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Preface

We would like to present, with great pleasure, the inaugural volume-10, Issue-12, December 2024, of a scholarly journal, *International Multispeciality Journal of Health*. This journal is part of the AD Publications series *in the field of Medical, Health and Pharmaceutical Research Development*, and is devoted to the gamut of Medical, Health and Pharmaceutical issues, from theoretical aspects to application-dependent studies and the validation of emerging technologies.

This journal was envisioned and founded to represent the growing needs of Medical, Health and Pharmaceutical as an emerging and increasingly vital field, now widely recognized as an integral part of scientific and technical statistics investigations. Its mission is to become a voice of the Medical, Health and Pharmaceutical community, addressing researchers and practitioners in below areas

Clinical Specialty and Super-specialty Medical Science:

It includes articles related to General Medicine, General Surgery, Gynecology & Obstetrics, Pediatrics, Anesthesia, Ophthalmology, Orthopedics, Otorhinolaryngology (ENT), Physical Medicine & Rehabilitation, Dermatology & Venereology, Psychiatry, Radio Diagnosis, Cardiology Medicine, Cardiothoracic Surgery, Neurology Medicine, Neurosurgery, Pediatric Surgery, Plastic Surgery, Gastroentrology, Gastrointestinal Surgery, Pulmonary Medicine, Immunology & Immunogenetics, Transfusion Medicine (Blood Bank), Hematology, Biomedical Engineering, Biophysics, Biostatistics, Biotechnology, Health Administration, Health Planning and Management, Hospital Management, Nephrology, Urology, Endocrinology, Reproductive Biology, Radiotherapy, Oncology and Geriatric Medicine.

Para-clinical Medical Science:

It includes articles related to Pathology, Microbiology, Forensic Medicine and Toxicology, Community Medicine and Pharmacology.

Basic Medical Science:

It includes articles related to Anatomy, Physiology and Biochemistry.

Spiritual Health Science:

It includes articles related to Yoga, Meditation, Pranayam and Chakra-healing.

Each article in this issue provides an example of a concrete industrial application or a case study of the presented methodology to amplify the impact of the contribution. We are very thankful to everybody within

that community who supported the idea of creating a new Research with *IMJ Health*. We are certain that this issue will be followed by many others, reporting new developments in the Medical, Health and Pharmaceutical Research Science field. This issue would not have been possible without the great support of the Reviewer, Editorial Board members and also with our Advisory Board Members, and we would like to express our sincere thanks to all of them. We would also like to express our gratitude to the editorial staff of AD Publications, who supported us at every stage of the project. It is our hope that this fine collection of articles will be a valuable resource for *IMJ Health* readers and will stimulate further research into the vibrant area of Medical, Health and Pharmaceutical Research.

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Research Area: Pediatric Surgery & Laparoscopy.

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Bipolar Disorder with Comorbid Substance Use Disorder in a Young Male not Responding to Combination Therapy: Endoxifen Use for 2 Years

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Abstract**—** *Impulsivity is common to both bipolar disorder (BD) and substance use disorder (SUD). Bipolar disorder is in fact a risk factor for SUD, wherein substances may be used to achieve symptom relief. Impulsivity is associated with excessive protein kinase C (PKC) activity, and is implicated in the development of BD. This case report describes the use of endoxifen, a direct PKC inhibitor, for the management of a young male with BD and SUD who was not responsive to combination therapy with pharmacotherapies including lithium, haloperidol, and risperidone. The inclusion of endoxifen in the treatment regimen while discontinuing haloperidol and tapering of the dose of lithium led to reduced substance use and improvement of the symptoms of bipolar I mania within 3 weeks. The patient tolerated the treatment well, including long-term use for 2 years. Therefore, the utility of endoxifen in the management of SUD could be explored in larger studies.*

Keywords— bipolar disorder, endoxifen, impulsivity, protein kinase C, substance use disorder.

I. INTRODUCTION

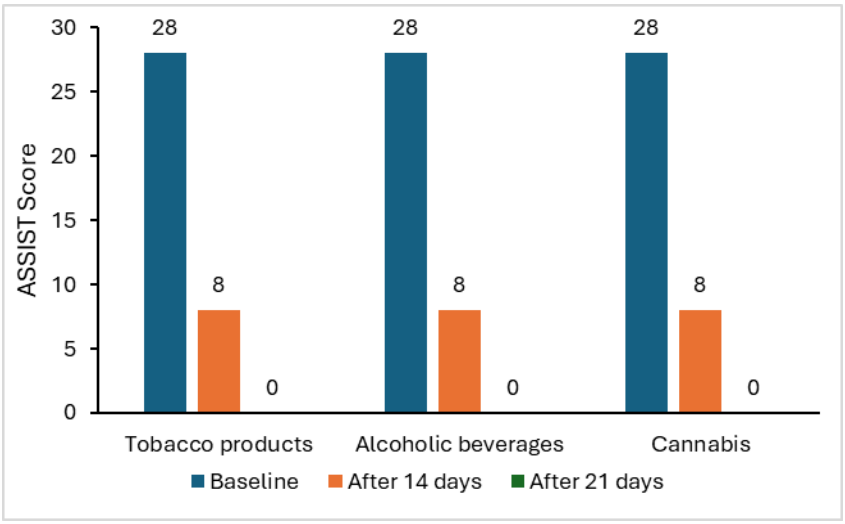
Impulsivity is a phenomenon that is common to bipolar disorder (BD) as well as substance use disorder (SUD). Excessive protein kinase C (PKC) activity is associated with prefrontal cortex deficits, and dysregulation in this brain region is associated with impulsivity.[1,2] Inhibition of PKC may help alleviate impulsivity in both BD and SUD patients. BD is a risk factor for addictions to alcohol, tobacco, opiates, cannabis, etc.[3] Comorbid addictions in BD could be mediated by shared neurobiology or involvement of neurotransmitter mechanisms. Furthermore, individuals with BD may "self-medicate" with substances to alleviate symptoms.[4]

This case report describes the management of a young male with BD and SUD (alcohol, tobacco, and cannabis), who was not responsive to combination therapy despite adherence to therapy. The inclusion of endoxifen in the treatment regimen led to a favorable response for mania, SUD and overall impulsivity. A full recovery was noted within 3 weeks of initiating endoxifen usage. Long-term treatment with endoxifen for 2 years did not lead to adverse effects and the patient did not consume substances during the treatment. Being a direct PKC inhibitor, endoxifen treatment leads to a faster response in reducing impulsivity in both SUD and BD.

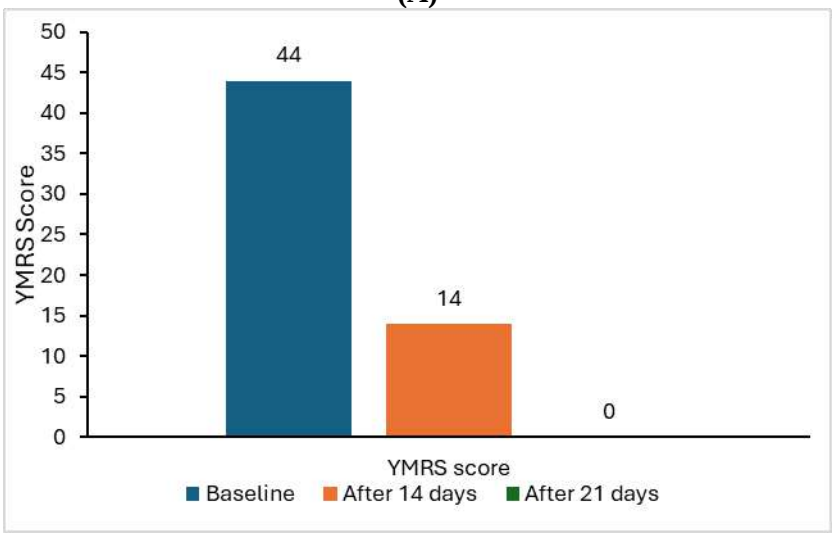
II. CASE REPORT

A 25-year-old male diagnosed with BD 2 years and 2 months prior presented with an increase in symptoms for 3-4 weeks. The patient had a history of polysubstance use (alcohol, tobacco, and cannabis) which was absent before the diagnosis of BD. He consumed 350 mL of alcohol, 30 cigarettes and two joints of cannabis daily.

