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Exploring the potential of *Laurus nobilis* as activators of insulin receptor activity

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Diabetes mellitus, a chronic metabolic disorder characterized by insulin resistance and impaired glucose metabolism, highlights the need for novel therapeutic agents with minimal side effects. Natural compounds from medicinal plants have gained attention as safer alternatives. *Laurus nobilis* (bay laurel) , traditionally used to treat digestive, respiratory, and skin ailments, holds untapped potential in diabetes management through insulin receptor activation. This study explored the drug-likeness, ADMET properties, molecular docking, and bioactivity of *Laurus nobilis* phytochemicals to evaluate their potential as insulin receptor activators. Ethanolic extracts were assessed for *In vitro* anti-diabetic activity, followed by computational analysis of 40 phytochemicals from the IMPPAT database. Drug-likeness was evaluated using Lipinski's Rule of Five *via* the SwissADME web server, while ADMET analysis provided pharmacokinetic insights. Molecular docking performed with PyRx (AutoDock Vina) and bioactivity prediction via the PASS web server identified 9 phytochemicals, including delta-cadinene, beta-selinene, epsilon-muurolene, beta-caryophyllene, and gamma-cadinene, exhibiting favorable binding affinities and interactions with key residues such as Met1103, Ala1055, Leu1105, and Val1037, comparable to the control drug, doxorubicin. ADMET analysis confirmed favorable pharmacokinetic properties, with all 9 compounds identified as non-BBB permeants. Bioactivity predictions indicated insulin promoter activity in 8 compounds, excluding beta-selinene. These findings suggest that *Laurus nobilis* phytochemicals have potential as natural insulin receptor activators, offering a promising avenue for diabetes management. Further *In vitro* and *in vivo* studies are required to validate their efficacy and bioavailability.

Keywords: Anti-diabetic, Bioactivity, Diabetes, Drug-likeness, Insulin, Molecular docking, Phytochemicals

Diabetes mellitus, a chronic metabolic disorder characterized by impaired insulin signaling and glucose homeostasis, continues to pose significant public health challenges worldwide. With over 537 million adults affected by diabetes globally, the need for novel therapeutic strategies has become more urgent than ever[1,2]. Insulin resistance, the primary defect in Type 2 Diabetes Mellitus (T2DM) , is associated with reduced insulin receptor (INSR) activity, leading to poor glucose uptake by cells[3]. Current treatments primarily focus on increasing insulin sensitivity or augmenting insulin production, but the long-term use of synthetic drugs often comes with side effects[4-6]. This has led researchers to explore natural alternatives, including phytochemicals, for their potential to modulate insulin receptor activity.

Laurus nobilis, commonly known as bay laurel, has been traditionally used in folk medicine for treating various ailments, including diabetes[7]. The plant is rich in bioactive compounds such as sesquiterpenes and phenolics, which have demonstrated anti-inflammatory, antioxidant, and antidiabetic properties in previous studies[8,9]. However, the specific potential of *Laurus nobilis* phytochemicals to activate insulin receptors and modulate glucose metabolism remains underexplored.

Recent advancements in computational biology have enabled the efficient screening of natural compounds for their drug-likeness, bioactivity, and molecular interactions[10,11]. *In silico* methods such as molecular docking, ADMET analysis and bioactivity prediction tools provide valuable insights into compounds' therapeutic potential before conducting costly and time-consuming laboratory experiments. These approaches have become especially useful in identifying natural compounds that could serve as insulin receptor activators.

This study aims to explore the potential of phytochemicals from *Laurus nobilis* as activators of insulin receptor activity using a combination of molecular docking, drug-likeness evaluation, and bioactivity prediction. By focusing on the insulin receptor's role in glucose metabolism and assessing

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the binding affinities of key *Laurus nobilis* compounds, this research seeks to uncover novel therapeutic candidates for improving insulin sensitivity and managing T2DM. The findings may pave the way for developing more effective and safer plant-based treatments for diabetes.

Materials and Methods

Plant collection, authentication and sample preparation:

Fresh ***Laurus nobilis*** leaves were collected, and authenticated byDr.Lakshmi Narasimhan, Botanist Former Dean, A. Veeriya Vandayar Memorial Sri Pushpam College, Poondi, and dried in the shade at room temperature (20-25°C). The dried leaves are then ground into a fine powder. The powdered material was subjected to extraction using ethanol as a solvent in a Soxhlet apparatus. The ethanolic extract is concentrated under reduced pressure using a rotary evaporator to obtain a semi-solid mass, which was stored at 4°C for further use.

The *Laurus nobilis* ethanolic extract (LNEE) stock solutions are prepared by dissolving the extract in dimethyl sulfoxide (DMSO). Working concentrations of 50, 100, 200, 400, and 800 µg/mL are prepared by serial dilution.

