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STUDY OF COMPUTER-BASED MOLECULAR DOCKING OF AEGLE MARMEOLES LINN (BEAL PLANT) AND MORINGA OLEIFERA IN DRUG DESIGN AND DEVELOPMENT

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ABSTRACT

Background: Type 2 diabetes mellitus is a chronic condition characterized by insulin resistance and elevated blood glucose levels. *Aegle marmelos* (Bael) and *Moringa oleifera* (Moringa) are medicinal plants known for their antidiabetic properties. However, their bioavailability in raw form is limited, hindering their effectiveness. Polyherbal formulations may improve bioavailability and enhance therapeutic outcomes in diabetes management. **Methods:** This study aimed to evaluate the antidiabetic potential of *Aegle marmelos* and *Moringa oleifera* through molecular docking, antioxidant activity assessment, and α-amylase inhibition. Hydroalcoholic extracts of both plant leaves were prepared and analyzed for their interaction with GSK-3 and GLP-1 enzymes via molecular docking. Antioxidant activity was assessed using the DPPH free radical scavenging assay, and α-amylase inhibition was determined using the 3,5-dinitrosalicylic acid method. Polyherbal tablets were formulated using the extracts by the direct compression method and evaluated for physical properties such as hardness, friability, and disintegration time. **Results:** Molecular docking revealed strong inhibitory interactions between plant compounds and both GSK-3 and GLP-1, suggesting their potential as natural antidiabetic agents. The antioxidant assays demonstrated significant radical scavenging activity, while the α-amylase inhibition test confirmed the extracts' ability to regulate blood glucose levels. The polyherbal tablets exhibited favourable physical characteristics and showed notable antidiabetic activity. **Conclusion:** This study highlights the potential of *Aegle marmelos* and

Moringa oleifera as natural inhibitors for managing type 2 diabetes. The polyherbal tablet formulation offers a promising strategy to enhance bioavailability and efficacy, paving the way for further exploration in diabetes treatment.

KEYWORDS: Aegle marmelos, Moringa oleifera, Natural inhibitors, Antioxidant activity, GSK-3, GLP-1, Polyherbal tablet, Type 2 Diabetes.

1. INTRODUCTION

Diabetes mellitus is a heterogeneous and chronic metabolic disorder characterized by persistent hyperglycemia, resulting from inadequate insulin production, impaired insulin action, or both. It disrupts the normal metabolism of carbohydrates, proteins, and lipids, leading to long-term complications such as cardiovascular diseases, nephropathy, neuropathy, and retinopathy. Diabetes mellitus is primarily classified into three types: Type 1 diabetes (T1DM), Type 2 diabetes (T2DM), and gestational diabetes, with T2DM being the most prevalent, accounting for approximately 95% of all diabetes cases worldwide. The global prevalence of diabetes has reached alarming rates, with over 422 million people affected and more than 25,000 deaths annually attributed to the disease. Pre-diabetes, a condition characterized by elevated blood glucose levels that do not yet meet the criteria for diabetes diagnosis, and rare forms of diabetes, such as monogenic and drug-induced diabetes, further contribute to the growing health burden of diabetes globally.

T1DM is an autoimmune disorder where the body's immune system attacks the insulin-producing pancreatic beta cells, rendering individuals incapable of producing insulin. This form of diabetes typically manifests in childhood or adolescence, although it can develop at any age. Insulin therapy is essential for managing T1DM, as patients require external insulin administration to regulate their blood glucose levels. On the other hand, T2DM is characterized by insulin resistance and insufficient insulin production, often exacerbated by obesity, sedentary lifestyle, and poor dietary habits. T2DM is commonly seen in middle-aged and older adults and is associated with metabolic syndrome. Over time, individuals with T2DM may develop beta-cell dysfunction, leading to the need for insulin therapy to control blood glucose levels effectively.

