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ROLE OF CINNAMON COMPOUNDS IN GLYCEMIC CONTROL AND DIABETES MANAGEMENT

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Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels, resulting from either insulin resistance or insufficient insulin production. Insulin resistance, particularly in Type 2 Diabetes, leads to impaired glucose metabolism and worsened insulin sensitivity. Cinnamon, known for its therapeutic properties, has been investigated for its potential to alleviate insulin resistance and improve glucose uptake. This study explores the impact of C. cassia extract on diabetic patients, particularly focusing on its antioxidant, anti-inflammatory, antimicrobial, and anti-diabetic properties. The C. cassia bark was extracted using methanol and ethanol, followed by qualitative and quantitative analyses to identify key phytochemicals such as polyphenols, flavonoids, and cinnamaldehyde. These compounds were found to significantly enhance insulin sensitivity and lower blood glucose levels. Antioxidant activity was assessed using the DPPH assay, showing promising radical scavenging effects, particularly in the ethanolic extract. Anti-diabetic activity was confirmed through alpha-amylase inhibition, while antimicrobial testing demonstrated significant inhibition against S. aureus. The results suggest that C. cassia extract, particularly its methanolic form, holds great promise as a natural, cost-effective adjunct to diabetes management, offering benefits in glucose regulation, wound healing, and infection prevention. The findings provide strong evidence for the potential role of cinnamon as a complementary therapy in diabetes care, contributing to a holistic approach for managing the disease and its complications.

INTRODUCTION

Diabetes is a chronic condition where the body either doesn't produce enough insulin or cannot use it effectively, leading to high blood sugar (Global Burden of Disease Collaborative Network, 2020). Insulin regulates blood sugar and metabolism of carbohydrates, fats, and proteins (Poznyak et al., 2020). Poorly managed diabetes can cause hyperglycemia, damaging blood vessels and nerves. In 2019, it caused about 1.5 million deaths, nearly half under age 70. Over two decades, the global age-standardized death rate rose by 3%, with a 13% increase in lower-middle-income countries. Regular care is vital to prevent complications and improve life quality.

Insulin resistance in diabetes disrupts metabolism in the liver, muscles, and fat tissues. Symptoms vary by type and disease duration, including excessive hunger, thirst, urination, weight loss, and vision

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issues, especially in youth with low insulin levels (Rossi et al., 2019). Early type 2 diabetes may be symptomless. Severe hyperglycemia can lead to confusion or coma, and rarely, untreated diabetes can cause death from ketoacidosis or hyperosmolar syndrome (Poznyak et al., 2020).

The American Diabetes Association classifies diabetes into four main types: type 1, type 2, various specific forms, and gestational diabetes mellitus (GDM). Wilkin's accelerator hypothesis suggests that type 1 and type 2 diabetes may be different expressions of the same issue—insulin resistance—in individuals with different genetic backgrounds (Kahanovitz, Sluss, & Russell, 2017).

In type 1 diabetes, symptoms and a decline in insulin levels can begin up to two years before diagnosis. Initially, insulin secretion increases as a compensatory response but rapidly declines after diagnosis, especially in the first year. Eventually, insulin production becomes minimal or absent. Even with normal blood sugar levels, significant fluctuations may indicate T1D. Monitoring markers like blood glucose and C-peptide can help assess risk (Kahanovitz, Sluss, & Russell, 2017).

In type 2 diabetes, insulin secretion defects are key. Insulin output varies based on sensitivity, and low disposition indices reflect poor compensation for insulin resistance. Obese individuals with T2D may have higher insulin levels than lean individuals, but it's insufficient due to significant insulin resistance (Galicia-Garcia et al., 2020).