***In vitro* anti-diabetic activity**

In vitro α-amylase inhibition assay

This assay evaluates the anti-diabetic potential of ***Laurus nobilis*** ethanolic extract (LNEE) follows a slightly modified method based on **Ononamadu CJ (2019)** [12]. In this procedure, porcine pancreatic α-amylase (0.5 mg/mL) is prepared in a phosphate buffer (20 mM, pH 6.9) , while a 1% starch solution is used as the substrate. Different concentrations of LNEE (25 µL) are mixed with 50 µL of the α-amylase enzyme in a 96-well plate and pre-incubated at 37°C for 10 min. Subsequently, 25 µL of starch solution is added, and the reaction mixture is incubated for another 10 min at 37°C. To stop the reaction, 100 µL of DNS (dinitrosalicylic acid) reagent is added, and the mixture is heated in boiling water for 5 min. After cooling, the absorbance is measured at 540 nm to assess enzyme activity. Acarbose, a known α-amylase inhibitor, is used as a positive control. The percentage inhibition of α-amylase by LNEE is calculated using the formula[13]:

$$\text{Inhibition}\,(\%) = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100$$

In vitro α-glucosidase inhibition assay

This assay assesses the anti-diabetic activity of ***Laurus nobilis*** ethanolic extract (LNEE) and is based on the method by **Bhatia A (2019)** with slight modifications[14]. The α-glucosidase enzyme (0.1 U/mL) is prepared in phosphate buffer (50 mM, pH 6.8) , while **p-nitrophenyl-α-D-glucopyranoside (pNPG, 5 mM)** is used as the substrate. In a 96-well plate, 50 µL of LNEE at various concentrations is mixed with 50 µL of α-glucosidase enzyme and pre-incubated at 37°C for 10 min. Following this, 50 µL of the pNPG solution is added to the mixture and incubated for 20 min at 37°C. The reaction is terminated by adding 100 µL of sodium carbonate (0.1 M) , and the absorbance is measured at 405 nm. **Acarbose**, a standard anti-diabetic drug, is used as a positive control. The percentage inhibition of α-glucosidase by LNEE is calculated using the same formula as in the α-amylase inhibition assay.

Phytochemical Identification from *Laurus nobilis* Extracts

Phytochemicals from *Laurus nobilis* were retrieved from the IMPPAT database, which compiles plant-based molecules known for their medicinal properties. The initial set of compounds was further filtered for downstream analyses. Based on their reported bioactivities and molecular structures, 30 phytochemicals were selected for computational analysis.

Drug-Likeness Screening

Drug-likeness properties of the selected phytochemicals were evaluated using Lipinski's Rule of Five, which includes parameters such as molecular weight, hydrogen bond donors, hydrogen bond acceptors, and logP (octanol-water partition coefficient). The SwissADME webserver (http://www.swissadme.ch/) was used to calculate these properties. Compounds that adhered to Lipinski's criteria were selected for further ADMET and molecular docking studies.

ADMET Analysis

The selected compounds' ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles were analyzed using the SwissADME webserver. Parameters such as water solubility, gastrointestinal absorption, blood-brain barrier (BBB) permeability, and cytochrome P450 enzyme inhibition were assessed. Compounds exhibiting poor ADMET profiles, such as low GI absorption or BBB permeability (if undesired) , were excluded to ensure potential efficacy and safety.

Interaction Network Analysis Using BioGRID

To investigate the interactions between insulin receptor proteins and other molecules, a network analysis was performed using the BioGRID database (https://thebiogrid.org/). BioGRID provided data on physical and genetic interactions between the insulin receptor (INSR) and various proteins involved in insulin signaling pathways. This analysis was complemented with GeneMANIA (https://genemania.org/) to visualize the target proteins' co-expression, co-localization, and shared pathways.

Molecular Docking and Binding Affinity Calculations

The docking of the *Laurus nobilis* phytochemicals against the insulin receptor (INSR) was performed using PyRx (AutoDock Vina). The crystal structure of the insulin receptor (PDB ID- 4ZXB (insulin receptor) was obtained from the Protein Data Bank[15]. The target protein was prepared by removing water molecules and adding hydrogen atoms. Phytochemicals were energy-minimized using Open Babel before docking.

Binding affinities were measured based on the docking scores (in kcal/mol) of each compound. A control drug, metformin (a known insulin receptor activator) , was docked to the insulin receptor to compare its binding affinity with the phytochemicals. Results were ranked based on their binding energy, with the lowest binding energy indicating the strongest interaction.

Amino Acid Interaction Analysis

After docking, the interaction patterns of the phytochemicals with the insulin receptor were analyzed using Discovery Studio Visualizer. Specific interactions such as hydrogen bonds, hydrophobic contacts, and π-π stacking were recorded. The key interacting amino acids involved in binding the ligand to the receptor's active site were noted. The results were compared with the control drug to identify phytochemicals that mimic the binding behaviour of known insulin receptor activators.

Bioactivity Prediction

Bioactivity prediction of the selected phytochemicals was performed using the PASS (Prediction of Activity Spectra for Substances) web server (https://genexplain.com/pass/). This tool predicts the biological activity of compounds based on their chemical structure. The key predicted activities related to insulin signaling pathways, such as insulin receptor activation, antidiabetic activity, and glucose metabolism regulation, were noted. Compounds with high Pa (probability of activity) and low Pi (probability of inactivity) scores were prioritized for further study.

Binding affinity and ranking of phytochemicals

The docking results were tabulated, listing the binding energies of each compound alongside the control drug. The phytochemicals were ranked based on their binding affinity, with the most promising candidates demonstrating binding energies comparable to or lower than metformin. The bioactivity prediction results were cross-referenced with the binding affinities to identify lead compounds with high binding potential and relevant biological activity.