This patient was an engineer who used to work from home. He lived with his family and was unmarried. The patient presented with grandiosity, overactivity, over-talkativeness, substance use and decreased sleep. There was a high impulsivity to consume alcohol, tobacco and cannabis. The Young Mania Rating Scale (YMRS) score was 44 out of 60, and the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) score was 28 out of 36 for tobacco products, 28 out of 36 for alcoholic beverages, and 28 out of 36 for cannabis, indicating the need for more intensive treatment (Figures 1A and 1B).



(A)



(B)

FIGURE 1. (A) Change in ASSIST scores with endoxifen treatment (B) Change in YMRS score with endoxifen treatment.

ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; YMRS: Young Mania Rating Scale. Maximum ASSIST score: 36 for each substance; maximum YMRS score: 60.

Based on the diagnosis of BD and SUD, the patient was initiated on lithium (450 mg twice-daily), haloperidol (15 mg daily) and risperidone (4 mg twice-daily) for 1 month. This treatment was targeted to mania, substance use, and impulsivity, since it was likely that SUD was linked to BD. The patient was adherent to the therapy and no side effects occurred; however, there was no improvement noted in the symptoms.

The patient was hospitalized and the treatment regimen was altered. Haloperidol was discontinued. Endoxifen 8 mg was prescribed for 2 days, after which the dose was increased to 8 mg twice-daily. Lithium was tapered off over 15 days, as endoxifen was included in the treatment regimen as a mood stabilizer. Risperidone was continued at a dose of 4 mg daily. The patient was discharged after 7 days. At the first follow-up visit (7 days after discharge) it was noted that alcohol consumption had reduced by 60-70% while the consumption of tobacco and cannabis had ceased. At this point the ASSIST score was 8 out of 36 for each of tobacco products, alcoholic beverages and cannabis, and the YMRS score was 14 out of 60 (Fig. 1A and 1B).

Full recovery was noted within 3 weeks of initiating endoxifen treatment, at which time the patient did not consume alcohol, tobacco and cannabis. In addition, symptoms of bipolar I mania, such as grandiosity, overactivity, over-talkativeness and decreased sleep had diminished. Overall impulsivity had reduced as well. The ASSIST score and the YMRS score were both 0 (Fig. 1A and 1B). The patient was stable on endoxifen 8 mg once-daily and risperidone 4 mg daily with no recurrent symptoms. The patient has been on endoxifen monotherapy for 2 years with no adverse events and no substance consumption.

The patient was compliant with the treatment and the patient's family was happy with the treatment. He continues his job as an engineer working from home without work distress and disability due to his psychiatric condition.

III. DISCUSSION

There is a strong association between BD and alcohol and nicotine dependence, as well as the use of illicit drugs.3 Individuals who consume illicit substances may be unable to quit or reduce consumption due to deficient impulse control.2 BD is characterized by dysregulation in the prefrontal cortical deficits, and lesions in this brain region are associated with impulsivity.1 Increased PKC activity can lead to impulsivity, and impulsivity is noted in both BD and SUD. Reducing PKC can reduce impulsivity and improve the patients of BD and SUD.[1,2,5]

In the case described, the patient was working from home, which could have led to increased stress due to the blurred boundaries of work-life balance. The paucity of face-to-face interactions and absence of workplace support can increase the likelihood of developing a mood disorder.[6] BD and the associated extreme mood states can damage social relationships, and patients with BD are less likely to be married.[7] Individuals with BD may consume illicit substances to improve mood, alleviate tension or boredom, increase energy, or to escape from reality. There are several consequences of comorbid SUD, including higher severity of BD with more relapses and poor response to pharmacotherapy. In addition, the risk of suicide and tendency to commit violent crimes is higher. Individuals with comorbid SUD and BD tend to have a higher lifetime risk of infection with hepatitis C virus and HIV. Therefore, effective pharmacotherapy is essential for the management of these comorbid conditions.[3] The complexity in the development of BD and the social impact of this condition underscores the need for an effective and safe therapeutic option which resolves both manic symptoms and substance use, and can be used for long-term treatment.

Both BD and SUD are characterized by impulsivity. Impulsivity involves the attenuation of control mechanisms that would otherwise suppress reward-driven responses. The resulting 'disinhibition' or predisposition towards can present as SUD.[2] Dysregulation in the prefrontal cortex are known to impulsivity and poor judgment. Individuals with BD have prefrontal cortical deficits, associated with altered PKC intracellular signaling. Excessive PKC activation can disrupt prefrontal cortical regulation, thus leading to signs of impulsivity.[1]

Endoxifen is a direct PKC inhibitor which reduces the signs of impulsivity in both mood disorder and substance use,[6,7] unlike lithium and valproate which are indirect inhibitors of PKC. Being independent of CYP2D6 genetic polymorphisms, endoxifen has predictable bioavailability and lacks drug-drug interactions unlike the parent molecule, tamoxifen. Endoxifen achieves early remission in patients with BD which could be attributed to the direct inhibition of PKC.[5]

In this case study, endoxifen was added to the treatment regimen as it is a direct PKC inhibitor. PKC can lead to impulsivity through its action in the prefrontal cortex, and endoxifen inhibits PKC, potentially alleviating symptoms of mania as well as impulsivity associated with substance abuse. This was needed as PKC inhibition is necessary to reduce impulsivity in BD and SUD. Endoxifen was well-tolerated and its rapid efficacy within 3 weeks permitted the reduction of other drugs and reduced the pill burden. Furthermore, long-term use of endoxifen for 2 years did not lead to adverse effects, and the patient did not consume substances throughout treatment and was maintained on remission. Phase II and III clinical trials have demonstrated that endoxifen has rapid antimanic effects compared with divalproex and reduces the YMRS score significantly.[5,8] There have been several recent case reports which highlight the efficacy of endoxifen in managing impulsivity in BD and SUD.[9-11] The current case report adds to the growing evidence base for the utility of endoxifen in mood disorders and the comorbid conditions thereof.

IV. CONCLUSION

Endoxifen is effective for the management of mania and comorbid SUD because it directly inhibits PKC and hence reduces impulsivity in both mania and SUD. This case study additionally demonstrates the safety of the 2 years of long-term use of endoxifen. It would be beneficial to explore the utility of endoxifen in the management of SUD based on its known tolerability profile and efficacy in reducing impulsivity.

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The Interactions between Heterocyclic Compounds and Target Proteins Involved with Cancer

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Abstract— *Cancer is the second leading cause of mortality globally. The World Health Organization forecasts that by 2030, there will be 22 million new cases of cancer globally. Extensive global research focuses on cancer prevention, diagnosis, and treatment procedures. The metabolic profile of cancer cells is distinct from that of normal cells, attributable to epigenetic and genetic abnormalities. Numerous anti-cancer drugs available commercially feature heterocycles as their main structural element. Furthermore, anticancer drugs approved by the FDA from 2010 to 2015 contain heterocyclic rings in their chemical structure. Their extensive cellular processes and mechanisms, along with their prevalence in nature, account for their inclusion in anti-cancer medications. This study elucidates several heterocyclic compounds exhibiting anticancer effects on various cell lines. These compounds feature rings composed of nitrogen, sulfur, and oxygen. The collection of information on heterocyclic rings may facilitate the discovery of novel compounds with potential anticancer properties in the future.*

Keywords— Heterocyclic compounds, Anticancer activity, Cell lines, Cytotoxicity, Natural product.