The escalating prevalence of diabetes has made it a major global health concern, particularly in low- and middle-income countries, where access to effective and affordable treatments remains a significant challenge. Conventional treatments, such as insulin and oral

hypoglycemic agents, are widely used to manage blood glucose levels; however, these therapies often have limitations in terms of efficacy, side effects, and accessibility. As a result, there has been a growing interest in alternative and complementary approaches, particularly the use of medicinal plants, to manage diabetes. Many medicinal plants, such as *Aegle marmelos* (Bael) and *Moringa oleifera* (Moringa), have demonstrated antidiabetic properties due to their bioactive compounds, including alkaloids, flavonoids, glycosides, and terpenoids, which exert beneficial effects on glucose metabolism by inhibiting key enzymes involved in carbohydrate digestion and absorption.

Despite the therapeutic potential of these plants, one major challenge lies in the bioavailability of their active compounds when consumed in raw form. To address this issue, polyherbal formulations have gained popularity as they combine multiple plant-based compounds to enhance the therapeutic effects while overcoming individual plant limitations. Polyherbal formulations, when developed using optimized extraction methods, may provide better bioavailability and synergistic effects, offering a promising alternative to conventional antidiabetic therapies. This research aims to investigate the potential of *Aegle marmelos* and *Moringa oleifera* in managing Type 2 diabetes mellitus by exploring their antidiabetic properties, molecular interactions through docking studies, and the development of polyherbal formulations. Through in vitro evaluation of antioxidant activity, enzyme inhibition, and molecular docking, this study seeks to contribute valuable insights into the role of medicinal plants in the management of diabetes and the development of natural therapies with enhanced efficacy and safety.

2. MATERIAL AND METHODOLOGY

2.1 In Silico Screening

The study commenced with an extensive literature review to identify medicinal plants known for their reported antidiabetic properties. The literature review shows that Aegle marmeoles linn (Beal Plant), *Moringa oleifera* (Moringa or drumstick tree) medicinal plants have antidiabetic properties independently

2.1.1 Target selection*:*

Gsk-3 [PDB ID-4IQ6], GLP-1 [4ZGM] enzyme inhibition was used as target protein for effect of anti-diabetes. The Gsk-3 as well GLP-1 enzyme inhibition was used as target protein for the effect of antidiabetic.

2.1.2 Ligands selection

The selection of ligands for docking studies was based on a comprehensive literature survey identifying phytoconstituents with known antidiabetic properties. More than 15 bioactive molecules derived from medicinal plants were chosen for their potential antidiabetic effects. For Aegle marmelos Linn. (Beal plant), the selected phytoconstituents included arecoline, arecaidine, baicalin, ellagic acid, luteolin, rutin, myricetin, caryophyllene, cineol, p-cymene, and quercetin. Similarly, for Moringa oleifera (drumstick tree), the phytoconstituents selected were 1,3-dibenzyl urea, aruantiamide, kaempferol, and myricetin. These compounds were selected for their reported efficacy in modulating key pathways involved in the management of diabetes, including inhibition of enzymes like α-amylase and glucagon-like peptide-1 (GLP-1), and their antioxidant potential. The chosen phytochemicals were further evaluated through molecular docking studies to assess their binding affinity and potential as effective inhibitors of GSK-3 and GLP-1, thus contributing to the exploration of natural therapeutic alternatives for diabetes management.

2.1.3 Target preparation

The receptor-associated proteins for the pertinent enzyme were acquired by using the database RCSB PDB (www.rcsb.org). For Glucagon-like peptide-1 [PDB ID: 4ZGM] complexed with semaglutide, glycogen synthase kinase-III [PDB ID: 4IQ6] complex with 6-chloro-Ncyclohexyl-4-(1H-pyrrolo[2,3-b] pyridin-3-yl) pyridin-2-amine are the 3D structure of these enzymes. Protein structure was prepared using Biovia Discovery studio 2021 software where the reference ligand molecule was deleted for the creation of cavity by deleting water molecules and adding polar hydrogen atoms.

2.1.4 Ligand preparation

A total of 15 phytochemical molecules were selected as ligands for docking studies, based on their reported antidiabetic activity. These phytochemicals were subjected to ligand-protein docking to evaluate their binding affinity and interaction with target receptor proteins. The receptor proteins chosen for the docking study were GSK-3 (PDB ID-4IQ6) and GLP-1 (PDB ID-4ZGM), both of which are key enzymes involved in diabetes pathophysiology. The selected phytoconstituents were sourced from the PubChem database, where their three-dimensional structures and SDF (Structure Data File) formats were retrieved for computational modeling. The molecules were then docked against the respective receptor proteins using standard molecular docking software to determine the most favorable

interactions and potential binding modes. This method allows for a detailed analysis of the phytochemicals' ability to inhibit the target proteins, offering insights into their potential efficacy as antidiabetic agents.