Results

***In vitro* anti-diabetic activity**

The ***In vitro*** enzyme inhibition analysis of ***Laurus nobilis*** ethanolic extract (LNEE) shows promising anti-diabetic activity, particularly in its ability to inhibit the key enzymes **α-amylase** and **α-glucosidase**, which are involved in carbohydrate digestion and glucose absorption. The inhibition of these enzymes slows the breakdown of complex carbohydrates into glucose, thus potentially reducing postprandial blood glucose spikes. The results demonstrate a clear dose-dependent response, where increasing concentrations of LNEE led to greater enzyme inhibition, with a maximum inhibition of 85% for α-amylase and 88% for α-glucosidase at 800 µg/mL (Fig. 1). While the standard drug, acarbose, exhibited slightly higher inhibition at each concentration, LNEE still showed substantial inhibitory activity, suggesting its potential as a natural alternative for managing diabetes. These findings support the potential use of ***Laurus nobilis*** in anti-diabetic therapies by modulating glucose metabolism.

Drug-likeness and ADMET screening

The drug-likeness evaluation followed Lipinski's Rule of Five, which screens compounds for oral bioavailability based on their molecular weight, hydrogen bond donors, hydrogen bond acceptors, and logP values. Several phytochemicals derived from *Laurus nobilis*, including beta-Caryophyllene, Eugenol, Linalool, and alpha-Pinene, were identified as compliant with Lipinski's rule, making them favorable candidates for further study in drug development (Fig. 2). These compounds exhibited

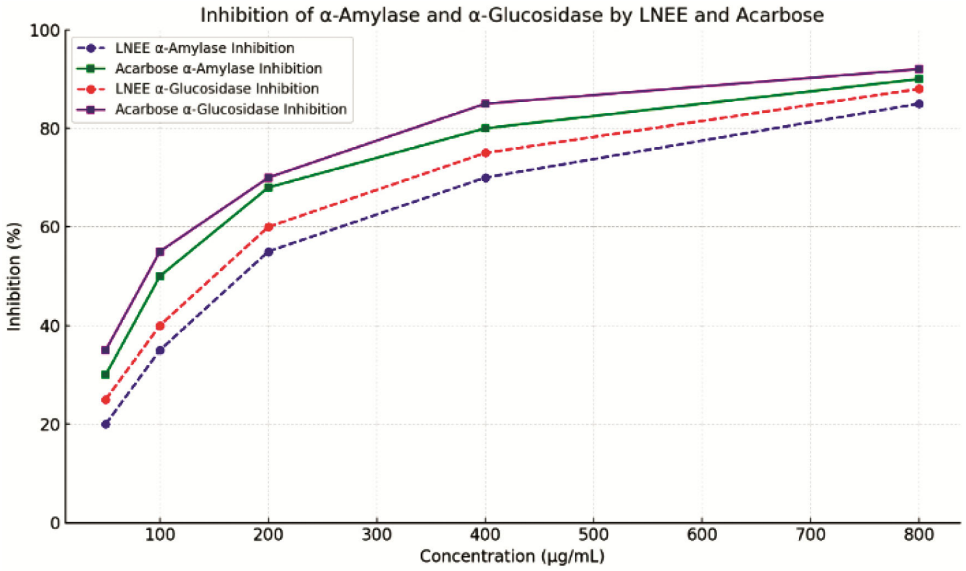

Fig. 1 — *In vitro* α-glucosidase inhibition assay and α-amylase inhibition assay of *Laurus nobilis*