I. INTRODUCTION

Most research has concentrated on VEFG as an initiator; however, various cancer targets have been identified, including enzymes that deacetylate histones, tyrosine kinase, the growth factor TGF-α, fibroblast growth factor (FGF), phosphoglycerate geranylgeranyl transferase (PGF), epidermal growth factor (EGF), and phosphodiesterase types I and II. Despite numerous instances of disease progression post-therapy, inhibition of VEGF signaling has not demonstrated significant efficacy. Numerous heterocyclic anticancer agents, originating from both natural and synthetic sources, are currently utilized, and investigations for further compounds are ongoing. Figure 1 illustrates several instances. The therapeutic properties of heterocyclic compounds, which are cyclic structures containing carbon along with one or more nitrogen, oxygen, or sulfur atoms, have been studied for their potential in treating cancer and various other conditions. Druggable candidates are optimized for ADMET (Adsorption, Distribution, Metabolism, Excretion, and Toxicity) through the introduction of heteroatoms, enhancing their solubility, polarity, and hydrogen bonding capacities. Brevilin A, also referred to as 11, is a natural substance derived from Centipeda minimum. It is a heterocyclic sesquiterpene lactone with demonstrated anticancer properties. Research indicates that Brevilin A may inhibit cell growth, induce apoptosis, and reduce cell metastasis by diminishing the activity of tyrosine kinase, signal transducer, and activator of transcription 3 (STAT3). Lee, Chan, and colleagues synthesized analogues of Brevilin A for their investigation. It was found that compounds 13 and 14, synthesized from paraformaldehyde and 11 via an aldol reaction with sodium carbonate, exhibited greater anticancer efficacy than 11. Cancer therapies frequently encounter issues such as drug resistance, systemic toxicity from treatments, and ineffective medications. Identifying novel anticancer agents as potential drug leads is essential due to the challenges in discovering effective therapeutic agents for tumor treatment. These challenges arise from the inherent variability of cancer cells and the intricate nature of signaling networks. A potential solution to these issues is the

application of multi-target heterocyclic inhibitors in cancer treatment. Several new heterocyclic compounds demonstrate established anticancer effects, including Midostaurin (16), Vorinostat (17), and Sunitinib (15). Their capacity to concurrently regulate multiple growth factors, such as VEGFR, c-Kit from PDGFRA, and FLT-3, is notable. Figure 2 illustrates that numerous drugs exhibiting promising inhibitory potentials are currently undergoing Phase 3 clinical trials. This includes various HER1 and HER2 inhibitors such as sotagliflozin (21), lapatinib (20), erlotinib (19), and gefitinib (18).

II. LITERATURE REVIEW

Ledade (2022) Fused nitrogen heterocyclic molecules have gained attention for their therapeutic properties in recent years. N-Heterocyclic scaffolds, which are versatile and easily synthesized, have numerous potential applications in synthetic organic chemistry and the biological domain. These compounds offer broad-spectrum antibacterial and anticancer medicines with low toxicity levels, but cytotoxicity levels are higher than those of cisplatin, the gold standard anticancer drug. Numerous synthetic techniques have been developed to synthesize N-heterocycles and their derivatives, offering a range of structural flexibility for targeted biological uses.

Martins (2015) Heterocycle molecules and fragments are essential in medicinal chemistry due to their adaptability, physicochemical characteristics, and prevalence in medicines. They are being studied for their potential effectiveness against various types of cancer. Their unique flexibility and dynamic structure have been specifically used in anticancer research. However, these compounds have drawbacks, including potential limiting concerns. This summary discusses the key biological objectives, structure-activity relationships, biochemical processes of action, and intrinsic limiting concerns with heterocyclic compounds, focusing on those beneficial for cancer treatment. The article also discusses the potential of nano vectorization to enhance the pharmacokinetic and pharmacodynamic features of heterocycles, particularly with the introduction of nanotechnology for effective selective drug targeting.

Didehban (2018) Heterocyclic systems are essential building blocks in organic synthesis and are found in numerous compounds, including over 90% of new drug structures. Researchers are working on innovative one-pot methods to synthesize these organic molecules using basic, cheap, and easily accessible building blocks. One of the most intriguing and encouraging synthetic operations is the chemical fixation of carbon dioxide onto organic molecules. This approach has evolved over the last five years, allowing for the synthesis of several biologically significant heterocyclic systems. This brief overview focuses on recent developments in this field of chemistry, particularly in terms of reactions' mechanisms.

Naturalista (2024) Pyrazole derivatives are heterocyclic compounds with diverse biological and therapeutic applications. They have a broad range of effects, including antibacterial, anti-inflammatory, antioxidant, antiviral, antidiabetic, and neuroprotective effects. Contemporary techniques, such as solvent-free methods, microwave-assisted synthesis, green chemistry, catalytic methods, and multicomponent reactions, have replaced traditional methods in synthesis. These developments have made pyrazole-based compounds more efficient and selective, improving their use in the pharmaceutical industry. This article provides a comprehensive overview of the synthetic processes used to generate pyrazole derivatives and investigates the structure-activity relationship (SAR) of these compounds. It highlights the importance of pyrazole derivatives in developing novel medicinal medicines and provides guidance for future studies. The comprehensive analysis aims to highlight the potential of pyrazole derivatives as flexible candidates for creating new medications, contributing to continuous advancements in medicinal chemistry.

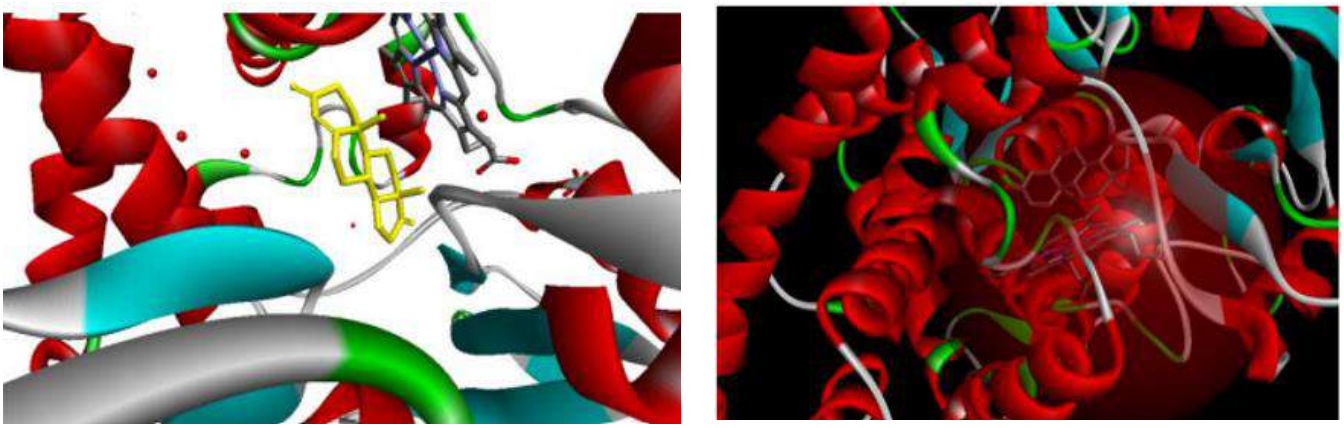
Mirza, Agha Zeeshan. (2019). Cancer is a major public health issue with millions of deaths annually. Chemotherapeutic medications, including synthetic versions of natural molecules, are effective in treating cancer. Nucleoside analogues, which have been used in antitumor chemotherapy, neoplasm treatment, and viral infection management, have become essential in cancer therapy. This review examines nucleosides and their potential utility in cancer treatment, including those pending FDA approval. The article also discusses the impact of substitution on nucleoside analogues and discusses the progress of computational chemistry in this field.

III. MATERIAL AND METHODS

3.1 Investigating Novel Non-Estradiol Chemo-Types as Aromatase Inhibitors in a Controlled Environment:

The urgent demand for innovative pharmaceutical discoveries requires the creation of new drug models, and in-silico trials offer an effective approach to achieve this goal. The activity of the aromatase enzyme has been elucidated, and advanced artificial intelligences have been developed, owing to in-silico studies conducted by various researchers utilizing state-of-the-art methodologies such as Structure-Guided Design, High-Throughput Docking, and pharmacophore-based modeling approaches. Advancements in understanding the structure and function of aromatase have been facilitated by sophisticated methods, including membrane-bound molecular dynamic simulations.

Results indicate that the charged amino acid sequence of aromatase, comprising alkyl and aryl amino acids, is essential for interaction with aromatase inhibitors. Heme porphyrin, located at the active site, stabilizes the transition state of the substrate through its oxidation state and functions as an electron donor. Park et al. demonstrated in their study on molecular modelling of the aromatase active site that the Aspartic acid 309 residue, located near the entrance of the active site, is essential for substrate access to the active site channel. The aromatase active site is frequently coordinated by the heme-porphyrin complex in the presence of sp2 nitrogen within the heterocyclic structure of aromatase inhibitors. Amino acid residues 133, 235, 395, 474, 302, 308, 309, Threonine, Serine 478, and 480 comprise sixteen distinct mutations in aromatase. Mutations significantly alter ligand binding affinity at the aromatase active site amino acid residues, either enhancing or diminishing it.