2.1.5 Molecular Docking

The 15 molecules were docked against target protein receptor using PyRx 0.8 software. A sizable macromolecule functions as the location where targets attach, and the objective of molecular docking is to predict how a ligand molecule will position itself, interact, and adopt a particular shape within that specific area. All of the ligand compounds are downloaded in SDF format from PubChem. The ligands were then used for molecular docking after being translated to PDB QT format using PyRx's open babel plugin. In next step from Vin wizard select a macromolecule then select the ligand molecules then click on start button the docking of ligand -protein get started. After completion of molecular interaction, we get a excel sheet of molecular binding affinity.

2.1.6 Docking analysis

The interactions of selected ligand molecules and considering their binding affinity, ligand interactions were screened using BIOVIA Discovery studio 4.0 where the analysis which included H-bond, Pi-stacking, Pi cation and C-H interactions. It looked into how the amino acid residue within the receptor’s molecule along with the functional components of the recently acquired ligands separated. The compounds of herbs with highest negative score in docking exhibited good activity against diabetes were selected.

2.2 Collection and Drying of Herbs:

The *Aegle marmeoles linn* (Leaves), *Moringa oleifera* (Leaves) was collected from Teurwadi and Nesari (Kolhapur). Furthermore, the gathered plants were cleansed and left to air-dry in the shade, following which they were mechanically pulverized.

2.3 Preparation of Extract

The maceration extraction process was employed to obtain the bioactive compounds from powdered herbal materials. Each herb was macerated individually using different solvents, including ethanol, water, and a 50:50 water-ethanol ratio, for a duration of 72 hours with periodic agitation to ensure efficient extraction. After the extraction period, the mixtures were filtered to remove any solid residues, and the resulting filtrates were carefully collected and preserved for further analysis. This method allows for the extraction of a wide range of

phytochemicals, which can be analyzed for their potential antidiabetic properties and bioactivity in subsequent studies. The solvent choices were made based on their ability to extract a diverse array of bioactive constituents from the herbs.

2.4 Phytochemical Screening

Qualitative analysis of phytoconstituents, including alkaloids, phenols, carbohydrates, tannins, and flavonoids, was conducted using standard procedures outlined in the literature. These methods involved specific chemical reactions and tests to identify and confirm the presence of these bioactive compounds, which are known for their therapeutic potential in managing diabetes.

2.5 Development of Polyherbal Tablet Formulation

The development of the polyherbal tablet formulation involved the extraction of bioactive compounds from selected medicinal plants using appropriate solvents. The extracts were then subjected to lyophilization, a freeze-drying process that removes moisture and converts the extract into a solid, stable powder. This method ensures the preservation of the active ingredients and enhances the shelf-life of the formulation. The lyophilized powder was then mixed with excipients, such as binders and disintegrants, to facilitate tablet formation. The mixture was compressed into tablets using standard tablet compression techniques, ensuring consistent quality and efficacy for therapeutic use.

2.6 Evaluation of Tablet formulation

From the above-prepared batches, one of the batches was optimized by using the response factors drug release at different time interval and hardness. To ascertain the drug release profile, a disintegration study was conducted. Meanwhile, by utilizing a Monsanto hardness tester, the formulation's hardness was gauged. Also check friability. Results obtained from statistical analysis of factorial design are implied to optimize one of the batches depending on response variables.

2.6.1 Weight variation: According to IP, BP, and USP, this method was performed on 20 randomly selected tablets by determining the average weight and comparing it to the individual tablet. Weight variations is given as a percentage deviation.