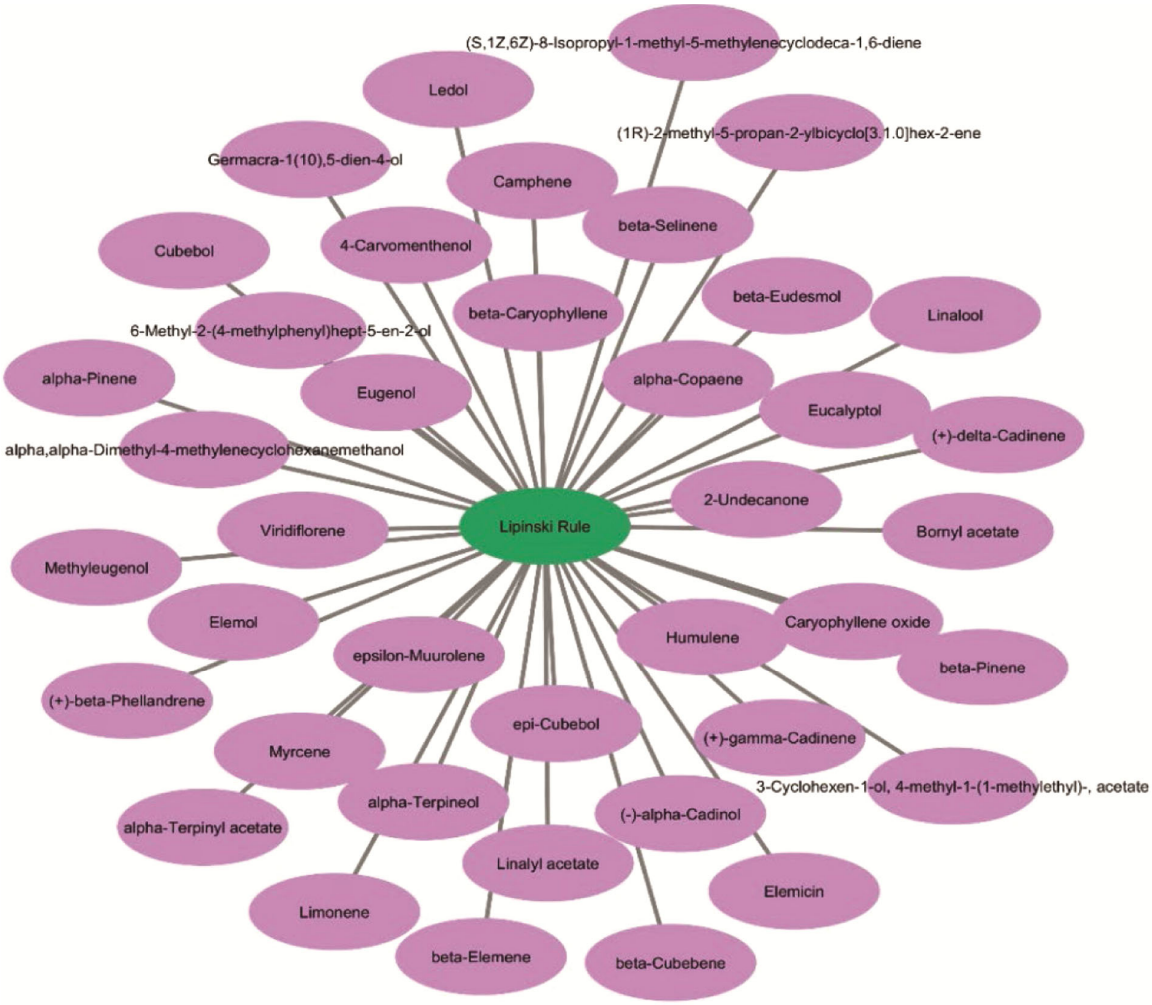

Fig. 2 — Shows compounds adhered to Lipinski's Rule of Five suitable for pharmacological analysis

optimal molecular properties necessary for pharmacokinetic studies, such as acceptable molecular weight and proper balance between hydrophilicity and lipophilicity, as indicated by logP values.

The ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis further evaluated the selected phytochemicals, highlighting epsilon-Muurolene, Viridiflorene, beta-Element, Humulene, and beta-Selinene among others for their favorable pharmacokinetics profiles. The ADMET analysis revealed that 9 out of the 40 compounds were not permeable to the BBB, which is an important consideration for drugs intended to avoid central nervous system (CNS) side effects (Fig. 3). While BBB permeability is essential for drugs targeting CNS disorders, it is not always required for other therapeutic applications. The remaining 31 compounds demonstrated BBB permeability, indicating their potential as candidates for CNS-related drugs.

BIOGRID analysis

Analysis from the BioGRID web server demonstrated that the INSR (Insulin Receptor) gene is deeply involved in multiple physiological processes, highlighting its critical role in metabolic regulation and cellular signaling pathways. The INSR gene interacts with a broad network of proteins, emphasizing its importance in glucose homeostasis, insulin-mediated signal transduction, and lipid metabolism (Fig. 4).

The INSR gene, which encodes the insulin receptor, is highly interconnected within cellular networks, playing a pivotal role in various physiological processes. Analysis from the BioGRID database revealed a total of 360 protein/gene interactions and 10 chemical interactions associated with this gene, underscoring its extensive involvement in cellular functions, particularly in metabolic regulation. Notably, 343 interactors were supported by physical evidence, including 269 with high-throughput physical (HTP) data, indicating the gene's role in large-scale cellular processes, and 74 with low-throughput physical (LTP) data, highlighting more specific, well-studied interactions critical to its core functions. The presence of 17 interactors with multiple types of evidence further reinforces the significance of these interactions in INSR-related pathways. Additionally, the 10 chemical interactors emphasize the gene's responsiveness to various molecules, essential for its role in metabolic regulation. The INSR gene's extensive network of interactions underscores its vital contribution to insulin signaling, glucose homeostasis, lipid metabolism, and energy balance. This broad

