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Formulation and characterization of bay leaf extract nanophytosomes (Syzgium polyanthum) and affinity study of interaction with alpha glucosidase enzyme as antidiabetic

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ABSTRACT

Introduction: Diabetes Mellitus is a metabolic syndrome disease in which around 90-95% of all cases of adults aged 20-79 years suffer from type 2 Diabetes Mellitus, with long-term conventional treatment causing side effects of hypoglycemia. Bay leaves which contain quercetin and kaempferol compounds are able to lower blood glucose levels, but have challenges in drug delivery due to easy oxidation and low bioavailability. Therefore, an innovative drug delivery system is needed, such as nanophytosomes, to increase its bioavailability. Objective: This study aims to develop a thin film formula of bay leaf extract nanophytosomes that have antidiabetic affinity with in silico studies and evaluate the physical characteristics of nanophytosomes. Method: in silico using the molecular docking method to evaluate the interaction of active compounds of bay leaves with the alpha glucosidase enzyme. Bay leaf nanophytosomes are formulated using heat homogenization and probe sonicator techniques. Characterization is carried out by measuring particle size, polydispersity index, zeta potential, and particle morphology. Results: The nanophytosome formula of bay leaf extract showed a particle size of <1000 nm, a polydispersity index of <0.5, and a zeta potential of ±25 mV. In silico studies showed that quercetin and kaempferol have a strong affinity for the α-glucosidase enzyme, which plays an important role in inhibiting glucose absorption. Conclusion: Bay leaf extract can be formulated into a phytosome-based nanoparticle delivery system that shows stable physical characteristics, high adsorption efficiency, and potential antidiabetic activity through the interaction of inhibiting the α-glucosidase enzyme.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by increased blood glucose levels due to impaired insulin secretion, insulin function, or both.(Antar et al., 2023). Type 2 DM is the most common form of the disease, accounting for about 90–95% of all diabetes cases in adults

aged 20–79 years. The increasing prevalence of type 2 DM is influenced by sedentary lifestyles, high-calorie diets, obesity, and genetic factors (Galicia-Garcia et al., 2020). If not optimally managed, diabetes can cause serious macrovascular and microvascular complications such as coronary heart disease, diabetic nephropathy, retinopathy, and peripheral neuropathy, which significantly reduce the quality of life of sufferers and increase the economic burden on the health system (Zakir et al., 2023).

Conventional therapy for type 2 DM is generally carried out by administering oral drugs such as metformin, sulfonylureas, thiazolidinediones, and α-glucosidase inhibitors (Padhi et al., 2020). Although these drugs are effective in lowering blood glucose levels, long-term use often causes various side effects such as gastrointestinal disorders, hypoglycemia, weight gain, and even drug resistance in some patients. This raises the need for alternative therapies that are safer, more effective, and able to provide long-term therapeutic benefits with minimal risk of side effects. In this case, the use of natural ingredients that have antidiabetic activity is an interesting approach to be developed further (Feingold, 2024).

Bay leaf (Syzygium polyanthum) is a medicinal plant widely known in traditional Indonesian medicine and has been proven to have pharmacological potential, including as an antidiabetic agent. Bay leaf extract contains bioactive compounds such as quercetin and kaempferol, which are known to have the ability to lower blood glucose levels through the mechanism of inhibiting the enzyme α-glucosidase (Dewijanti et al., 2020). This enzyme plays a role in the breakdown of complex carbohydrates into simple glucose in the digestive tract, so its inhibition can slow down glucose absorption and reduce postprandial blood sugar spikes. However, the therapeutic effectiveness of these active compounds is often limited by their easily oxidized chemical properties, low solubility in water, and low bioavailability after oral administration (Kashtoh & Baek, 2022).

In overcoming these problems, nanotechnology approaches such as nanophytosomes can be an innovative solution. Nanophytosomes are lipid vesicles formed from phospholipids and active phytochemical compounds, which can increase the solubility, stability, and permeability of bioactive compounds through biological membranes (Palol et al., 2023).

In addition to formulation development, an in silico approach was also used in this study to support the mechanism of action of the active compounds of bay leaf extract. Molecular docking results showed that quercetin and kaempferol have strong affinity for the α-glucosidase enzyme, which strengthens the therapeutic potential of bay leaves as an antidiabetic agent (Naji Bin-Asal et al., 2025). Thus, this nanophytosome-based delivery system is expected to significantly increase the effectiveness of antidiabetic therapy from bay leaf extract, as well as provide an alternative natural treatment solution that is more efficient and safe compared to conventional therapy.

