidant, anti-inflammatory, anti-hyperlipidemic, hepatoprotective, cardioprotective, anticancer, antimicrobial, antiulcer, antipyretic, antifertility and anti-venom [15]. The current study utilises computational methods to evaluate phytocompounds from seven different medicinal plants explored for their anti-inflammatory, antidiabetic and antimicrobial properties towards the target protein to develop therapeutics against Diabetic foot ulcers.

MATERIALS AND METHODS

Structure retrieval

The 3D structure of human fibroblast collagenase was retrieved from a protein data bank (www.rcsb.org). The activate site of the protein was predicted using the online tool Ligsite (http://projects.biotec.tu-dresden.de/pocket/) [16-18]. Based on the literature survey, the structure of phytocompounds from *Cassia auriculata, Ficus carica, Allium cepa, Abrus precatorius, Aloe barbadensis Miller, Vitex negundo* and *Bauhinia purpurea* was retrieved from PubChem database (http://www.ncbi.nlm.nih.gov/pccompound) [19].

Preparation of proteins and ligands

Schrodinger's protein preparation wizard was utilised to add hydrogen atoms and remove the water molecules within het groups. Optimisation of the 3D structure of the protein was achieved via energy minimisation, and ligand preparation was achieved by the LigPrep module, where the addition of hydrogen atoms occurs to generate the 3D structure of ligands [20].

ADME studies

For a molecule to be considered a drug, it should fulfil its properties as a vital step in drug development. Qikprop module assessed the pharmacokinetic properties and compounds' absorption, distribution, metabolism, excretion and toxicity profile by considering Lipinski's rule of five parameters like rotatable bonds, molecular weight, dipole moment, hydrogen bond donor, and blood barrier coefficient [21].

Docking studies

Grid-based Ligand Docking with Energetics (GLIDE) module of Schrodinger software (http://www.schrodinger.com/) was used to predict the interactions between the chosen phytocompounds and the active site residues of collagenase. The glide score is important in determining the prominent interactions [22].

RESULTS

Structure retrieval

2D structures of phytochemicals from *Ficus carica, Abrus precatorius, Cassia auriculata, Allium cepa, Aloe barbadensis miller, Vitex negundo* and *Bauhinia purpurea* were retrieved from the PubChem database and tabulated in Table 1. Simultaneously, the 3D structure of human fibroblast collagenase was retrieved from a protein data bank with PDB ID: 2CLT, as shown in Figure 1.

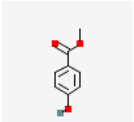
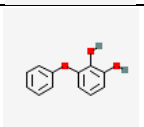
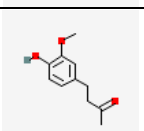
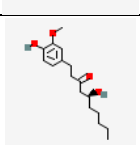
ADME

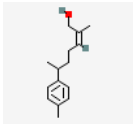
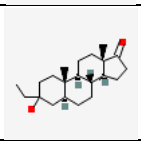
Initially, 215 compounds from plants were chosen for this study; however, only 19 compounds obeyed Lipinski's rule, exhibiting drug-like properties and thus being considered for further docking studies. Compounds within Lipinski's limit were tabulated in Table 2.

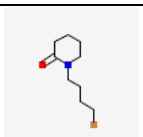
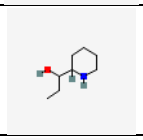
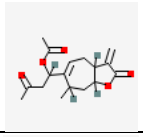
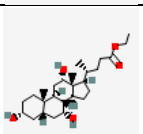
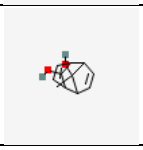
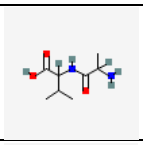
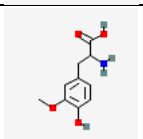
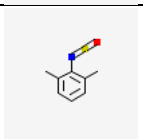
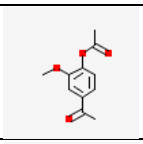
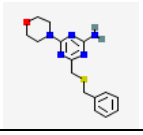
Docking