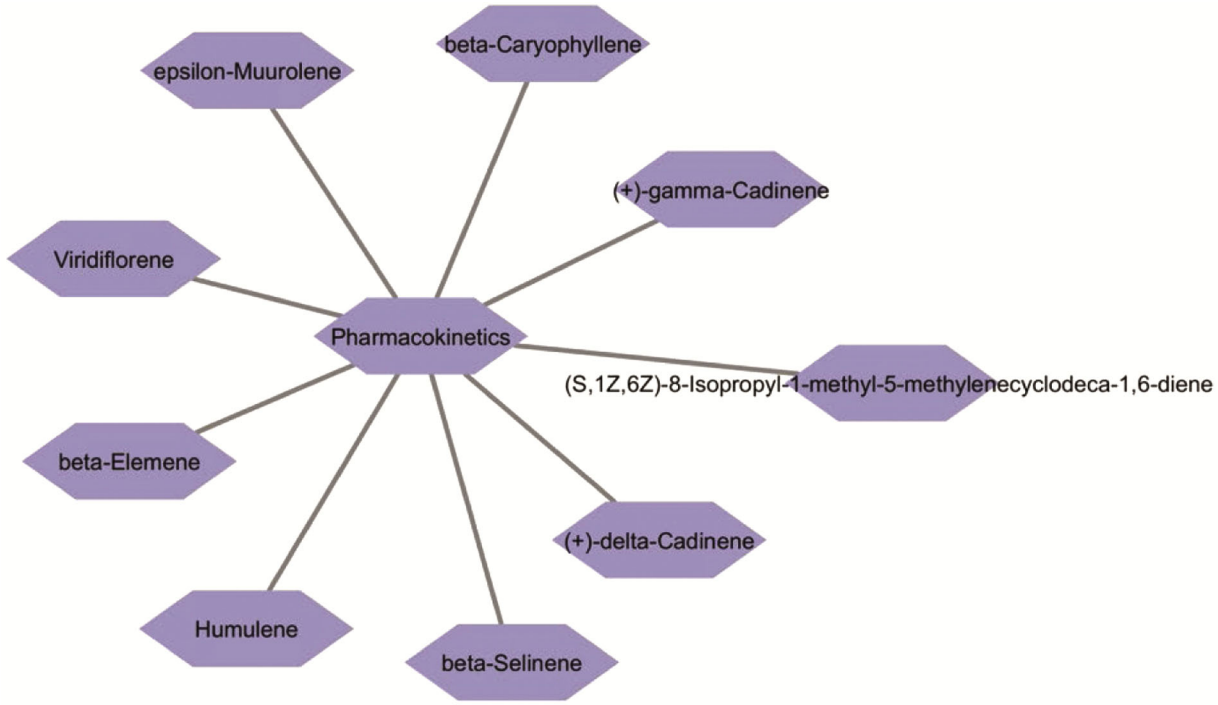

Fig. 3 — Shows 9 phytochemicals not crossing blood-brain barrier after ADMET analysis

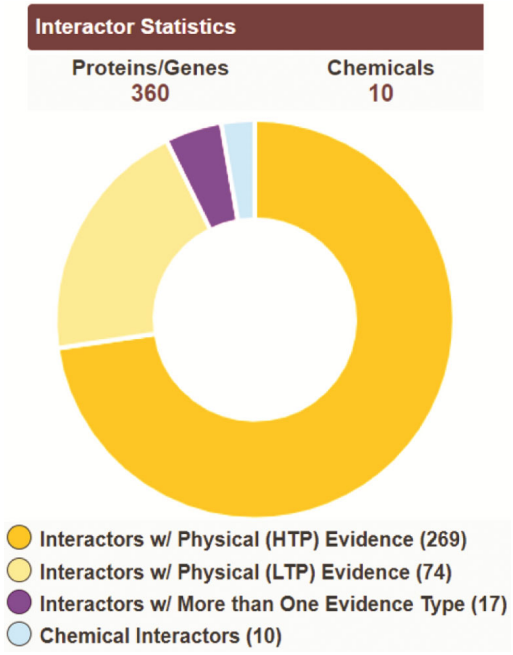

Fig. 4 — Shows BioGRID analysis illustrating protein/gene interaction with *Laurus nobilis*

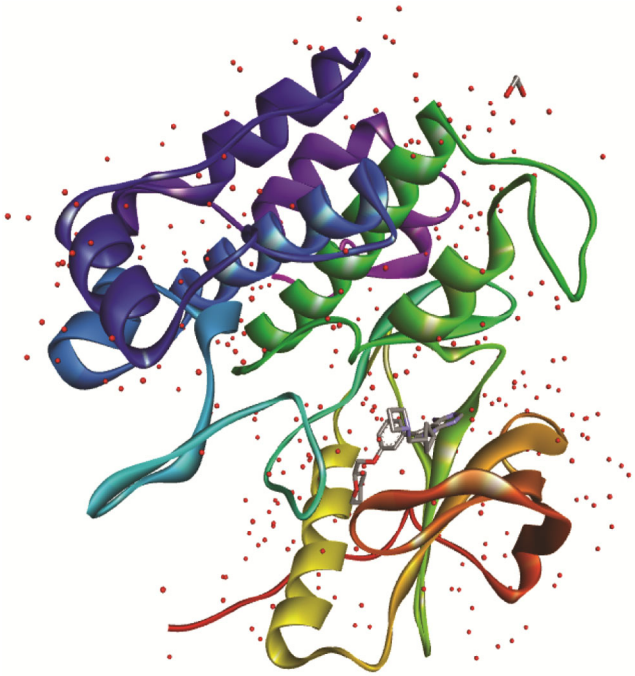

Fig. 5 — Shows the molecular docking of *Laurus nobilis* phytochemicals against the insulin receptor

involvement in protein interactions suggests its influence over multiple downstream signaling pathways, impacting cellular processes such as growth, differentiation, and survival. Overall, these findings highlight INSR as a key component in cellular signaling, metabolic regulation, and the maintenance of cellular homeostasis.

Molecular docking & binding affinities

The docking of *Laurus nobilis* phytochemicals against the insulin receptor (INSR) was conducted using PyRx software with the AutoDock Vina tool to assess the binding affinity of each compound. The results revealed that several phytochemicals exhibited strong interactions with the active site of INSR, indicating their potential to modulate the receptor's activity. The binding affinity of the nine phytochemicals from *Laurus nobilis* with the insulin receptor (INSR) was assessed through docking studies using AutoDock Vina. Binding affinity is a critical parameter that indicates how strongly a compound interacts with a receptor, influencing its potential effectiveness as a modulator of the receptor's activity (Fig. 5).