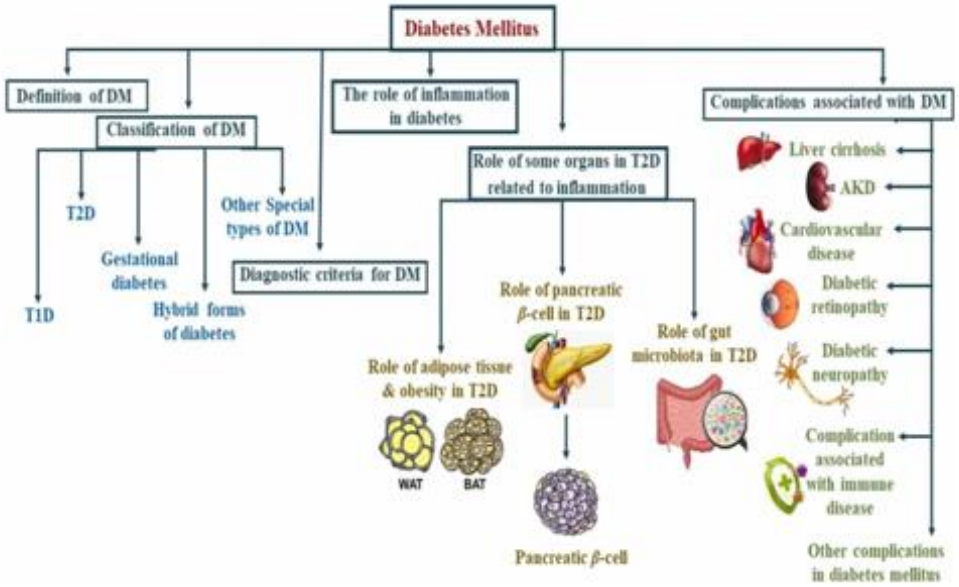

Figure 1. **Diabetes mellitus: types, inflammation-related complications, and the interactions between organs in T2D**

Type 2 diabetes, which accounts for about 95% of all diabetes cases globally, worsens over time due to the gradual decline in beta-cell function, leading to persistent hyperglycemia (Wysham & Shubrook, 2020). Risk factors include aging, obesity, poor diet, physical inactivity, PCOS, hypertension, and high cholesterol (Olimjonovna, 2024). Gestational diabetes, influenced by similar factors such as obesity, age, family history, PCOS, and environmental toxins, can lead to complications like preeclampsia, cesarean delivery, and macrosomia (Plows et al., 2018). Hormone-based therapies like GLP-1 receptor agonists are now widely used for managing type 2 diabetes and obesity (Olimjonovna, 2024).

Cinnamon, derived from the genus *Cinnamomum* in the Lauraceae family, has long been used for culinary and medicinal purposes, dating back to 1400 BCE (Mollazadeh et al., 2016; Dugoua et al., 2017). The European Scientific Cooperative on Phytotherapy and the German Commission E recognize *C. zeylanicum* and *C. cassia* for their therapeutic use (Blumenthal et al., 2018). Cinnamon bark, rich in

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procyanidins and catechins, exhibits antioxidant and anti-inflammatory properties (Nonaka et al., 2020). It contains compounds like cinnamaldehyde, cinnamic acid, and various polyphenols that provide neuroprotective, cardioprotective, and hepatoprotective effects (Nabavi et al., 2015). Cinnamon phyto-complexes also show promise in managing conditions like colitis, rheumatoid arthritis, and diabetes by reducing inflammation (Hemmati et al., 2018).

Inflammation is a natural immune response to injury or infection, but chronic inflammation can lead to various health problems. Compounds in cinnamon may help regulate this response, offering potential therapeutic benefits. The ethanolic extract of *Cinnamomum cassia* has shown strong anti-inflammatory effects by inhibiting NF-κB activation via the Src/Syk pathway. Additionally, its aqueous extract has been found to reduce blood levels of tumor necrosis factor-α induced by lipopolysaccharides (Hong et al., 2022).

Cinnamon bark extracts help lower postprandial glucose by inhibiting α-amylase and α-glucosidase (Adisakwattana et al., 2021). Cinnamaldehyde enhances insulin sensitivity via PPARδ, PPARγ, and RXR activation (Hafizpur et al., 2015). Its water-soluble extracts boost insulin signaling and stimulate GLUT4, IRS1, and IR-β production, aiding glucose uptake (Cao et al., 2020). These effects improve blood sugar control and metabolism, making cinnamon a potential natural aid for diabetes management (Miyazak et al., 2021).

Methodology:

The bark of *Cinnamomum cassia* was collected from a nursery in Lahore, ground into a fine powder, and stored in an airtight container. For extraction, 50 g of the powdered bark was macerated separately in 500 mL of methanol and ethanol for 72 hours, filtered, and stored. Qualitative phytochemical screening was performed using standard methods to detect carbohydrates, alkaloids, saponins, flavonoids, and steroids. Antimicrobial activity was assessed via the well diffusion method against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, while antioxidant activity was evaluated using the DPPH assay, with ascorbic acid as a standard. Anti-diabetic activity was tested through alpha-amylase inhibition using metformin as a control, and anti-inflammatory activity was assessed using BSA denaturation inhibition, with NSAIDs as the standard.

GC-MS analysis identified multiple bioactive metabolites in the extracts, including fatty acids, sugars, flavonoids, and alkaloids. The analysis was performed on an Agilent GC-7890A/MS-5975C using a DB-5MS column, and results were validated using the NIST and PubChem libraries. Additionally, in-silico molecular docking studies were conducted to evaluate the binding affinity of sulfur-containing compounds like germacrene and alpha-calacorene (PubChem IDs: 5371402, 2346, 7505) with target protein 1OET obtained from the Protein Data Bank.