(A) **(B)**

FIGURE 1: The 3S7S and 3EQM aromatase proteins

3.2 Creating a QSAR prototype:

The IC50 activity and chemical diversity of the ligands in the aligned training set were employed to validate the model. The objective was to produce significant predictions. Four distinct PLS components were utilized to develop a series of models for regression through a partial least squares (PLS) approach. Table 1 indicates that the highest overall model significance and statistical significance were attained with PLS factor 4 (# Factor), chosen based on the robust correlation between the training set and Partial Least Square factors. The predictive power of the test set was assessed, yielding a Q2 of 0.7854, RMSE of 0.5284, and Pearson R of 0.9111. The measure of variance is denoted as F. Regressions exhibiting higher F values are deemed more statistically significant. P denotes the significance level of the variance ratio. Smaller P values indicated a higher level of certainty. The Q-squared value of the expected activities is the product of Q2 with itself. Pearson-R quantifies the extent of concordance between the anticipated and observed activity in the test set. The most effective 3D QSAR models for prediction were those that fulfilled all of these criteria concurrently.

TABLE 1
ASSESSMENT OF THE BEST PHARMACOPHORE HYPOTHESIS ARR.1 USING PARTIAL LEAST SQUARES

S. No.	# Factors	SD	R-Squared	F	P	Stability	RMSE	Q-Squared	Pearson-R
1	1	0.7851	0.5544	27.4	3.014e-005	0.6157	0.8218	0.4809	0.7716
2	2	0.5422	0.7972	41.3	5.3l3e-008	0.3104	0.6054	0.7183	0.8589
3	3	0.2807	0.9482	122.1	5.006e-013	0.1769	0.5096	0.8003	0.9302
4	4	0.1265	0.99	470.6	l.033e-018	0.094	0.5284	0.7854	0.9111

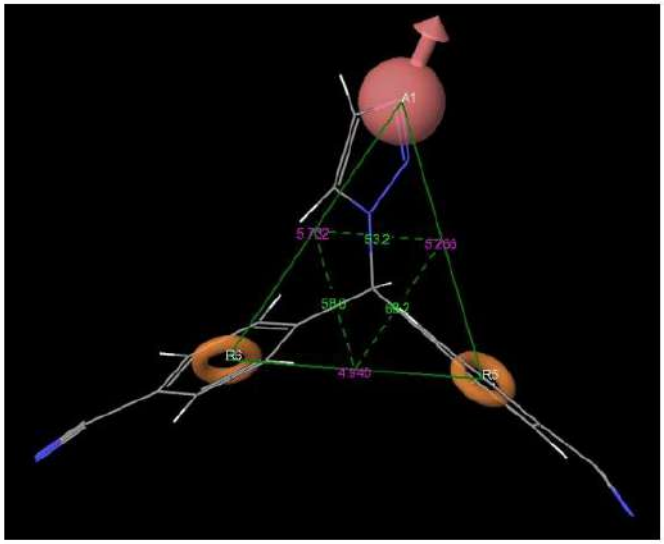
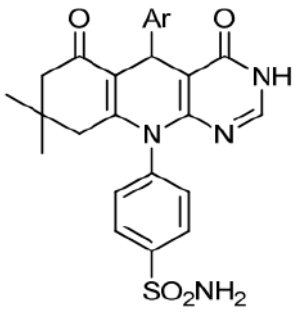


FIGURE 2: Potential structure of a pharmacophore

TABLE 2
ANALYSIS OF COMPOUNDS 6A AND 6B USING MICROSCOPY AND PHYSICAL DATA

Compd. No.	*Ar*	M,p, ('C)	Yield (%)	Mol. Formula(M. wt.)	Microanalysis	
					Calculated	Found
6a	**C_6H_4F-4**	**282-4**	*86*	**$C_{24}H_{23}FN_4O_3S$** (466.53)	C: 61.79 H:4.97 N:12.01	C: 61.91 H:4.73 N:11.80
6b	**C_6H_4Cl-4**	**280-2**	85	**$C_{24}H_{23}ClN_4O_3S$** (482.98)	C: 59.68 H:4.80 N:11.60	C: 59.92 H:5.00 N:11.33

5-[5-(4-fluorophenyl)-8,8-dimethyl-4,6-dioxo-3,4,6,7,8,9-hexahydro-pyrimido[4,5-b]quinolin-10(5H)-yl]`(7a) benzenesulfonamide and 4–[5-(4-chlorophenyl)-8,8-dimethyl-4,6-dioxo-3,4,6,7,8,9-hexahydropyrimido[4,5-b] quinolin-10(5H)-yl]isothiocyanate (7b)



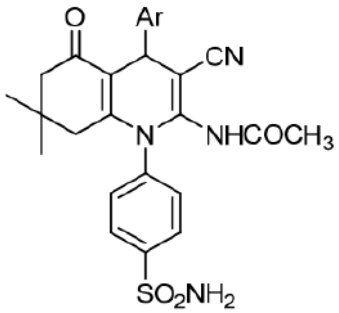
(7a & 7b)

After refluxing a solution of compound 6a or 6b (0.001 mol) in 20 ml of formic acid for 5 hours, cooling the mixture, and 7a and 7b were produced when the ensuing solid was crystallised from dioxane after it was ultimately poured into cold water.

TABLE 3
MICROANALYSIS AND PHYSICAL DATA OF MOLECULES 7a and 7b

Compd. No.	Ar.	M.p. (°C)	Yield (%)	Mol. Formula (M. wt.)	Microanalysis	
					Calculated	Found
7a	**C_6H_4F-4**	168-70	79	**$C_{24}H_{23}FN_4O_4S$** (494.54)	C: 60.72 H:4.69 N:11.33	C: 60.82 H:4.84 N:11.49
7b	**C_6H_4Cl-4**	162-4	78	**$C_{24}H_{23}ClN_4O_4S$** (510.99)	C: 58.76 H:4.54 N:10.96	C: 58.94 H:4.38 N:11.18

1,4,5,6,7,8-hexahydroquinolin-2-yl -[3-Cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1-(4-sulfamoyl-phenyl)] Eighthly, acetamide in addition to N-[4-(4-chlorophenyl)-3- cyano-7, 7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl] 8-benzoic acid



(8a & 8b)

For the preparation of 8a and 8b, respectively, after a solution of compound 6a or 6b (0.001 mol) was refluxed in 20 ml of acetic anhydride for 5 hours, the reaction mixture was concentrated. The solid that had separated was then crystallised from ethanol.

TABLE 4
ANALYSIS OF COMPOUNDS 8A AND 8B USING MICROSCOPY AND PHYSICAL DATA

Compd. No.	Ar.	M.p. (°C)	Yield (%)	Mol. Formula (M. wt.)	Microanalysis	
					Calculated	Found
8a	**C_6H_4F-4**	150-2	97	**$C_{24}H_{23}FN_4O_4S$** (508.56)	C: 61.40 H:4.95 N:11.01	C: 61.68 H:5.11 N:10.83
8b	**C_6H_4Cl-4**	149-51	82	**$C_{24}H_{23}ClN_4O_4S$** (525.02)	C: 59.48 H:4.80 N:10.67	C: 59.31 H:5.05 N:10.49

IV. RESULTS

4.1 3D QSAR:

The ARR three-point pharmacophore model includes one hydrogen bond acceptor (A) and two aromatic rings (R). The 3D-QSAR model successfully predicted the performance of both the training and test sets, in accordance with the

pharmacophore-based alignment hypothesis. Analysis of the 3DQSAR model presented in the Workspace allows for the assessment of the influence of ligand properties on the expected activity, whether positive or negative. This 3D QSAR model depicts letrozole in its prototype form. The presence of oxygen and nitrogen in the blue cubes within the hydrogen bond acceptor region indicates an optimal environment for the binding of these atoms, subsequently enhancing biological activity. An unfavorable environment for the attachment of functional groups, indicated by the red cubes adjacent to the H-bond acceptor zone, negatively affects biological activity. Aromatic rings and acceptors are vector characteristics that significantly influence aligned structures, as evidenced by higher vector score values. The overlapping van der Waals models of non-hydrogen atoms assess the volume score for each pair of structures. To enhance the efficacy of the ligand, a hydrogen bond acceptor (A), which may be nitrogen or oxygen, is necessary.