All compounds showed moderate binding affinity towards the IR with the affinity ranging from -6 to -7 Kcal/mol. Delta-Cadiene exhibited a binding affinity of -8.5 kcal/mol, forming several key interactions within the active site of the insulin receptor (INSR) , suggesting a strong potential for enhancing insulin signaling. Beta-Selinene demonstrated a binding affinity of -8.3 kcal/mol, indicating significant interaction with the INSR, with favorable interactions involving crucial amino acids that may facilitate receptor activation. Epsilon-Muurolene showed a binding affinity of -8.0 kcal/mol, suggesting a robust interaction profile supported by hydrogen bonds and hydrophobic interactions, indicating its potential as an insulin receptor modulator. Beta-Caryophyllene had a binding energy of -7.8 kcal/mol, supported by multiple non-covalent interactions, which could positively influence INSR activity. Humulene exhibited a binding affinity of -7.5 kcal/mol, highlighting stable interaction with the INSR that may help modulate its function in metabolic regulation. Gamma-Cadinene showed a binding affinity of -7.3 kcal/mol, indicating a moderate interaction with the receptor, with specific interactions that suggest a role in enhancing the receptor's activity. Beta-Elemene displayed a binding affinity of -7.1 kcal/mol, suggesting reasonable potential for interacting with the INSR and influencing its signaling pathways. Viridiflorene exhibited a binding energy of -6.9 kcal/mol, indicating moderate interaction with the receptor, while 8-Isopropyl-1-methyl-5-methylene-cyclodeca-1,6-diene showed a binding affinity of -6.7 kcal/mol, suggesting potential for influencing INSR

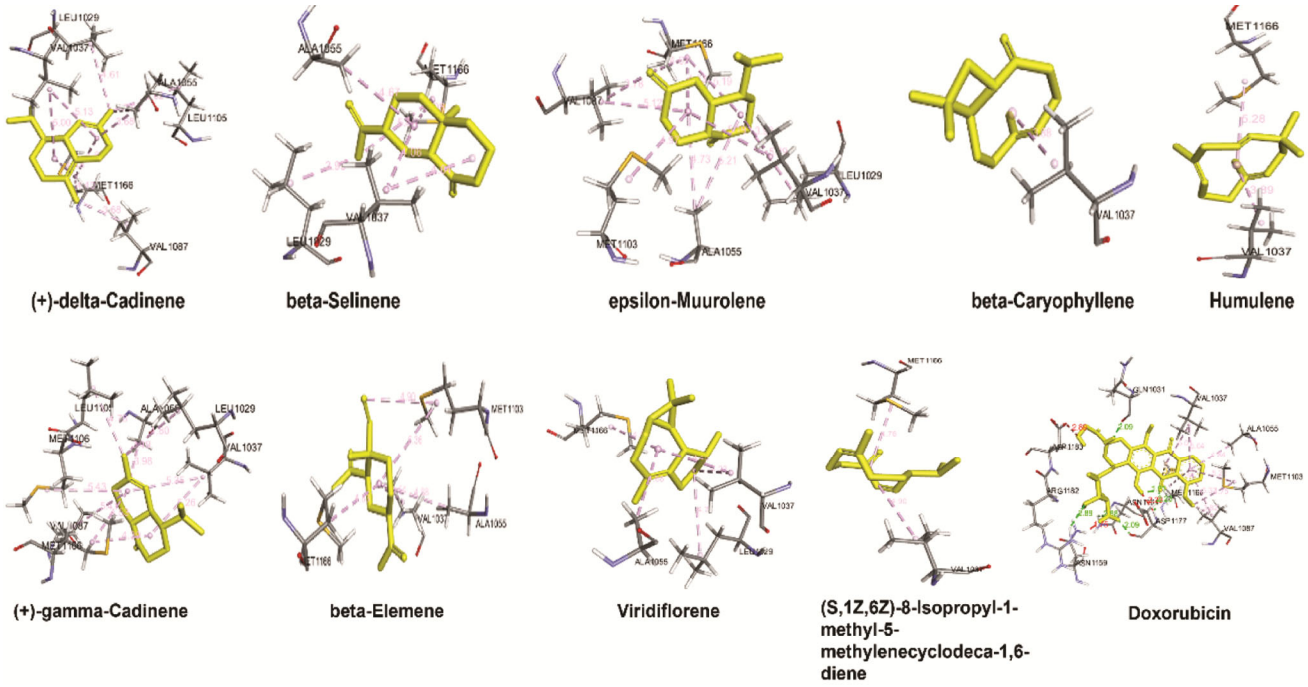

Fig. 6 — Shows the binding affinity of the nine phytochemicals from *Laurus nobilis* with the insulin receptor

activity despite a lower binding strength compared to other compounds as illustrated in (Fig. 6).

Interaction with amino acids

The molecular docking analysis revealed significant interactions between the *Laurus nobilis* phytochemicals and the insulin receptor (INSR) , with compounds such as Beta-Elemene, Gamma-Cadinene, Delta-Cadinene, Beta-Selinene, and Epsilon-Muurolene showing strong binding affinities. These compounds interacted with critical amino acid residues including Met1103, Met1166, Ala1055, Met1106, Leu1029, Leu1105, Val1037, Lys1057, Ser1033, Gly1032, Asp1177, Gln1031, Val1087, and Gly1176 (Table 1). These interactions are essential for receptor stabilization and activation. For instance, Beta-Elemene and Epsilon-Muurolene formed key contacts with Lys1057, Asp1177, and Leu1105, crucial for signal transduction. Similarly, Gamma-Cadinene interacted with Met1103, Ala1055, and Val1037, contributing to receptor conformational stability. The consistent engagement of these phytochemicals with residues like Asp1177 and Met1106, which are integral to the receptor's kinase domain, suggests their potential to enhance insulin receptor activity, positioning these compounds as promising modulators for therapeutic applications in metabolic regulation.