RESULTS

The phytochemical screening of *Cinnamomum cassia* extracts revealed the presence of key bioactive compounds such as alkaloids, flavonoids, carbohydrates, and saponins, which are known to contribute to various pharmacological effects. Notably, steroids were absent in all tested fractions. These phytochemicals play a crucial role in the therapeutic potential of the plant, supporting its traditional use in treating ailments such as infections, inflammation, oxidative stress, and metabolic disorders. The identification of these constituents through qualitative analysis highlights the medicinal relevance of *C. cassia* and provides a foundation for further pharmacological investigation.

Table 1: ***Phytochemical analysis and their corresponding indications confirm the presence of the plant compounds listed above***

Serial No	Test Name	Results	M	E
01	Benedict`s Test(Reducing Carbohydrates)	Dark brown color indicates the presence of Reducing Carbohydrates	++	++

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02	Hager`s Test	Light Yellow Color Indicates the Presence of Alkaloids.	++	++
03	Wagner`s Test	Reddish brown color indicates the presence of alkaloids.	++	++
04	Foam Test (Saponins Test)	Foam indicates the presence of saponins	++	++
05	Steroid Test	No Presence of lower reddish Brown +layer / Noresults	_	_
06	Flavonoids test	Intense yellow to become colorless solution indicate the presence of flavonoids	++	++