Docking results, as shown in Table 3, revealed that the compound methylparaben from *Ficus carica* shows the least Glide score of -4.29 Kcal/mol by interacting with its amino acid residues ARG-195 (O-H), SER-224 (H-O), ARG-281 (O-H) having bond lengths 2.7, 2.2 and 2.7Å respectively (Figure 2). This was followed by the interaction of dextro and levo- Alanyl-dextro and levo-Valine (DL-Alanyl-DL-Valine) from *Abrus precatorius* towards the active site residues ASN-307 (O-H), ASN-307 (O-H), ASP-226 (H-O) and ASP-226 (H-O) with bond lengths 2.1, 1.6, 1.6 and 1.6 Å having a Glide score -3.70 Kcal/mol. Several compounds like Conhydrin, Xanthinin, Ethyl Cholate and 9-Methyltricyclo [4.2.1.1(2,5)] deca-3,7-diene-9,10-diol from plant *Cassia auriculata* shows good binding towards target protein. Likewise, compounds such as 3-Phenoxypyrocatechol, Zingerone, and Gingerol from the plant *Ficus carica* bind well with the target protein. Similarly, compounds from *Abrus precatorius* like 3-methoxytyrosine, 4-benzylsulfanylmethyl-6-morpholin-4-yl- [1,3,5] triazin-2-ylamine and 12-(Methylamino) dodecanoic acid shows excellent binding with human fibroblast collagenase with G score -3.47, -2.55 and -2.24 Kcal/mol respectively. Compounds from *Allium cepa* also exhibit some affinity towards the target protein of the study. However, the least interactions were found for the compounds from *Bauhinia purpurea, Vitex negundo,* and *Aloe barbadensis miller*.

Table 1: Structure of Phytocompounds from PubChem database

S No	Compound no	Compound name	Molecular formula	Molecular weight g/mol	Structure
Ficus carica					
1	7456	Methylparaben	$C_8H_8O_3$	152.15	
2	179618	3-Phenoxypyrocatechol	$C_{12}H_{10}O_3$	202.21	
3	31211	Zingerone	$C_{11}H_{14}O_3$	194.23	
4	442793	Gingerol	$C_{17}H_{26}O_4$	294.4	

5	6430906	Cis-nuciferol	$C_{15}H_{22}O$	218.33	
7	249954812	3-Ethyl-3-hydroxyandrostan-17-one	$C_{21}H_{34}O_2$	318.5	

Cassia auriculata					
6	536377	1-(4-Bromobutyl)-2-piperidinone	$C_9H_{16}BrNO$	234.13	
11	10314	Conhydrine	$C_8H_{17}NO$	143.23	
12	160533	Xanthinin	$C_{17}H_{22}O_5$	306.4	
13	6452096	Ethyl cholate	$C_{26}H_{44}O_5$	436.6	
15	539160	9-Methyltricyclo [4.2.1.1(2,5)] deca-3,7-diene-9,10-diol	$C_{11}H_{14}O_2$	178.23	
Abrus precatorius					
8	137276	dl-Alanyl-dl-valine	$C_8H_{16}N_2O3$	188.22	
9	1670	3-Methoxytyrosine	$C_{10}H_{13}NO_4$	211.21	
10	591697	1,3-dimethy1-2-(sulfinylamino) benzene	G_8H_9NOS	167.23	
14	81903	12-(Methylamino) dodecanoic acid	$C1_3H_{27}NO_2$	229.36	
Allium cepa					
16	521535	4-Acetyl-2-methoxyphenyl acetate	$C_{11}H_{12}O_4$	208.21	
17	606837	4-Benzylsulfanymethyl-6-morpholin-4-yl- [1,3,5] triazin-2-ylamine	$C_{15}H_{19}N_5OS$	317.4	

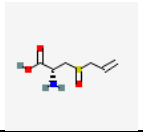
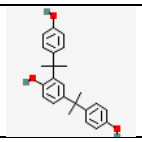
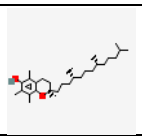
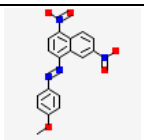
18	87310	Alliin	$C_6H_{11}NO_3S$	177.4	
Bauhinia pupurea					
19	75304	Phenol, 2,4-bis[1-(4-hydroxyphenyl)-1-methylethyl]-	$C_{24}H_{26}O_3$	362.5	
Vitex negundo					
20	14985	Vitamin E	$C_{29}H_{50}O_2$	430.7	
Aloe barbadensis miller					
21	572336	(4,7-Dinitronaphthalen-1-yl)-(4-methoxyphenyl) diazene	$C_{17}H_{12}N_4O$	352.30	