Bioactivity prediction

According to the bioactivity predictions from the PASS web server, eight of the nine compounds were forecasted to exhibit insulin promoter activity, except Beta-Selinene (Table 2). Compounds such as Delta-Cadinene, Gamma-Cadinene, Epsilon-Muurolene, Beta-Caryophyllene, Humulene, Beta-Elemene, Virudiflorene, and 8-Isopropyl-1-Methyl-5-Methylene-Cyclodeca-1,6-Diene demonstrated a high probability of enhancing insulin receptor activity. These predictions suggest that these phytochemicals could act as insulin promoters, making them promising candidates for further investigation as therapeutic agents to modulate insulin signaling pathways. The absence of insulin promoter activity in Beta-Selinene indicates that its bioactivity may lie in other physiological pathways, thus requiring additional analysis for alternative therapeutic potential.

Discussion

The *In vitro* enzyme inhibition analysis of *Laurus nobilis* ethanolic extract (LNEE) has demonstrated promising anti-diabetic potential by effectively inhibiting two key enzymes involved in carbohydrate metabolism—α-amylase and α-glucosidase. These enzymes play a critical role in the breakdown of complex carbohydrates into simple sugars, which are then absorbed into the bloodstream. Inhibition of

Table 1 — Shows interactions between the *Laurus nobilis* phytochemicals and amino acids

S. No	Compounds	PubChem ID	Binding affinity (Kcal/mol)	Interacting amino acids
1	Viridiflorene	10910653	-7	Leu1029, Asp1177, Lys1057, Ala1055, Gly1032, Met1166, Val1087, Met1106, Val1037, leu1105
2	beta-Elemene	6918391	-6.1	Val1087, Asp1177, Gly1176, ys1057, Met1103, Gly1032, Met1166, Ser1033, Val1037, Ala1055, Gly1109, Leu1-29, Leu1105, Met1106
3	(S,1Z,6Z) -8-Isopropyl-1-methyl-5-methylenecyclodeca-1,6-diene	91723653	-6.7	Gly1109, Leu1029, Ala1055, Leu1105, met1106, Met1103, Val1087, Val1037, Gly1176, Met1166, Asp1177
4	Humulene	5281520	-6.7	Gln1031, Gly1032, Gly1030,Asp1110, Gly1109, Leu1029, Val1087, Met1106, Ala1055, Met1103, Met1166, Val1037
5	(+) -gamma-Cadinene	6432404	-6.8	Val1087, Val1037, Met1106, Ala1055, Leu1029, Glu1104, Leu1105, Met1166, Gly1176, Asp1177, Gly1030, Gly1032, Gln1031
6	(+) -delta-Cadinene	441005	-6.9	Gly1032, Gln1031, Gly1030, Val1037, Ala1055, Met1106, Leu1029, Glu1104, Leu1105, Val1087, Met1103, Met1166, Gly1176, Asp1177
7	beta-Selinene	442393	-6.7	Gly1109, eu1029, Met1106, Met1166, eu1105, Ala1055, Val1087, Val1037, Gly1176, Met1103, Asp1177, Lys1057, Gly1032, Ser1033
8	beta-Caryophyllene	5281515	-6.9	Met1103, Val1087, Met1106, Ala1055, Met1166, Gly1109, Leu1029, Asp1110, Gly1030, Val1037, Gln1031, Gly1032
9	epsilon-Muurolene	520461	-6.9	Met1103, Met1166, Ala1055, Met1106, eu1029, Leu1105, Val1037, Lys1057, Ser1033, Gly1032, Asp1177, Gln1031, Val1087, Gly1176
C	Doxorubicin		-10.9	Met1103, Ala1055, Val1087, Gly1176, Arg1163, Ser1033, Asp1177, Arg1187, Thr1181, Tyr1189, Gly1179, Asn1164, Phe1178, Asn1159, Asp1183, Glu1186, Gly1032, Gln1031, Gly1030, Leu1029, Val1037, Met1166

Table 2 — Shows bioactivity prediction of nine compounds exhibiting insulin promoter activity

S. No	Lead	SMILIES	Pa	Pi	Activity
1	Viridiflorene	CC1CCC2=C (CCC3C (C^{12}) C3 (C) C) C	0.368	0.081	Insulin promoter
2	beta-Elemene	CC (=C) C1CCC (C (C1) C (=C) C) (C) C=C	0.25	0.222	Insulin promoter
3	(S,1Z,6Z) -8-Isopropyl-1-methyl-5-methylenecyclodeca-1,6-diene	CC1=CCCC (=C) C=CC (CC1) C (C) C	0.329	0.109	Insulin promoter
4	Humulene	CC1=CCC (C=CCC (=CCC1) C) (C) C	0.269	0.184	Insulin promoter
5	(+) -gamma-Cadinene	CC1=CC2C (CC1) C (=C) CCC2C (C) C	0.462	0.039	Insulin promoter
6	(+) -delta-Cadinene	CC1=CC2C (CCC (=C2CC1) C) C (C) C	0.475	0.035	Insulin promoter
7	beta-Selinene	CC (=C) C1CCC2 (CCCC (=C) C2C1) C	0.197	0.018	Antidiabetic (type 1)
8	beta-Caryophyllene	CC1=CCCC (=C) C2CC (C2CC1) (C) C	0.342	0.099	Insulin promoter
9	epsilon-Muurolene	CC (C) C1CCC (=C) C2C1CC (=C) CC2	0.438	0.047	Insulin promoter

these enzymes can slow the release of glucose postprandially, helping to regulate blood sugar levels in individuals with diabetes.