RESEARCH METHOD

Tool

The tools used in this study were digital scales, simplex scales, a set of maceration tools, a set of reflux tools, porcelain evaporator cups, probe sonicators, magnetic stirrers, zeta sizer instruments, Particle Size Analyzers (PSA) (Malvern Instruments Ltd), glassware, desiccators.

Material

The materials used were bay leaf simplicia, 96% technical ethanol, n-hexane pa, phosphatidylcholine pa, Plantacare 1200, Cremophor® RH40, and ethanol.

Detailed Procedure

Preparation, Collection & Inspection of Bay Leaves. Bay leaves (Syzygium polyanthum) were collected and checked for suitability based on the determination results to ensure species suitability. Additional materials used were evaluated for suitability based on references from the Handbook of Pharmaceutical Excipients (HOPE) (Primary, 2024).

Making Bay Leaf Extract

A total of 500 grams of bay leaf simplicia powder was macerated using 5000 mL of 96% ethanol for 3×24 hours with periodic stirring. After that, the maceration results were filtered using batis cloth and filter paper, then the solvent was evaporated using a rotary evaporator at a temperature of 50°C until a thick bay leaf extract was obtained (Christian et al., 2022).

Phytochemical Screening

Phytochemical screening was conducted to detect bioactive compounds in plant samples, including flavonoids, alkaloids, tannins, saponins, steroids/triterpenoids, and quinones. The procedure for flavonoids involved weighing the sample and dissolving it with hot distilled water, followed by the addition of Mg powder and HCl, where red, yellow, or orange colors indicated the presence of the compound. Meanwhile, alkaloids were tested by adding ammonia and chloroform, then using Mayer and Dragendorff's reagents, with white and brick red precipitates as positive indicators. For tannins, the solution mixed with FeCl3 produced a blackish green or blackish blue color. Saponins were tested by shaking the filtrate and waiting for the foam to stabilize, while steroids/triterpenoids were identified through a test with the Lieberman-Burchard reagent. Quinones were tested by adding NaOH, producing a red color as a positive sign (Praptiwi et al., 2020).

Preparation of Bay Leaf Extract Nanophytosomes

Thick extract of bay leaf, phosphatidylcholine, plantacare/cremofor were dissolved in ethanol separately, mixed and refluxed at 40–50°C for 3 hours. The mixture was evaporated until a small volume remained, then n-hexane was added and left for 90 minutes to precipitate. The precipitate was dried in a desiccator, then hydrated with distilled water and ultrasonicated for 30 minutes to produce nanophytosome preparations (Saputra et al., 2023).

Characterization of Nanophytosomes

Characterization of nanophytosomes includes testing particle size, polydispersity index (PDI) using a psa or Particle Size Analyzer and zeta potential using a zeta sizer. The sample was diluted with distilled water up to 10 mL, placed in a cuvette, and analyzed to determine the size distribution and stability of the preparation (Jafar et al., 2025).

In silico test

The in silico test begins with ligand preparation in the form of active bay leaf compounds downloaded from PubChem (.sdf), converted to .pdb format using Avogadro, and geometry optimized using Gaussian with the Density Functional Theory (DFT) method to obtain the most stable conformation. Furthermore, the physicochemical properties were analyzed using the Lipinski Rule of Five via the scfbio-iitd page, while pharmacokinetic and toxicity predictions were carried out via preADMET to evaluate the feasibility of the compound as a drug candidate. Protein preparation was carried out by downloading the α-glucosidase structure (PDB ID: 5NN8) from RCSB PDB, then cleaned from water molecules and natural ligands using Discovery Studio and added hydrogen atoms using AutoDock. Validation of molecular docking was carried out through redocking with AutoDock 1.5.7, with success criteria if the RMSD value ≤ 2Å and gridbox settings at the center of the original ligand. Molecular docking simulations were performed with AutoDock 4.2.3 using the gridbox settings from the previous validation, with analysis of the results based on the binding free energy (ΔG) and inhibition constant (Ki) values. Molecular interaction visualization was performed using Discovery Studio Visualizer 2024 and Visual Molecular Dynamics (VMD) to observe intermolecular binding between ligands and amino acid residues in the active site of the target protein.