Table 2: ADME profile of phytocompounds

Compound ID	No. of rotatable bonds	Molecular weight	Dipole moment	SASA	Donor hydrogen bonds	Acceptor hydrogen bonds	QPlogP for octanol/gas
Normal range	**0.5-15**	**130.0-725.0**	**1.0-12.5**	**300.0-1000.0**	**0.0-6.0**	**2.0-20.0**	**8.0-35.0**
7456	2	152.149	4.249	370.71	1	2.75	8.38
137276	5	188.226	8.955	425.44	3.25	4.75	14.389
1670	6	211.217	7.302	419.49	4	4.5	15.187
591697	2	167.225	5.019	378.70	0	5	8.51
10314	3	143.228	2.152	382.62	2	3.2	8.967
160533	5	306.358	3.7	570.46	0	7	14.031
6452096	8	436.631	6.082	743.59	3	7.1	23.299
521535	3	208.213	4.89	453.35	0	5.25	9.935
606837	5	317.408	2.154	605.04	2	6.2	17.26
87310	6	177.218	9.919	393.62	2	6	12.903
179618	4	202.209	4.096	412.58	2	2	11.09
81903	12	229.362	5.89	602.31	2	3.5	12.674
539160	2	178.23	2.526	371.08	2	2.45	9.702
31211	5	194.23	3.812	449.81	1	3.5	9.745
442793	12	294.39	3.216	614.20	1	4.2	13.09
6430906	6	218.338	1.84	534.97	1	1.7	10.544
572336	5	352.306	8.212	604.81	0	4.75	15.417
14985	13	430.713	0.743	910.04	1	1.5	18.377
75304	7	362.468	1.82	641.85	3	2.25	18.792

Compound ID	QPlogP water/gas	QPlog octanol/water	QPlog BB for brain/blood	QPlog Kp for skin permeability	No. of metabolic reactions	Human oral absorption	Rule of five	Rule of three
Normal range	**4.0-45.0**	**-2.0 to 6.5**	**-6.5 to 0.5**	**-8.0 to -1.0**	**1-8**	**1,2 or 3**	**Max 4**	**Max 3**
7456	6.198	1.823	-0.493	-2.831	1	3	0	0
137276	12.363	-2.277	-0.79	-6.289	4	2	0	1
1670	11.603	-1.694	-0.952	-6.232	6	2	0	1
591697	8.97	0.622	-0.051	-2.155	3	2	0	0
10314	6.381	0.772	0.398	-4.166	1	3	0	0
160533	8.17	1.53	-1.088	-3.635	5	3	0	0
6452096	12.202	3.817	-1.48	-3.653	4	3	0	1
521535	6.583	0.992	-0.46	-2.683	1	3	0	0
606837	11.283	2.775	-0.604	-1.965	3	3	0	0
87310	12.273	-2.29	-0.919	-6.265	5	1	0	1
179618	7.535	2.659	-0.412	-1.661	2	3	0	0
81903	5.792	1.016	-1.139	-4.852	2	2	0	0
539160	6.929	1.478	-0.165	-2.342	6	3	0	0
31211	6.016	1.803	-0.643	-2.574	4	3	0	0
442793	5.718	3.553	-1.357	-2.253	6	3	0	0
6430906	2.894	2.768	-0.385	-1.85	2	3	0	0
572336	8.234	2.789	-1.691	-3.592	4	3	0	0
14985	2.409	8.953	-0.647	-0.832	5	1	1	1
75304	9.254	4.661	-1.196	-2.478	3	3	0	0