TABLE 5

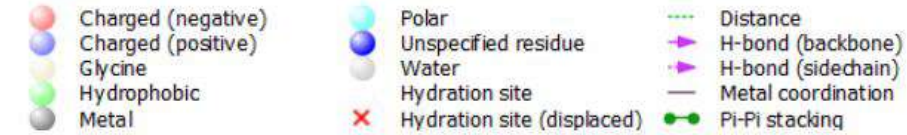
NOVEL CHEMOTYPES' 3D QSAR FINDINGS (COMPOUND 35-66)

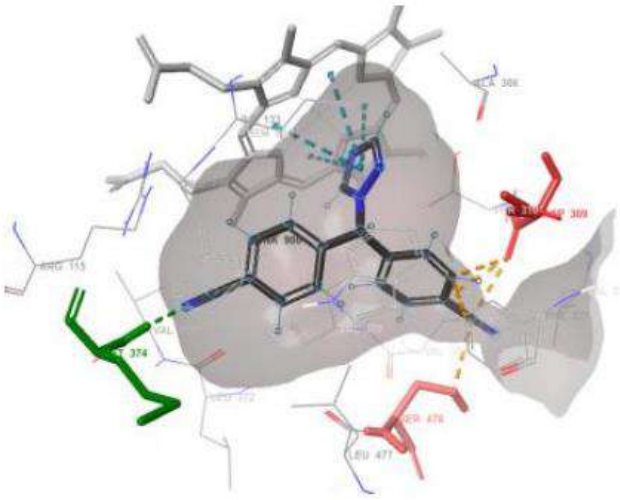
S.No.	Ligand	Predicted Activity	Align Score	Vector Score	Volume Score	Fitness
1	35	0.8697	0.043914	0.923434	0.553571	2.440411
2	36	-0.80296	0.256423	0.784339	0.442922	2.013576
3	37	-0.80296	0.2564	0.784376	0.454333	2.025042
4	38	-0.80296	0.256671	0.784165	0.457547	2.02782
5	39	-0.80296	0.256245	0.78448	0.456471	2.027413
6	40	0.737991	0.044625	0.923212	0.425	2.311024
7	41	0.852453	0.043946	0.923415	0.563636	2.450429
8	42	-0.73642	0.256497	0.784367	0.464115	2.034734
9	43	-0.73642	0.25638	0.784372	0.460808	2.03153
10	44	-0.70664	0.277472	0.772249	0.478673	2.019696
11	*4S*	0.800144	0.277472	0.712249	0.478673	2.0 19696
12	46	-0.7974	0.043947	0.92334	0.S70SS2	2.457269
13	47	-0.7974	0.25642	0.784365	0.468599	2.03928
14	48	-0.7974	0.256828	0.784019	0.454333	2.024329
15	49	-0.7670 1	*0.256095*	0.784621	0.465228	2.036436
16	*50*	0.965794	0.428475	0.805351	*0.5075*	l.955788
17	51	-0.47892	0.066766	0.949119	*0.566265*	2.459746
18	52	-0.81155	0.407089	0.839301	0.453488	1.953549
19	SJ	-0.69853	0.407735	0.839245	0.447005	1.946471
20	S4	-0.59219	0.40921	0.839001	0.45093.S	1.948927
21	*SS*	0.633341	0.406863	0.834213	0.44213	1.93729
22	S6	-0.66154	0.066775	0.9491	0.533851	2.477305
23	S7	*-0.654*	0.417373	0.760761	0.459135	l .872085
24	$8	--0.654	0.417764	0.839176	0.455399	1.95477 1
25	S9	-0.654	0.4-07765	0.839 1 27	0.46747	1.96()792
26	60	0.791436	0.4078	0.839162	0.472019	1 .971348
27	61	0.767623	0.044013	0.923331	0.561934	2.448587
28	62	-0.61032	0.066866	0.949051	0.582043	2.475373

4.2 Docking Results:

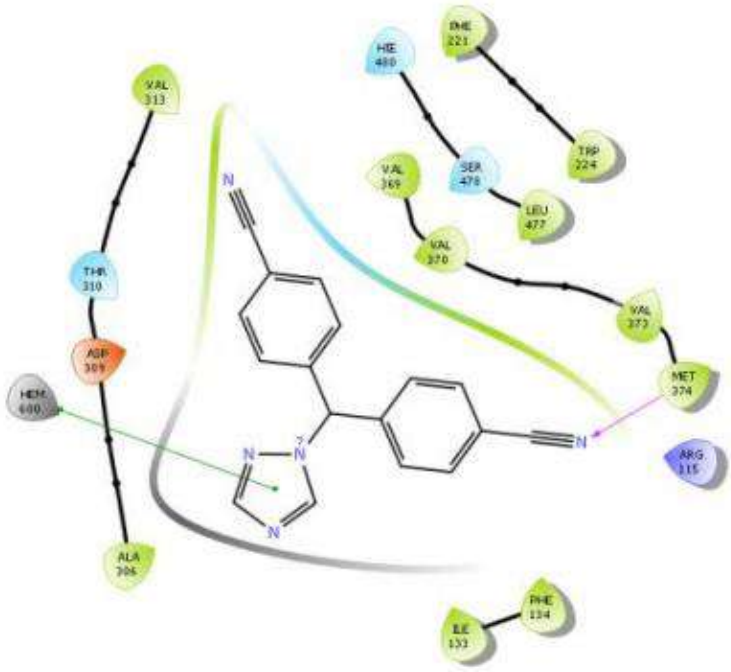
In order to enhance the interactions between ligands and receptors, the maestro workspace's Glide XP Visualiser was used to construct the active site surface mesh. Among the intriguing discoveries is the geometry of the aromatase receptor site. It resembles a standard iodine flask in appearance. The active cite is hydrophobic and has a conical entrance composed of L-phenylalanine 221 and L-Valine 313. The flat base of the flask, formed by the heme prosthatic group (grey), is essential for aromatisation because it provides electrons to the substrate.

Legend: Orange (charged-negative); Violet (charged-positive); Green (hydrophobic); Grey (metal); Sky blue (polar); (S) = Sinister configuration





Letrozole 3D docking



Letrozole 2D docking

4.3 Biological Activity:

4.3.1 In vitro anticancer screening:

The pharmacology department at Cairo University's National Cancer Institute conducted in vitro anticancer screening. This study utilized the MCF7 human breast tumor cell line. The cytotoxic activity of the newly synthesized compounds was assessed in vitro utilizing the Sulfo-Rhodamine-B stain (SRB) assay, as outlined by Skehan et al. The SRB test, established in 1990, is one of the most widely utilized methods for in vitro cytotoxic screening. This study evaluates SRB's binding

affinity for trichloroacetic acid (TCA)-fixed cell protein components on tissue-culture plates. Under mildly acidic conditions, the bright-pink aminoxanthene dye SRB interacts with basic amino acid residues; however, it dissociates in alkaline environments. The dye comprises two sulfonic groups.

Prior to treatment with the compounds under investigation, cells were permitted to adhere to the plate wall by being plated on a 96-well plate at a density of 10^4 cells per well for a duration of 24 hours. Three distinct wells were created for each concentration. The cells were incubated with the substance(s) for 48 hours at 37 ˚C in a 5% CO2 environment. After 48 hours, the cells were fixed, washed, and stained for 30 minutes using a solution of 0.4% (wt/vol) SRB in 1% acetic acid. Four washes with 1% acetic acid were required to remove the excess unbound color, followed by the application of Tris-EDTA buffer to restore the attached stain. The 570 nm wavelength was employed to measure color intensity in an ELISA reader.