In this study, LNEE exhibited a clear dose-dependent inhibition of both α-amylase and α-glucosidase, with maximum inhibition rates of 85% and 88% respectively at a concentration of 800 µg/mL. This significant inhibitory effect suggests that LNEE could help attenuate postprandial hyperglycemia, which is a crucial therapeutic target in managing type 2 diabetes mellitus (T2DM). By preventing the rapid breakdown of carbohydrates and subsequent glucose absorption, LNEE may help in maintaining more stable blood glucose levels, reducing the likelihood of spikes that are often harmful in diabetic patients[16].

While the standard anti-diabetic drug acarbose exhibited slightly higher inhibitory activity across all

concentrations tested, LNEE still showed substantial enzyme inhibition. This suggests that *Laurus nobilis* could serve as a natural alternative or adjunct to conventional anti-diabetic medications. Moreover, the use of plant-based inhibitors like LNEE could offer additional benefits, such as fewer side effects, lower costs, and availability from a natural source, making it a viable therapeutic option for long-term diabetes management[17].

Compared with previous studies involving phytochemicals from other medicinal plants, our findings are consistent with the broader trend of plant-derived compounds showing potential for insulin receptor modulation. A molecular docking study involving Momordica charantia (bitter melon) phytochemicals demonstrated similar insulin receptor activation, with compounds like charantin and vicine showing high binding affinities and favorable interactions with key amino acids in the insulin receptor's active site[18,19]. This is comparable to our study, where compounds such as beta-elemene, gamma-cadinene, and delta-cadinene exhibited strong binding interactions with critical residues like Met1103, Ala1055, and Val1037 of the insulin receptor.

In both studies, the identified compounds showed hydrogen bonding and hydrophobic interactions with key amino acids that are crucial for receptor activation[20]. A study on a trypsin inhibitor from tamarind seeds indicated strong binding affinity to the insulin receptor, suggesting its potential as a hypoglycemic agent[21]. These interactions indicate the potential of plant-derived compounds in modulating receptor activity, suggesting that these natural molecules could serve as promising leads for developing insulin receptor activators. Additionally, similar to the findings in our study, docking studies with Gymnemasylvestre phytochemicals have also shown significant binding to insulin receptor-related targets, further supporting the therapeutic potential of natural compounds in managing diabetes through insulin signaling pathways[22,23].

While the binding affinities observed in our study are promising, the results must be interpreted with caution. Docking studies, though useful for predicting interactions, do not provide a complete picture of the bioavailability and efficacy of these compounds *in vivo*. Other factors, such as the compounds' metabolism, distribution, and excretion, need to be considered[24]. In this regard, our study went a step further by performing an ADMET analysis, which highlighted that the majority of the *Laurus nobilis* compounds possessed favorable drug-likeness properties, reinforcing their potential as orally active drugs. Previous studies have often limited their focus to docking analysis, while our comprehensive approach included both pharmacokinetic and bioactivity prediction, adding more depth to the evaluation of these phytochemicals[25].

Moreover, while some studies have focused primarily on the glucose-lowering effects of plant compounds through pancreatic mechanisms (such as insulin secretion) , our research emphasizes direct interaction with the insulin receptor. This is particularly important for treating insulin resistance in Type 2 Diabetes Mellitus (T2DM) , where enhancing insulin receptor sensitivity is crucial[26]. In this context, our findings align with studies suggesting that phytochemicals like berberine (from Berberis aristata) and resveratrol (from Polygonum cuspidatum) act through similar mechanisms, enhancing insulin receptor activity and improving insulin sensitivity[27].

The phytochemicals from *Laurus nobilis* identified in this study require further validation through comprehensive *In vitro* and *in vivo* studies to confirm their potential as insulin receptor activators, as well as to assess their safety and efficacy. A notable limitation is the exclusion of compounds capable of crossing the blood-brain barrier (BBB) , which may limit the therapeutic application of these phytochemicals for central nervous system-related metabolic disorders. Additionally, the study was confined to a specific set of compounds, potentially overlooking other bioactive constituents of *Laurus nobilis* that may possess significant pharmacological effects. Future research should focus on experimentally validating the top compounds through cell-based assays and animal models. Investigating potential synergistic effects between these phytochemicals and other plant-derived compounds or existing anti-diabetic drugs could further enhance their therapeutic potential. Advanced pharmacokinetic studies are also essential to evaluate the bioavailability and toxicity profiles, facilitating the development of these compounds into promising candidates for managing diabetes and other metabolic disorders.

Conclusion

Based on findings from docking and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analyses, phytochemicals from *Laurus nobilis* have emerged as promising candidates for

activating the insulin receptor. These compounds demonstrate significant potential in modulating insulin receptor activity, showing effects comparable to those of phytochemicals from other well-known medicinal plants. This highlights their potential role in managing type 2 diabetes mellitus (T2DM).

To fully realize their therapeutic potential, future research should prioritize *in vivo* validation of these *Laurus nobilis* compounds, alongside the development of effective formulations for clinical application. The growing body of evidence supporting the efficacy of plant-derived compounds in targeting insulin receptors underscores the potential for novel, natural-based treatments for diabetes. Such approaches could provide safer and more sustainable alternatives to current therapies, offering new hope in the fight against T2DM.

Conflict of interest

All authors declare no conflict of interest.

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