Table 3: Interaction of phytocompounds with Human Fibroblast Collagenase

S No	Compound ID	Residue interacted	Bond length (A)	No. of Bond	G Score (Kcal/mol)
1	Methylparaben (7456)	ARG-195(O-H) SER -224 (H-O) ARG -281(O-H)	2.7 2.2 2.7	3	-4.29
2	DL-Alanyl-DL-Valine (137276)	ASN-307(O-H) ASN-307 (O-H) ASP-226 (H-O) ASP-226 (H-O)	2.1 1.6 1.6 1.6	4	-3.70
3	3-Methoxytyrosine (1670)	ASP-226 (H-O) GLN-228(H-O) ARG-281(O-H) ASN-307 (O-H) ASN-307 (O-H)	2.2 1.9 2.0 2.2 2.6	5	-3.47
4	1,3-Dimethyl-2-(Sulfinylamino) Benzene (591697)	ASP-226 (O-H) GLY-225 (O-H) SER-224 (O-H) SER-224 (N-H)	2.3 2.7 2.2 2.5	4	-3.00
5	1-(Piperidin-2-yl) Propan-1-ol (10314)	SER-224 (H-O) PRO-303(H-O) PRO-303(H-O)	2.1 1.9 2.6	3	-2.86
6	Xanthinin (160533)	GLN-228 (O-H) GLN-254 (O-H)	2.0 1.9	2	-2.84
7	Ethyl Cholate (6452096)	GLN-254 (O-H) ASP-280 (H-O)	2.1 1.8	2	-2.75
8	4-Acetyl-2-Methoxyphenyl Acetate (521535)	ASN-307 (O-H) ASN-307 (O-H) ASN-307 (O-H)	2.5 2.2 2.2	3	-2.67
9	4-Benzylsulfanylmetyl-6-morpholin-4-yl-[1,3,5]triazin-2-ylamine (606837)	GLN-228 (H-O) GLN-228 (N-H)	2.7 2.2	2	-2.55
10	Alliin (87310)	ASP-226 (H-O) ASN-307 (O-H) ASN-307 (O-H)	1.7 2.1 2.0	3	-2.42
11	1,2-Benzenediol,3-phenoxy- (179618)	LYS-257 (O-H) ASP-260 (H-O) ASP-260 (H-O)	2.7 1.8 1.8	3	-2.39
12	12-(Methylamino) dodecanoic acid (81903)	LEU-305 (H-O) PRO-303 (H-O) SER-224 (O-H) ARG-281 (O-H)	1.9 1.9 2.8 2.0	4	-2.24
13	9-Methyltricyclo [4.2.1.1(2,5)] deca-3,7-diene-9,10-diol (539160)	GLN-228 (O-H) GLN-228 (H-O) ASN-307 (O-H)	2.6 2.2 2.0	3	-2.16
14	Zingerone (31211)	ASP-280 (H-O) ASN-307 (O-H)	2.0 2.0	2	-1.90
15	Gingerol (442793)	GLN-254 (O-H) LYS-257 (O-H) ASP-260 (H-O)	2.2 2.1 2.1	3	-1.81
16	Cis-Nuciferol (6430906)	ASP-260 (H-O) LYS-257 (O-H)	1.9 1.8	2	-1.76
17	(4,7-Dinitronaphthalen-1-yl)-(4-Methoxyphenyl) diazene (572336)	GLN-228 (N-H) ASN-307 (O-H)	2.6 2.2	2	-0.55
18	Vitamin E (14985)	ASN-307 (O-H)	2.2	1	0.55
19	Phenol,2,4-bis[1-(4-Hydroxyphenyl)-1-methylethyl] (75304)	GLN-228 (H-O) GLN-254 (O-H)	1.8 2.2	2	0.16

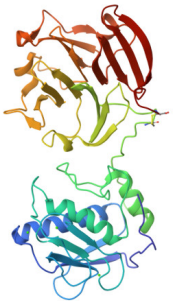


Figure 1: Human fibroblast collagenase (2CLT)

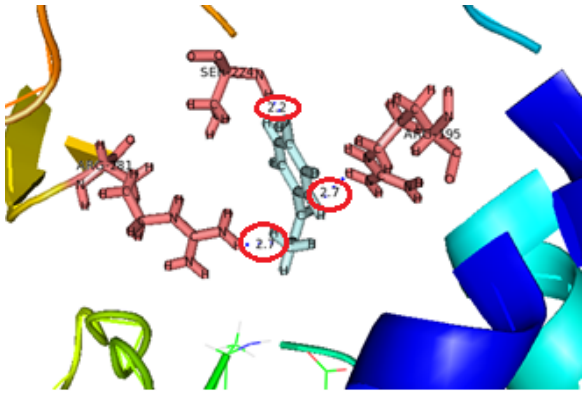


Figure 2: Diagrammatic representation of the interaction between Methylparaben with human fibroblast collagenase
Note: The pale cyan colour represents the compound that binds to the target protein's active pocket, which is represented in red salmon colour.

DISCUSSION

Diabetic mellitus is a complex illness with various adverse effects on the body. Although treatments are available, prolonged usage of drugs gradually results in side effects. Therefore, to overcome these disadvantages, studies were focused on various molecular targets to investigate the mechanism of ficusonolide's antidiabetic effect. Studies reported that treatment of type-II diabetes mellitus (DM-II) might involve targeting dipeptidyl peptidase-IV (DPP-IV), protein tyrosine phosphatase 1B (PTP-1B), -amylase, and -glucosidase since the selection of an appropriate target is essential for drug discovery [23]. This study chooses human fibroblast collagenase as the target protein because of its vital role in wound development in diabetic foot ulcers. Recently, there has been an increased focus on creating plant-based natural antidiabetic medications to treat diabetic problems. According to recent investigations, crude extracts and active compounds of different Ficus species have reported antidiabetic activities in both *in vitro* and *in vivo* studies. In particular, substances extracted from Ficus species effectively reduced all the rat models with streptozotocin and alloxan-induced diabetes [24]. Thus, in this study, we focused on phytocompounds from different plants, including *Ficus carica* and found out that in addition to methylparaben, compounds such as 1,2-Benzenediol,3-phenoxy-, Gingerol and Cis-Nuciferol from *Ficus carica* also exhibited affinity against ASP-260 residue which in turn showed the ability of compounds from *Ficus carica* in the treatment of diabetic foot ulcers. SARS-CoV-2, a first-choice target in COVID-19 drug discovery reports, suggests that compounds from *Opuntia Ficus-indica*, a common cactus plant, exhibited excellent phyto-therapeutic properties [25].