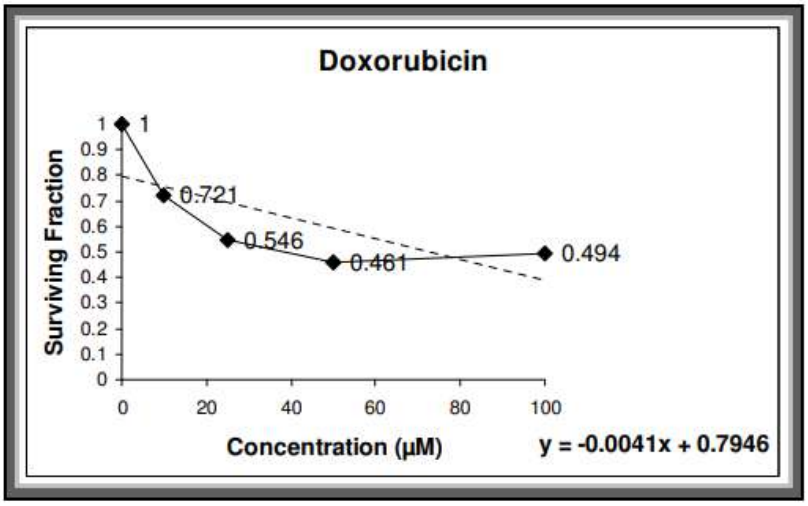


FIGURE 3: Time to death plot for doxorubicin

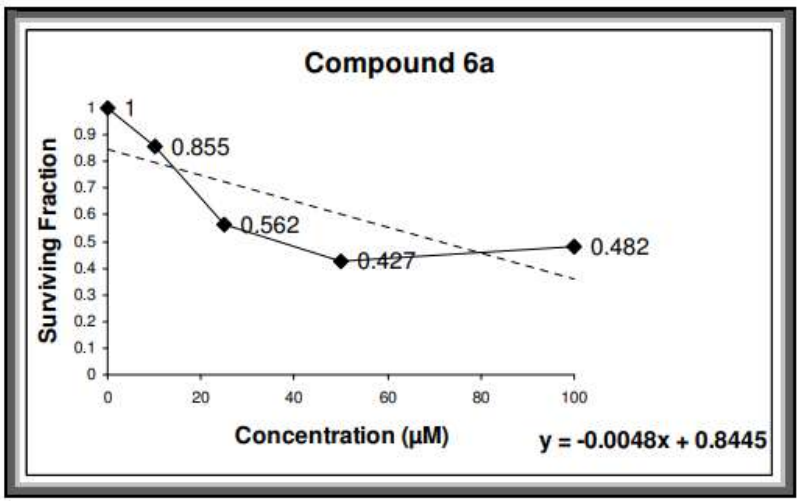


FIGURE 4: Time required for component 6a to degrade

V. CONCLUSION

This study focuses on recent advances in synthesizing anticancer derivatives that incorporate heterocyclic rings, emphasizing the development of targeted anticancer therapies. Anticancer medicines' pharmacokinetic and pharmacodynamic qualities are enhanced by the presence of heterocyclic moieties, which are found in the majority of medications. Approximately 30% of FDA-approved anticancer medications contain one or more heterocyclic rings that include oxygen, nitrogen, and sulfur. Heterocyclic moieties play a significant role in the metabolic reactions that are crucial for the survival of all living organisms. Approximately two-thirds of the anticancer medications approved by the FDA in the first half of the decade incorporated them, highlighting their pivotal role in cancer research and treatment efforts. Recent advancements in the

application of heterocyclic compounds as anticancer agents and innovative strategies for their development have been central to these efforts.

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Assessment of Wound Healing Potential of *Passiflora foetida* L. Stem in Streptozotocin-Induced Diabetes Mellitus

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Abstract— *The study investigates the wound healing potential of Passiflora foetida L. stem in a Streptozotocin (STZ)-induced diabetic rat model. Diabetes mellitus is a major contributor to delayed wound healing, and traditional plant-based treatments offer promising alternatives. In this experiment, diabetic wounds were induced in Wistar albino rats using STZ, and the healing process was evaluated following the topical application of Passiflora foetida L. stem extracts. The rats were divided into various treatment groups, with one group receiving the extract, while others were treated with a standard wound healing agent or a control. Parameters such as wound closure rate, histopathological changes, and biochemical markers associated with healing (collagen content, inflammatory mediators, and antioxidant levels) were assessed over a period of time. The results demonstrated a significant improvement in wound healing in the group treated with Passiflora foetida L. stem extract, showing accelerated wound closure and enhanced tissue regeneration compared to the control group. These findings support the traditional use of Passiflora foetida for wound healing and suggest that it may possess therapeutic potential for diabetic wound care. Further studies to isolate the active compounds and evaluate their mechanisms of action are warranted.*

Keywords— Passiflora foetida L, ethyl acetate extract, ethanol extract, Streptozotocin, antidiabetic acitivity.

I. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels and is associated with a range of complications, including impaired wound healing. In diabetic patients, wounds, particularly diabetic ulcers, often heal at a slower rate due to factors such as poor circulation, immune dysfunction, and prolonged inflammation. The delayed healing of wounds in diabetic individuals poses a significant challenge to both patients and healthcare systems, necessitating the exploration of new therapeutic strategies.

Passiflora foetida L., a species of the passionflower, is traditionally used in various cultures for its medicinal properties, including wound healing. The plant is known for its diverse phytochemical profile, which includes alkaloids, flavonoids, and terpenoids, all of which have demonstrated potential biological activities such as antioxidant, anti-inflammatory, and antimicrobial effects. Despite its historical use, scientific evidence supporting its efficacy in wound healing, particularly in diabetic conditions, remains limited.

Streptozotocin (STZ)-induced diabetes is a widely used experimental model that mimics the pathophysiological features of type 1 diabetes in humans, including delayed wound healing. This model provides a valuable platform to investigate the effectiveness of various therapeutic agents, including plant extracts, in enhancing the wound healing process.

This study aims to assess the wound healing potential of Passiflora foetida L. stem in STZ-induced diabetic rats. By evaluating parameters such as wound closure rate, histopathological changes, and biochemical markers of healing, we aim to provide scientific evidence supporting the traditional use of Passiflora foetida for treating diabetic wounds and to identify its potential as an alternative therapeutic option for managing diabetic ulcers.

II. MATERIALS AND METHODS

Streptozotocin (Sigma–Aldrich Canada, Oakville, Ontario, Canada). All other chemicals and reagents used were of analytical grade.

2.1 Reagents:

Buffer (pH 5): 50 g citric acid monohydrate, 12 ml glacial acetic acid, 120 g sodium acetate trihydrate, and 34 g sodium hydroxide added to distilled water up to 1000 ml.

2.2 Animals:

Wistar albino rats, weighing between 150–200 g, were used for the experiment. These rats were obtained from the disease-free small animal facility at Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar (Reg. No. 1669/GO/abc/12/CPCSEA Dated 08/04/2013). They were kept in pathogen-free conditions. The rats were housed, fed, and treated in accordance with international guidelines and principles for laboratory animal use and care. They were maintained in polypropylene cages under standard conditions (25±2°C, 12-hour light and dark cycle) and were provided with pelleted food (Purina), with tap water available ad libitum (Hedrich HH, 2006). The rats were acclimatized to the standard pellet diet and water for 2 weeks before the study began. All experimental procedures and protocols were approved by the Institutional Animal Ethics Committee, Department of Pharmaceutical Sciences, M.D. University, Rohtak (1767/GO/Re/S/14/CPCSEA, 18/07/2014).

2.3 Diabetes Induction:

2.3.1 Streptozotocin-induced diabetes mellitus:

After over night fasting, streptozotocin (STZ; 50 mg/Kg, i.p.) (Sigma–Aldrich Canada, Oakville, Ontario, Canada), prepared in citrate buffer (0.1M, pH 4.5), was administered to rats to induce diabetes (Junod A et al., 1969). 24 hours after the injection, fasting blood glucose levels were determined using a Glucometer (Accu-Chek® Extra Care, Roche Diabetes Care India Pvt. Ltd., 601B, Silver Utopia, Chakala Road, Andheri (East), Mumbai, Maharashtra) with glucose oxidase reagent strips after withdrawing blood from the retro-orbital plexus. Animals with a glucose level greater than 250 mg/dl were used for the study, 7 days after streptozotocin injection.