RESULTS AND DISCUSSIONS

Bay leaves (Syzygium polyanthum) used in this study have been collected and obtained appropriate identification results based on the determination results from the Biology Laboratory of FMIPA, Padjadjaran University, which ensures that the species used are correct and authentic. All additional materials used in the formulation process have also been assessed for their suitability based on references from the Handbook of Pharmaceutical Excipients (HOPE), indicating that all excipients used are safe and suitable for the formulation of nanophytosome preparations (Primary, 2024).

The maceration process of bay leaf simplicia powder produces a thick greenish brown extract with a distinctive thick consistency, indicating that the extract was successfully obtained optimally. Evaporation of the solvent using a rotary evaporator at a temperature of 50°C runs efficiently until a concentrated extract is obtained that is ready to be used in the formulation process. The yield obtained shows good extraction results and is representative of the active compound content of bay leaves (Christian et al., 2022).

The results of the phytochemical screening test on bay leaf extract showed the presence of various secondary metabolite compounds. Alkaloid tests with Mayer, Dragendorff, and Wagner reagents showed positive results which were marked by the formation of white, brick red, and brown deposits. Flavonoid compounds were detected by the formation of color on the amyl alcohol layer. The tannin test gave positive results with a color change to greenish black in the FeCl reagent.$_3$1% and white sediment in 1% gelatin reagent. The saponin test showed stable foam, indicating the presence of saponin compounds. The triterpenoid test produced a bluish green color indicating the presence of triterpenoid compounds. Meanwhile, the test for quinone compounds showed negative results because no red color was formed. Overall, bay leaf extract was proven to contain alkaloids, flavonoids, tannins, saponins, and triterpenoids, which have the potential to play a role in the pharmacological activity of the extract (Praptiwi et al., 2020).

Table 1. Phytochemical screening of bay leaf extract

Compound Groups	Literature	Test Results	Information
Alkaloid	Alkaloids form precipitates with Mayer, Dragendorff, and Wagner reagents.	White (Mayer), brick red (Dragendorff), and brown (Wagner) precipitates are formed.	+
Flavonoid	Flavonoids produce color in the amyl alcohol layer.	Color is formed on the amyl alcohol layer.	+
Quinone	Quinones produce a red color when they react with certain reagents.	No red color is formed.	-
Tannin	Tannin gives a greenish black color with $FeCl_3$and white precipitate with gelatin.	Greenish black color ($FeCl_3$), white sediment (gelatin).	+
Saponins	Saponins produce a stable foam when shaken.	A stable foam is formed.	+
Steroids/Triterpenoids	Triterpenoids produce a bluish green color.	A bluish green color is formed.	+

Bay leaf extract nanophytosomes were successfully obtained by reflux, precipitation, drying, hydration and ultrasonication processes (Jafar et al., 2022). The bay leaf extract nanophytosomes formed were then characterized including particle size, polydispersity index, and zeta potential.

Table 2. Formulation and characterization of h-1 bay leaf extract nanophytosomes

H-1 Formulation					Z-Ave		ZP
					nm	PdI	mV
Code	Bay Leaf Extract	Phosphatidylcholine	Plantacare	Cremophor			
F1	0.095	4	13.5	-	209.73±1.22	0.33±0.02	-26.30±1.54
F2	0.095	4.25	31.75	-	240.77±20.07	0.72±0.23	-28.83±9.91
F3	0.095	4.5	50	-	164.67±7.83	0.66±0.04	-31.10±2.41
F4	0.095	4.37	40.8	-	149.43±3.50	0.56±0.05	-35.87±3.71
F5	0.095	4.12	22.6	-	89.19±0.59	0.16±0.01	-29.47±2.16
F6	0.095	4	-	13.5	115.14±3.11	0.50±0.07	-18.73±1.81
F7	0.095	4.25	-	31.75	77.09±40.97	0.27±0.09	-12.93±0.45
F8	0.095	4.5	-	50	124.17±57.34	0.46±0.02	-19.23±0.35
F9	0.095	4.37	-	40.8	281.47±143.57	0.37±0.05	-20.33±3.23
F10	0.095	4.12	-	22.6	79.48±29.63	0.52±0.15	-31.80±2.82