Similarly, our study reveals that some phytocompounds from various medicinal plants possess therapeutic properties, whereas ADME studies reported drug-like molecules among a group of molecules considered for the study. Experimental techniques were performed to test the antidiabetic potential of *Ficus foveolate,* which was used as a diabetic medication for a long time and whose phytocompounds increased glucose absorption by 53% [26]. In this study, the Molecular docking strategy helps to identify the most promising phytocompound Methylparaben that prominently binds to the active site pockets of human fibroblast collagenase (2CLT) protein of diabetic foot ulcer having 367 amino acid sequence in length. Computational studies revealed that Ficusonolide has a robust computational interaction with the role of protein tyrosine phosphatase and strongly inhibits the protein, suggesting that it has antidiabetic properties [27]. Thus, we performed docking studies only for compounds showing drug likeliness in ADME profiling, and their interactions have been discussed throughout the study. Antidiabetic and immune protective properties of *Cassia auriculata* have been hypothesised based on the findings from *in vivo* and *in silico* investigations where they exert their activity by activating the (Insulin Receptor Substrate) IRS signalling pathway, which in turn increases glucose absorption and production of glucose transporters [28]. Table 3 revealed the biological property of *Cassia auriculata* against diabetic foot ulcers with the binding affinities recorded in the phytocompounds 1,3-Dimethyl-2-(Sulfinylamino) Benzene, 1-(Piperidin-2-yl) Propan-1-ol and Xanthinin towards the binding pocket SER-224 residue of the target protein collagenase. The flowers of *Cassia auriculata* have been characterised as antidiabetic drugs against several targets like Human monoamine oxidase B (MAO B), Aldo- keto reductase family one member B10 (AKR 1 B10), Liver fatty acid-binding protein (LFABP) and Human cytochrome P450 2E1(CYP450-2E1) using computational techniques [29].

Similarly, findings of the present study suggest that compounds from various parts of *Cassia auriculata,* including flowers, possess activity towards diabetic ulcers. Preliminary docking studies serve as a foundation which helps use bioactive chemicals found in medicinal plants as excellent therapeutics [30]. Flavonoids highly present in fruits were hypothesised to positively affect health via their respective antioxidant effects and involvement in cell signalling pathways [31]. Thus, in the current study, ADME studies were performed, focusing on parameters like donor hydrogen bond, acceptor hydrogen bond, molecular weight, blood-brain barrier, and solvent-accessible surface area to analyse the drug-like properties of phytocompounds to be selected. This research paves the way for developing novel, prominent yet safe drugs in treating diabetic foot ulcers, and studies need to be performed to validate the strength of the interactions and to analyse the biological changes that occur in the pathogenesis of diabetic foot ulcers.

CONCLUSION

A combination of peripheral vascular disease, neuropathy, and other conditions in people with diabetes causes diabetic foot ulcers. Patients often face challenges with wound health due to deep tissue necrosis, ulceration and infection, especially in the lower limb. Initial symptoms include bleeding around the lesion followed by irritation, swelling, or an unpleasant odour. The present study provides insight into phytocompounds and their affinity towards human fibroblast collagenase. Most compounds from *Abrus precatorius,* such as DL-Alanyl-DL-Valine, 3-Methoxytyrosine and 1,3-Dimethyl-2-(Sulfinylamino) Benzene were observed with significant affinity followed by methylparaben towards the active site residues ASN 307 and ASP 226. However, only methylparaben from *Ficus carica* was found to have prominent interactions with the target protein in its

binding pocket with residues ARG-195, SER -224 and ARG -281, suggesting its potency towards collagenase. Overall findings indicate that compounds from *Ficus carica* and *Abrus precatorius* could be excellent agents in treating diabetic foot ulcers. However, further studies are required to develop drug molecules from these plant extracts against diabetic foot ulcers by conducting stability analysis computationally, followed by validating their efficacies under laboratory conditions.

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