Formula,

Weight variation= Individual wt. of tablet/ avg. wt. of tablet x 100

✓Acceptance Criteria:

As per IP and BP specification in mg	As per USP specification in mg	Percentage Deviation %
80 mg or less	130 mg or less	±10 %
More than 80 and less than 250	More than and less than 324	± 7.5%
250 mg or more	324 mg or more	± 5%

2.6.2 Friability: To determine how friction and shock, which frequently result in chipping, capping, or breaking of tablets, affect them, a friability test was conducted. When a tablet is subjected to mechanical shock, a phenomenon known as surface damage or breakage can occur. The weight loss of compressed tablets shouldn't be greater than 1% w/w (Indian Pharmacopoeia, 1996). The Roche Friabilator was used in this test to measure weight loss.

The percentage (%) of friability is used to express it.

2.6.3 Thickness test: The tablet's thickness is determined by the compressing movement's lower & upper punch. Device for measuring vernier caliper thickness. Thickness measured by keeping tablet in vernier caliper. Acceptable limit ± 5% variation of standard.

2.6.4 Hardness: Using a Monsanto hardness tester, which uses a spring to apply pressure to the tablet in a diametrically opposed manner, the degree of hardness was assessed. A triplicate analysis was performed after the tester was initially set to zero. Acceptable limit 2.5 to 5 kg / cm^2.

2.6.5 Disintegration time: The disintegrating test measured how long it took for the tablet to break up into pieces; the disintegration testing only measured how long it took for a batch of tablets to break up into pieces under a certain set of circumstances. The purpose of this experiment is to determine how quickly tablets disintegrate. Six pills, one for each glass tube with stimulating gastric juice, are used to conduct this test.

2.6.6 Dissolution test: Utilizing a type-II dissolution test device from the US Pharmacopoeia (USP), in vitro dissolution was conducted. The solubility and stability test findings were used to determine the best 0.1N HCL to use as the dissolution media. The tablets were dissolved for 60 minutes in a dissolving media that had been heated to 37 0.5°C. The experiment was conducted using apparatus 2 (paddle), 500 millilitres of 0.1 M HCl , 50 rotation per minute stirring speed, at 37±0.5 ºC temperature. For the assay of total flavonoids, 50 mL aliquots were collected by hand at 0, 10, 20, and 30 minutes. They were then filtered and subjected to spectrophotometry at 401 nm following the reaction, applying the equation. where MF% is total flavonoids percentage in the dissolving media, TF% is total flavonoids percentage in the

herbal products examined. Q is the number of total flavonoids dissolved about the entire flavonoids within the herbal product assays.

3. RESULT AND DISCUSSION

3.1 In Silico Screening

3.1.1 Target Selection

The target proteins for the study were GSK-3 (PDB ID: 4IQ6) and GLP-1 (PDB ID: 4ZGM), both of which play pivotal roles in the pathophysiology of diabetes. These enzymes were selected for their significant involvement in glucose metabolism and regulation, making them ideal targets for potential antidiabetic agents.

3.1.2 Ligand Selection

Following an extensive literature survey, 15 bioactive phytochemicals with known antidiabetic properties were selected from medicinal plants such as *Aegle marmelos* (Beal Plant) and *Moringa oleifera* (Drumstick Tree). The selected compounds included arecoline, arecaidine, baicalin, ellagic acid, luteolin, rutin, myricetin, caryophyllene, cineol, p-cymene, quercetin, 1,3-dibenzyl urea, aruantiamide, kaempferol, and myricetin. These compounds were chosen based on their ability to modulate key enzymatic pathways, including α-amylase inhibition and enhancement of GLP-1 activity, contributing to their potential antidiabetic effects.

3.1.3 Target Preparation

The 3D structures of the receptor proteins were obtained from the RCSB Protein Data Bank. The GLP-1 complexed with semaglutide (PDB ID: 4ZGM) and GSK-3 complexed with a specific inhibitor (PDB ID: 4IQ6) were selected for docking studies. The receptor proteins were prepared using Biovia Discovery Studio 2021, where the reference ligand molecules were deleted, water molecules removed, and polar hydrogen atoms added to create binding cavities for ligand docking.