Table 3. Formulation and characterization of h-30 leaf extract nanophytosomes

H-30 Formulation					Z-Ave		ZP
					nm	PdI	mV
Code	Bay Leaf Extract	Phosphatidylcholine	Plantacare	Cremophor			
F1	0.095	4	13.5	-	249.00±1.68	0.26±0.04	-28.95±1.27
F2	0.095	4.25	31.75	-	46.52±11.25	0.39±0.06	-19.05±0.40
F3	0.095	4.5	50	-	45.05±3.93	0.42±0.05	-19.40±0.67
F4	0.095	4.37	40.8	-	73.40±1.32	0.51±0.02	-21.80±1.93
F5	0.095	4.12	22.6	-	133.70±2.00	0.19±0.03	-32.90±1.56
F6	0.095	4	-	13.5	68.41±1.05	0.17±0.03	-14.35±0.60
F7	0.095	4.25	-	31.75	143.70±44.47	0.28±0.02	-17.95±3.07
F8	0.095	4.5	-	50	392.21±451.52	0.92±0.09	-12.15±0.85
F9	0.095	4.37	-	40.8	14.73±0.55	0.22±0.02	-12.80±1.10
F10	0.095	4.12	-	22.6	61.12±4.11	0.39±0.03	-16.25±1.31

The results of particle size characterization in the bay leaf extract nanophytosome formulation showed that the smallest particle size on day 1 (D-1) was in formula F5 of 89.19±0.59 nm, while on day 30 (D-30) the smallest particle size was in formula F3 of 45.05±3.93 nm. In general, the particle size is still in the range of <1000 nm, indicating that changes in particle size during storage at room temperature do not provide significant differences and remain within the appropriate nanoparticle size range (Jafar et al., 2020).

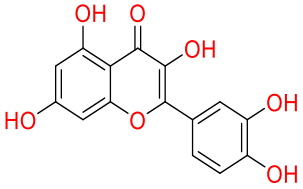
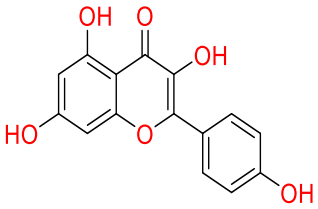
The polydispersity index (PdI) in all formulas showed varying values but remained within the range indicating a relatively even particle size distribution. At H-1, the smallest PdI value was found in formula F5 at 0.16±0.01, while at H-30 the smallest PdI value was also found in formula F6 at 0.17±0.03. PdI values below 0.3 indicate good particle size homogeneity, although there are several formulas with higher PdIs that are still within reasonable limits, indicating that the dispersion system is still physically stable (Jafar et al., 2021; Wanjiru et al., 2022).

Zeta potential characterization shows that the zeta potential value at H-1 ranges from -12.93 mV to -35.87 mV, with the highest value shown by formula F4 (-35.87±3.71 mV), while at H-30 the zeta potential value ranges from -12.15 mV to -32.90 mV, with the highest value shown by formula F5 (-32.90±1.56 mV). The large negative zeta potential value indicates the presence of repulsive forces between particles which can increase the stability of the nanoparticle system. Overall, all formulas show good stability potential because they are in the range of ±-25 mV, which is generally considered the threshold for electrostatic stability of a nanoparticle system (Jafar et al., 2020; Sahin et al., 2022).

In silico tests were conducted to evaluate the potential interaction of active compounds of bay leaves against the enzyme α-glucosidase computationally. The process began with the

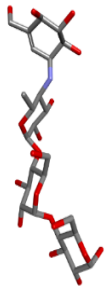
preparation of ligands, namely Quercetin and Kaempferol downloaded from PubChem in .sdf format, converted to .pdb using Avogadro, and geometry optimized using Gaussian with the Density Functional Theory (DFT) method to obtain the most stable conformation. Analysis of physicochemical properties was carried out based on Lipinski's rules, while pharmacokinetic and toxicity predictions used the preADMET webserver (Torres et al., 2019).

Table 4. Test ligand preparation

Ligand	2D Structure Ligand Code	Pubchem ID
Quercetin		5280343
Camellia		5280863

Preparation of the target protein was carried out by downloading the structure of α-glucosidase (PDB ID: 5NN8) from RCSB PDB, followed by cleaning water molecules and natural ligands using Discovery Studio, and adding hydrogen atoms using AutoDock (Riyaphan et al., 2021).