2.4 Diabetic Excision Model for Wound Healing Activity:

2.4.1 Surgical Procedures and Treatment:

On the 7th day after diabetes induction, excision wounds were created. These wounds were used for biochemical parameters study and for the rate of wound contraction. Using thiopentone sodium (40 mg/Kg i.p.), animals were anesthetized, and each rat was shaved from the right side. Ethanol 70% v/v was used for disinfection of the shaved area. From the shaved area on the dorsal middle line, excision wounds of size 4 cm^2 were made by cutting a 2 cm x 2 cm piece of skin. For 21 days, ethanol and ethyl acetate extracts in concentrations of 100 mg/Kg, 200 mg/Kg, and 400 mg/Kg were orally given. The control group received an equal amount of vehicle (citrate buffer).

2.5 Excision Wound:

The epithelialization time (Villegas LF et al., 1997) was noted when no raw wound was left behind and when the scar fell off. Excision wounds on a transparent paper with a millimeter scale were traced to determine the rate of wound contraction. The percentage of wound area healed was calculated using the change in wound size. The number of days taken for complete epithelialization was expressed as the period of epithelialization (when no raw wound was left behind).

2.5.1 Excision Wound Model:

As mentioned above, the excision wound model was performed. Parameters like percentage contraction in the wound, the period of epithelialization, and granulated tissue scar area were evaluated (Nayak BS et al., 2007). Every third day, photographs were taken, and the wound boundaries were traced on transparent paper to measure the area of wounds in all groups.

2.6 Parameters Monitored:

2.6.1 Rate of Wound Contraction:

At 0 days, before extract treatment and after wounding on days 3, 6, 9, 12, 15, and 18, excision wounds were traced on a transparent paper with a millimeter scale. On every third day, the change in wound size was calculated as the percentage of wound area that had healed. The percentage contraction of the wound was calculated using the formula:

$$\%\{\text{wound contraction}\} = (A_0 - A_t)\ /A_0 * 100 \quad (1)$$

Where (A_0) is the original wound area and (A_t) is the area of the wound at a specific time period after wounding (Yates CC et al., 2007; Rashed AN et al., 2003).

2.6.2 Epithelialization Period:

Epithelialization period is the number of days required for the scar to fall off without any raw wound left behind. The epithelialization period of the wound was expressed as the number of days taken for complete epithelialization (when no raw wound was left behind) (Dinesh M et al., 2010).

2.6.3 Animals Grouping:

Nine groups of animals, each consisting of six rats, were made. Rats were given extracts for 21 days. Among all the extracts, ethyl acetate and ethanol extracts were selected for the study of pharmacological activities. Ethyl acetate and ethanol extracts of different plant species showed the maximum number of potent chemical constituents determined by qualitative phytochemical analysis and chromatographic profiles. For these reasons, ethyl acetate and ethanol extracts in different doses were selected for further study. In the literature survey of plants, it is clearly mentioned that the above-mentioned two extracts are safe at a dose level of 2000 mg/Kg; the dose level was selected as 100 mg/Kg (1/20th), 200 mg/Kg (1/10th), and 400 mg/Kg (1/5th) of the safe dose, i.e., 2000 mg/Kg (Vikram PK et al., 2012; Bhide NK, 1962).

Group I: Standard (Metformin 5 mg/Kg)

Group II: Diabetic rats with wound without treatment (normal control group)

Group III: Diabetic rats without wound (for diabetes only)

Group IV: Diabetic rats with wound treated with ethyl acetate extract by oral route at a dose of 100 mg/Kg

Group V: Diabetic rats with wound treated with ethyl acetate extract by oral route at a dose of 200 mg/Kg

Group VI: Diabetic rats with wound treated with ethyl acetate extract by oral route at a dose of 400 mg/Kg

Group VII: Diabetic rats with wound treated with ethanol extract by oral route at a dose of 100 mg/Kg

Group VIII: Diabetic rats with wound treated with ethanol extract by oral route at a dose of 200 mg/Kg

Group IX: Diabetic rats with wound treated with ethanol extract by oral route at a dose of 400 mg/Kg

2.7 Statistical Analysis:

Wound area was measured as the percentage contraction in wound size. Analysis of data was performed using Dunnett's t-test with GraphPad Prism 7.0. When $P < 0.05$ compared with control, the data is considered significant.

III. RESULTS AND DISCUSSION

The oral dose of the ethyl acetate and ethanol leaves extracts of Passiflora foetida had shown a dose-dependent effect on the blood glucose level and wound healing effect on the diabetic rats.

On the 0th day, 7th day, and 14th day, there was a significant decrease in plasma glucose levels in the ethanolic extract at the dose levels of 200 mg/Kg and 400 mg/Kg. This activity may be due to the various chemical constituents present in the extract. The hypoglycemic activity is attributed to the presence of flavonoids in the ethyl acetate extract.

There was an increase in the percentage area of wound contraction from 30.12% to 93.14% and 24.73% to 85.81% respectively on the 12th day in the ethanolic and ethyl acetate extracts at the dose level of 400 mg/Kg. There was not much increase in the percentage contraction in the wound area at the lower doses (100 mg/Kg and 200 mg/Kg) in both the ethyl acetate and ethanol extracts.

Complete wound healing was shown by the ethyl acetate and ethanol extracts at the dose level of 400 mg/Kg on the 14th day. The 100 mg/Kg and 200 mg/Kg doses showed complete healing of the wound on the 18th day.

The present study reveals that the ethyl acetate and ethanol extracts accelerate the healing of wounds in diabetic rats. The results suggest that the extracts may have a beneficial effect on wound healing phases. It is quite possible that the increase in the healing of wounds in diabetic rats is due to the hypoglycemic activity (Rosenthal SP, 1968).

The study confirms the traditional use of *Passiflora foetida* stem for the treatment of diabetic wounds. This result motivates us to carry out an extensive study to isolate the responsible potent active chemical constituents and to better evaluate the diabetic wound healing activity of the plant.

3.1 Antidiabetic activity of stem of *Passiflora foetida* L. in streptozotocin-induced diabetes mellitus

TABLE 1
ANTIDIABETIC ACTIVITY OF STEM OF *PASSIFLORA FOETIDA* L. IN STREPTOZOTOCIN-INDUCED DIABETES MELLITUS

S. No	Group	Plasma glucose level(mg/dl)		
		0 day	7th day	14th day
1	Standard (Metformin)	275.83±4.945	151.66±3.626*	160.33±2.21*
2	Diabetic Control with wound	285.16±2.072	296.33±3.412	304.16±6.263
3	Diabetic Control without wound	281.66±5.420	284.16±4.490	285.00±5.721
4	Ethyl acetate extract 100mg/Kg	277.00±12.000	181.50±4.500*	185.00±7.000*
5	**Ethyl acetate extract 200 mg/Kg**	**280.00±5.000**	**162.50±6.500***	**165.50±11.500***
6	**Ethyl acetate extract 400 mg/Kg**	**286.50±3.500**	**158.50±5.500***	**163.50±7.500***
7	Ethanol extract100 mg/Kg	295.00±4.000	165.50±6.500*	168.03±3.000*
8	**Ethanol extract 200 mg/Kg**	**282.50±6.500**	**157.50±5.500***	**163.50±6.500***
9	**Ethanol extract 400mg/Kg**	**277.00±12.000**	**152.50±3.500***	**161.50±6.500***

Values are expressed as mean±SEM, n=6, p<0.05 versus diabetic control group (Dunnett'st-test after analysis of variances)