3.1.4 Ligand Preparation

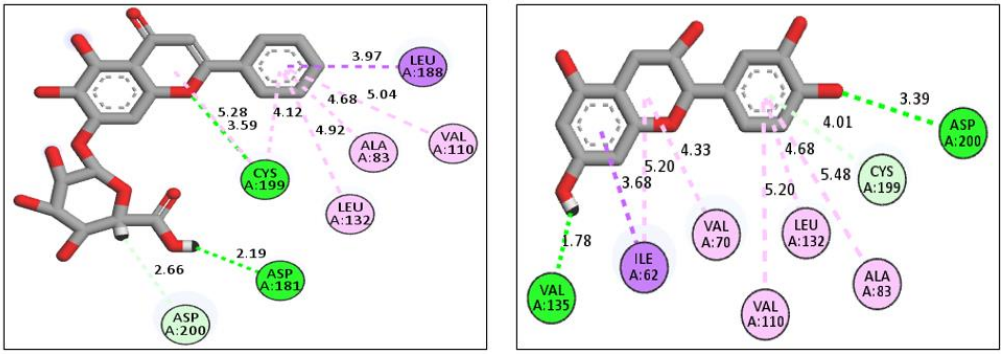
The 15 selected phytochemicals were retrieved in SDF format from the PubChem database for docking studies. These molecules were subjected to ligand-protein docking analysis to evaluate their binding affinity and interactions with the target receptor proteins. The compounds' 3D structures were prepared and optimized for docking analysis, providing insight into their potential as inhibitors of GSK-3 and GLP-1 enzymes.

3.1.5 Molecular Docking

Molecular docking was performed using PyRx 0.8 software, with ligands converted to PDB QT format using the open babel plugin. The ligands were docked against the target proteins GSK-3 and GLP-1, and the binding affinities were computed. The docking analysis predicted the positioning and interaction of each ligand within the binding site of the target proteins. The results were then analyzed to determine the most favorable docking conformations and interactions.

3.1.6 Docking Analysis

Docking results were analyzed using BIOVIA Discovery Studio 4.0, which provided detailed insights into the ligand-receptor interactions, including hydrogen bonds, π-stacking, π-cation interactions, and C-H interactions. The compounds that exhibited the highest negative docking scores, indicating strong binding affinities, were identified as potential inhibitors of GSK-3 and GLP-1 enzymes. These compounds were considered to have significant antidiabetic activity, and their potential as therapeutic agents was further evaluated. Here is result of best 2 docking molecules Baicalin and Luteolin in fig.



3.2 Preparation of Extract

The maceration extraction method successfully yielded bioactive compounds from the powdered herbal materials. The herbs were individually macerated with solvents (ethanol, water, and a 50:50 water-ethanol ratio) for 72 hours with periodic agitation. The resulting extracts were filtered to remove solid residues, and the filtrates were collected and preserved for further analysis. This extraction approach facilitated the extraction of a broad spectrum of phytochemicals, which were subsequently analyzed for their potential antidiabetic properties. The solvent selection ensured the extraction of a diverse range of bioactive constituents, enhancing the study's ability to explore the herbs' therapeutic potential.

3.3 Phytochemical Screening

The phytochemical screening of the herbal extracts revealed the presence of various bioactive constituents known for their potential therapeutic properties. Qualitative tests indicated the presence of alkaloids, phenols, carbohydrates, tannins, and flavonoids in the extracts of both Aegle marmelos (Beal plant) and Moringa oleifera (Drumstick tree). The identification of these compounds suggests that the selected herbs contain a diverse array of phytochemicals, which may contribute to their antidiabetic and antioxidant activities. These findings provide a foundation for further investigation into the medicinal potential of these plants in managing diabetes and related conditions.

Sr. No.	Test		Extracts		
			Tridax procumbens linn	Catharanthus roseus	Tinospora cardifolia
1	Alkaloids:	Dragendroff	+	+	+
		Hager's Test	+	+	+
2	Phenols: Ferric chloride test		+	+	+
3	Flavonoids	Alkaline Reagent Test	+	-	+
		Lead acetate Test	+	+	+
4	Tannins: Ferric chloride test		+	+	+
5	Carbohydrate:Benedict's test		+	+	+

3.4 Development of Polyherbal Tablet Formulation

The development of the polyherbal tablet formulation involved the extraction of bioactive compounds from selected medicinal plants, followed by lyophilization to preserve the active ingredients and enhance stability. The lyophilized powder was combined with excipients, including binders and disintegrants, to facilitate tablet formation. Compression of the mixture resulted in uniform, high-quality tablets, ensuring consistency in dosage and therapeutic efficacy. This formulation approach, utilizing lyophilized extracts, optimizes the stability and bioavailability of the bioactive compounds, making the tablets a promising candidate for antidiabetic therapy.