Table 5. Target proteins

PDB code	Macromolecules	Native Ligand
5NN8		 Acarbose

Next, the docking method was validated through redocking with an RMSD result of 1,660 Å, indicating a valid method. Molecular docking simulations were performed using AutoDock 4.2.3 with gridbox settings based on the validation results (Shivanika et al., 2020). The highest binding energy value was recorded at -10.11 kcal/mol, with an inhibition constant of 38.83 nM.

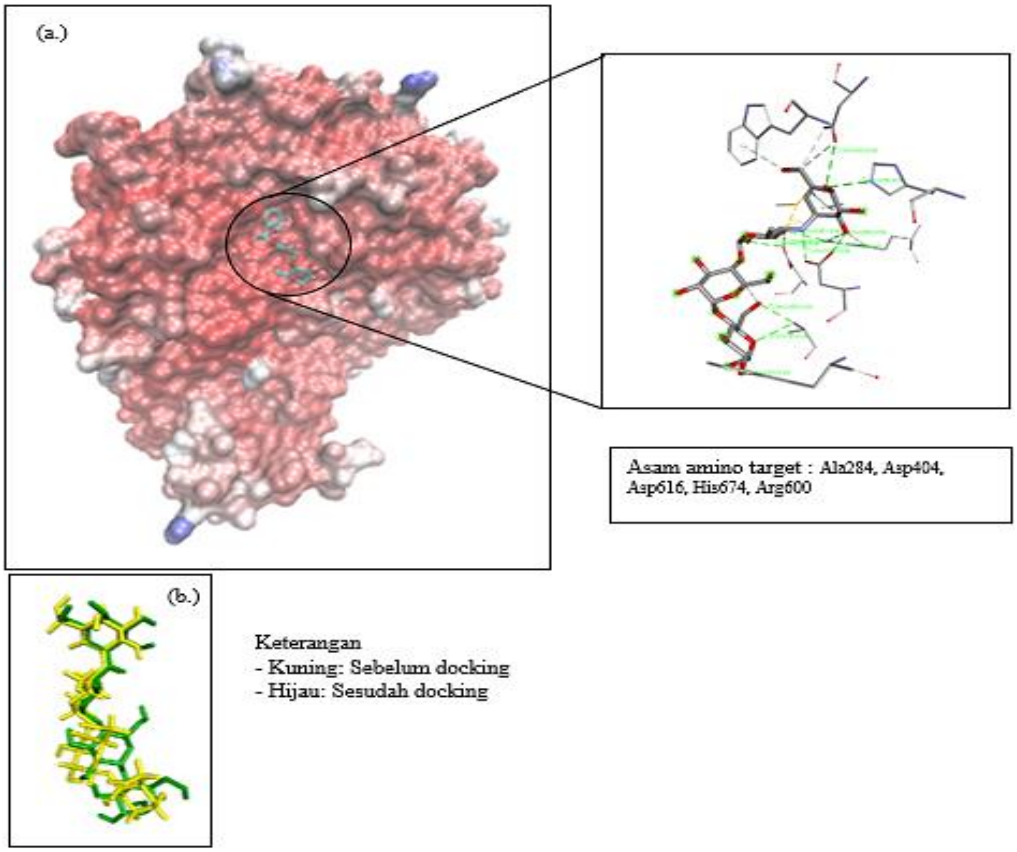


Figure 1. Molecular docking visualization validation of native protein ligand acid-alpha-glucosidase (a) visualization overlay (b)

Table 6. Results molecular docking of ligand to protein tyrosine-protein kinase BTK

Ligand	Binding energy (kcal/mol)	Inhibition constant	Number of hydrogen bonds (HB)	Number of hydrophobic interactions (HI)
Native Ligand	-10.11 kcal/mol	38.83 nM	11 HB : Ala284, Arg600, Trp618, Asp282, Asp616, Asp404, His674	1 HI : Trp376
Quer	-5.67 kcal/mol	69.73 uM	7 HB : Arg281, Ala284, Arg600, Asp518, Asp616, Asp282, Asn524	1 HI : Ala555
Kaem	-5.83 kcal/mol	53.17 uM	5 HB : Arg281, Ala284, Asp616, Asp282, Asn524	2 HI : Trp481, Ala555