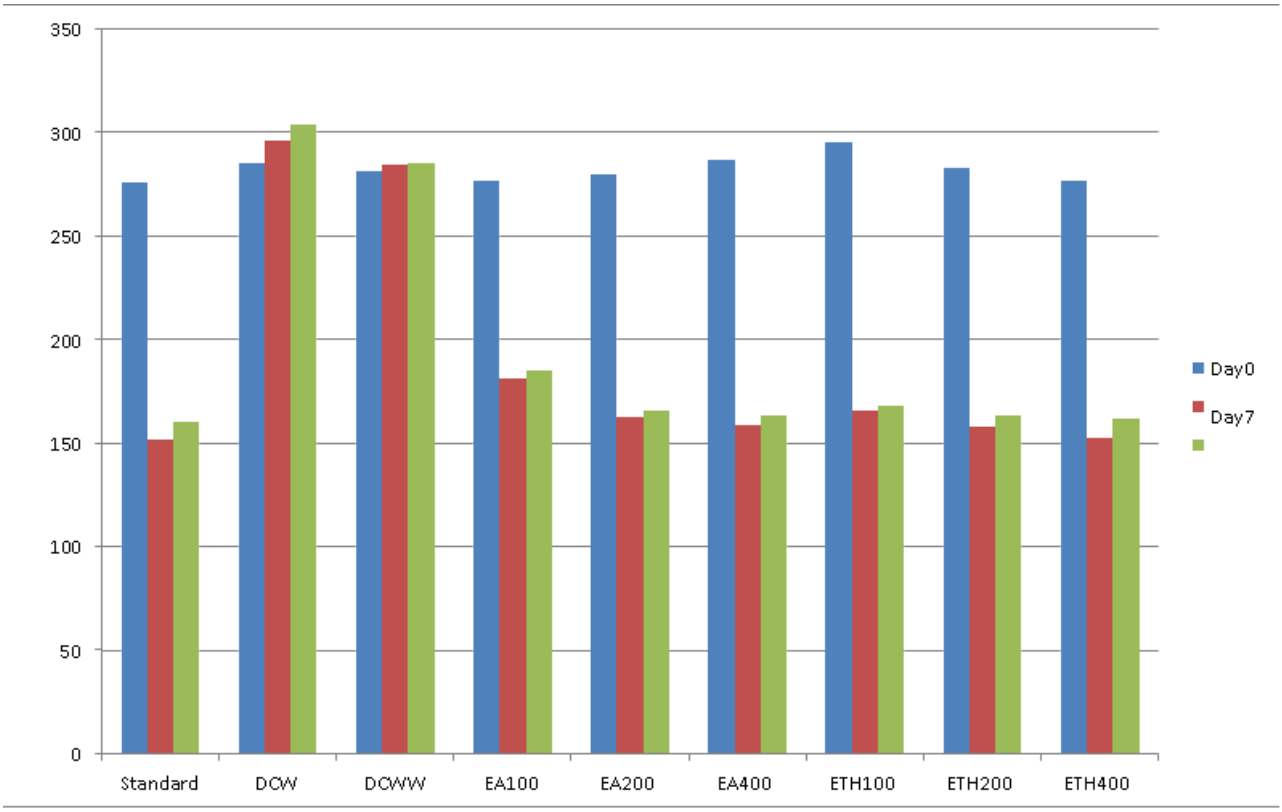

FIGURE 1: Effect of *Passiflora foetida* L. in streptozotocin-induced diabetes mellitus

TABLE 2

WOUND HEALING ACTIVITY OF STEM OF *PASSIFLORA FOETIDA* L. IN DIABETIC EXCISION MODEL

S. No.	Group	Percentage contraction in wound area							Epithelization period (in days)
		3rd day	6th day	9th day	12th day	15th day	18th day	21st day	
1	Standard (Metformin)	33.30±0.304	56.34±0.432*	78.71±0.354*	96.96±0.692*	100	100	100	14.86±0.307*
2	Control with wound	15.54±0.164	35.06±0.284	48.37±0.189	67.19±0.276	78.62±0.392	95.45±0.761	100	20.50±0.365
3	Ethylacetate extract 100 mg/Kg	20.35±0.350	44.58±0.145*	59.02±0.445*	77.06±0.300*	91.99±0.425*	100	100	17.50±0.50
4	Ethylacetate extract 200 mg/Kg	21.83±0.215	46.06±0.420*	62.10±0.055*	79.45±0.545*	95.79±0.415*	100	100	16.50±0.50*
5	Ethylacetate extract 400 mg/Kg	**24.73±0.005**	**52.83±0.315***	**74.23±0.500***	**85.81±0.035***	**100**	**100**	**100**	**14.50±0.50***
6	Ethanolextract extract 100 mg/Kg	23.71±0.285	43.11±0.110*	67.09±0.090*	81.36±0.640*	92.09±0.090*	100	100	17.50±0.50
7	Ethanolextract extract 200 mg/Kg	27.73±0.175	54.72±0.410*	73.28±0.315*	87.95±0.145*	93.70±0.	100	100	17.50±0.50
8	Ethanolextract extract 400 mg/Kg	**30.12±0.120**	**55.71±0.770***	**78.47±0.470***	**93.14±0.510***	**100**	**100**	**100**	**14.00±0.00**

Values are expressed as mean ± SEM, n=6,p<0.05 versus diabetic control group (Dunnett'st-test after analysis of variances)

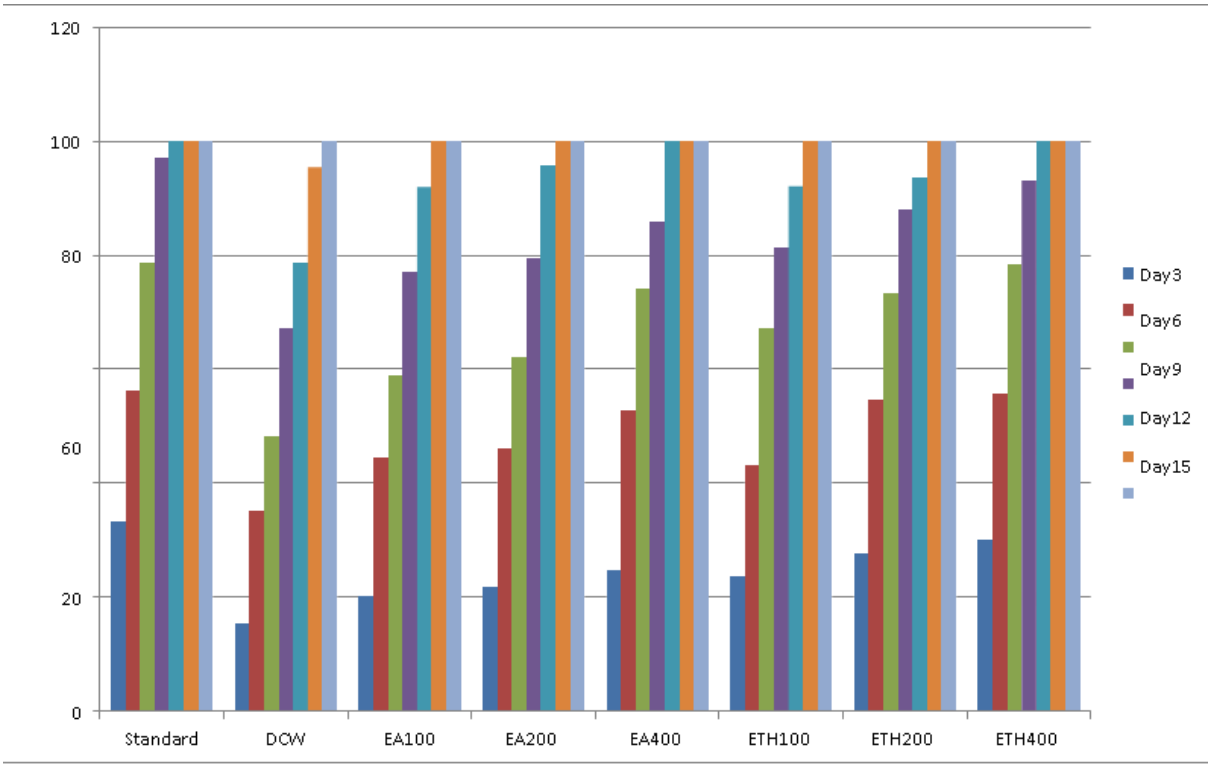

FIGURE 2: Wound healing activity of *Passiflora foetida* L. in diabetic excision model.

IV. CONCLUSION

This study demonstrates that the ethyl acetate and ethanol extracts promote faster wound healing in diabetic patients. The findings indicate that these extracts may positively influence various phases of wound healing. It is likely that the improved wound healing in diabetic rats is attributed to the hypoglycemic effects (Rosenthal SP, 1968).

The study supports the traditional use of Passiflora foetida leaves for treating diabetic wounds. This outcome encourages further research to isolate the active chemical components responsible and to more thoroughly assess the plant's effectiveness in promoting diabetic wound healing.

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