3.5 Evaluation of Tablet formulation

3.5.1 Weight variation: A weight variation test is performed to guarantee that all of the tablets manufactured have the same weight. The average tablet weight ranges from 499.8 mg to 500.1 mg. According to IP, there is no weight on the tablet that deviates from the mean weight by more than the indicated percentage.

3.5.2 Friability: The Roche Friabilator instrument was employed to assess the tablet's friability. Friability is a phenomenon that identifies surface damage or shows the location of mechanical shock damage on a tablet. The friability of the tablet was determined to be 0.18%, which corresponds to the IP's criterion of less than 1% drop in tablet friability.

3.5.3 Hardness: The Monsanto hardness tester was employed to figure out the tablet's hardness. The tablet hardness is changed from 4.7 to 5.1 kg/cm2, which is within the typical range of oral tablet hardness. The hardness of the table was tested to see if they could withstand the stress and strain of production and transportation. With the help of hardness, we may change the pressure on the tablet hardness machine to produce the appropriate tablet hardness. The tablet's hardness is significant because it impacts its disintegration; if a tablet is excessively hard, it will not disintegrate in the desired period.

3.5.4 Disintegration time: A disintegration test was performed on the tablet using a USP-compliant disintegration instrument. The dissolution of the dose form is the first physical change that is detected after it enters the body. All batches of tablets dissolve within 6–7 minutes, which meets the IP criteria for the disintegration test.

3.5.5 Dissolution test: The USP type II apparatus was employed for studying the in vitro dissolution of the prepared polyherbal tablets. It was operated at 37 °C with 50 rpm of rotations. A phosphate buffer solution with a pH of 6.8 & 0.1N HCl was used as the medium for dissolution in a volume of 900 mL. Releasing within the pill was carried out in 0.1N HCl for the first two hours, while for the remaining period, phosphate buffer pH 6.8 was used. It was examined at a wavelength of 275 nm using a UV-visible spectrophotometer. A comparison was conducted between the commercially marketed tablets and the produced tablets. A prepared, optimized commercialized tablet displayed 90.03 percent DR at 24 hours, while a marketed tablet had 94.21% DR at the same time. Plotting of the cumulative DR vs. time graph was done.

Batch Name	Hardness (Kg/cm2)	Friability (%)	Weight Variation (%)	Disintegration Time (sec)
Polyherbal Tablet	5± 0.2	0.18 %	0.47± 0.05	420± 0.11

4. CONCLUSION

The in silico screening of bioactive phytochemicals from Aegle marmelos (Beal Plant) and Moringa oleifera (Drumstick Tree) demonstrated the potential of these compounds as effective inhibitors of GSK-3 and GLP-1, key enzymes involved in diabetes pathophysiology.

Molecular docking studies revealed Baicalin and Luteolin as the most promising antidiabetic agents based on their strong binding affinities and favorable interactions with the target proteins. The maceration extraction method successfully yielded bioactive compounds, which were then subjected to phytochemical screening, confirming the presence of alkaloids, phenols, carbohydrates, tannins, and flavonoids, known for their therapeutic benefits.The polyherbal tablet formulation, utilizing lyophilized extracts, demonstrated excellent stability, with promising physical characteristics including uniform weight, low friability (0.18%), appropriate hardness (4.7-5.1 kg/cm²), and rapid disintegration time (6-7 minutes). The dissolution studies showed that the tablet achieved satisfactory drug release, with a 90.03% release after 24 hours, demonstrating its potential as a therapeutic candidate. The formulation successfully met all quality control standards, indicating its suitability for further development and potential as an antidiabetic therapeutic. This study highlights the potential of combining traditional plant medicine with modern pharmaceutical techniques to develop novel, effective treatments for diabetes management.

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