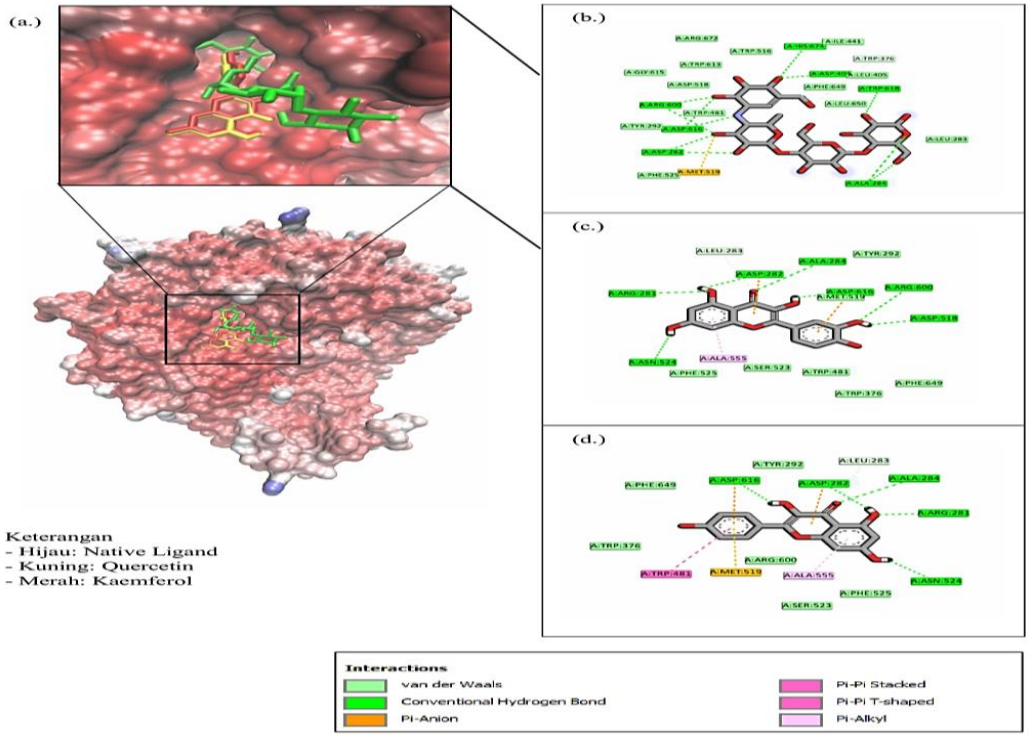


Figure 2. Visualization of molecular docking of ligand-protein acid-alpha-glucosidase (a.) native ligand (b.) quercetin (c.) kaemferol (d.)

The docking results were visualized using Discovery Studio Visualizer and VMD, which showed the presence of intermolecular interactions between the ligand and the active residues of the target protein. Geometry optimization showed that both compounds have stable minimum energy, as well as low HOMO-LUMO gap values, indicating high stability and low reactivity (Maalaoui et al., 2023).

These results indicate that although both ligands bind the enzyme with sufficient strength, they are less effective than NL, but slightly better than quercetin in terms of inhibition. The test ligands This indicates that they have variations in affinity and inhibition ability, but are not as effective as ligands with lower binding energy. By showing a negative binding energy value, it means that the ligand can interact with the target using minimal energy to interact, a low binding free energy value indicates a stable ligand-target complex (Salehi et al., 2020).

CONCLUSION

The nanophytosome formula of bay leaf extract showed good physicochemical characteristics with a particle size of <1000 nm, a polydispersity index (PDI) of <0.5 reflecting particle homogeneity, and a zeta potential of ±25 mV indicating the stability of the dispersion system. These parameters indicate that the nanophytosome-based delivery system is able to increase the stability and potential bioavailability of active compounds contained in bay leaf extract. In silico studies support the pharmacological potential of bay leaf extract, where the main active compounds such as quercetin and kaempferol show strong binding affinity to the α-glucosidase enzyme, playing an important role in the mechanism of glucose absorption inhibition. Thus, bay leaf extract in the form of nanophytosome preparations not only shows a stable physical profile, but also has prospects as an antidiabetic agent through the mechanism of molecular inhibition of target enzymes.

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