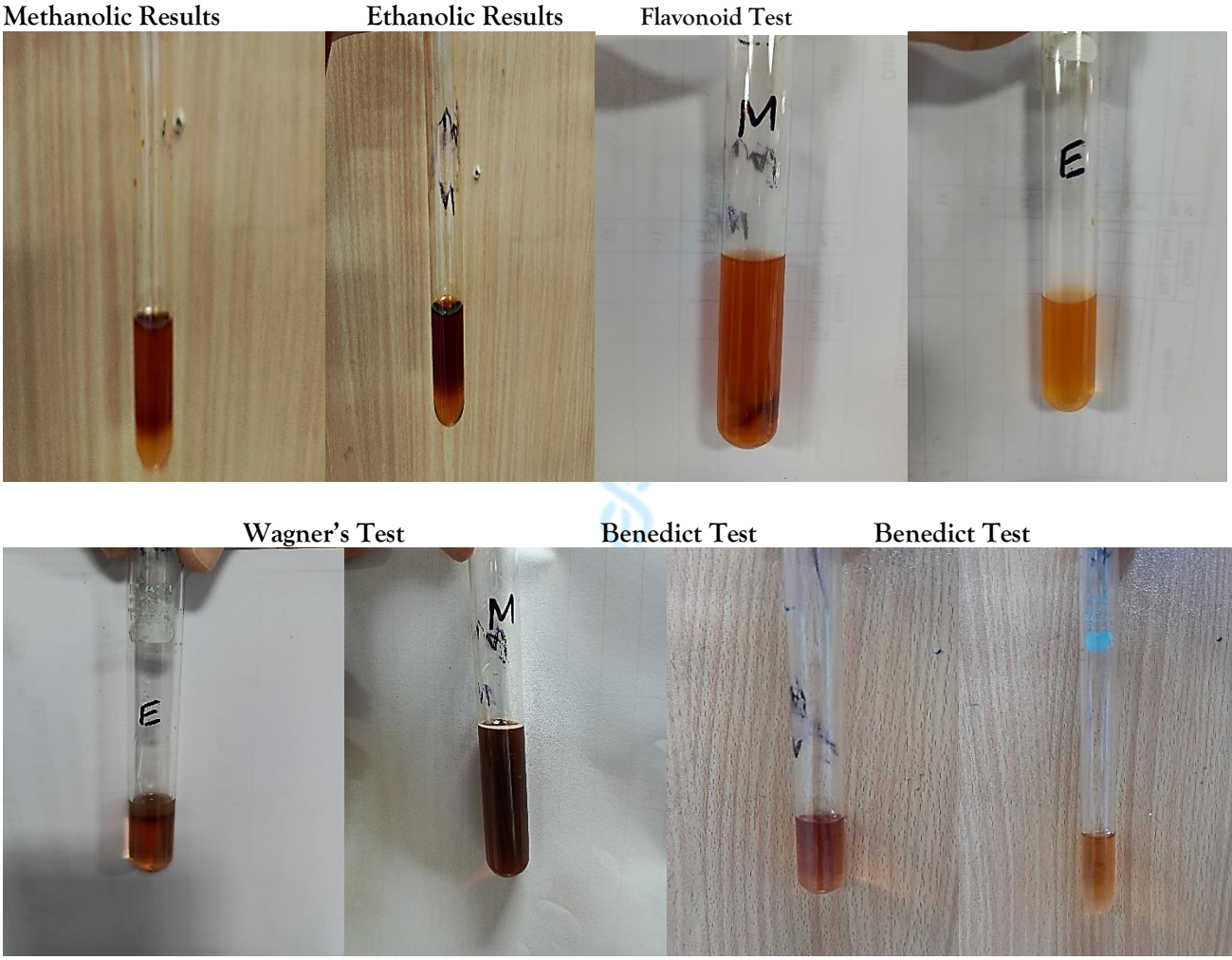

***Figure 2*: Qualitative tests results of phytochemical analysis methanolic and ethanolic fractions, all results positive except steroids.**

The methanolic extract of *C. cassia* showed strong antimicrobial activity against *Staphylococcus aureus*, with the highest inhibition zone of 23 mm at 5 µg/10 mL. In contrast, ethanolic extracts displayed weaker effects, with a maximum zone of 17 mm. Activity against *Pseudomonas aeruginosa* was comparatively lower in all samples. Against *P. aeruginosa*, the methanolic extract showed stronger

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inhibition (26 mm at 5 µg/10 mL) than the ethanolic extract, confirming its superior antibacterial potency at higher concentrations.

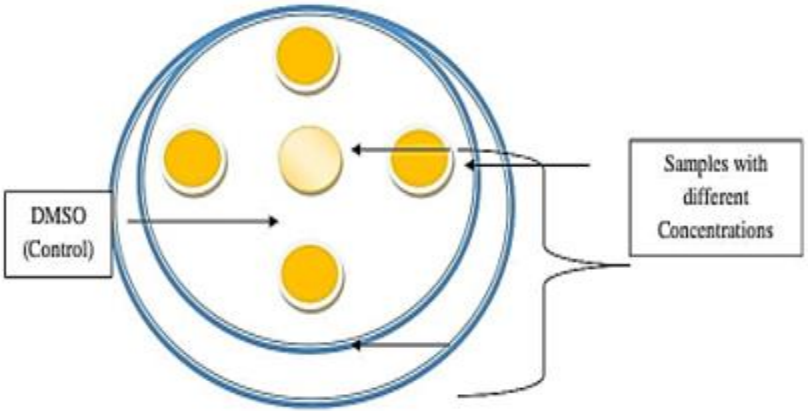

Figure 3. **This figure showing that petri plate with wells and control**

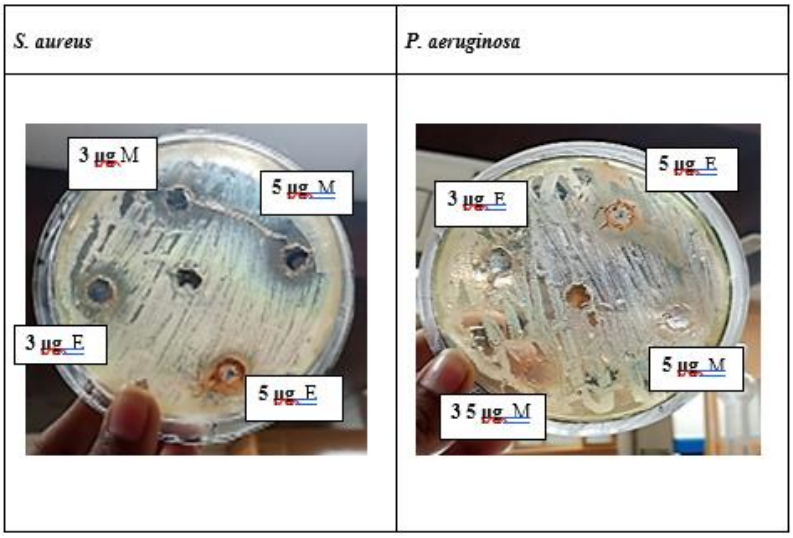

Figure 4: **Outcomes of antimicrobial efficacy against *S. aureus* and *P. aeruginosa* using methanolic and ethanolic extracts at varying concentrations**

Figure a) The antimicrobial activity against *Staphylococcus aureus* was assessed using methanolic and ethanolic extracts at concentrations of 5 µg in 10 mL DMSO and 3 µg in 10 mL DMSO. DMSO served as the control, positioned at the center of the agar plates. The inhibition zones were observed around the discs containing the extracts, with the control (DMSO) showing significant antimicrobial activity. **Figure b)** The antimicrobial activity against *Pseudomonas aeruginosa* was evaluated using methanolic and ethanolic extracts at concentrations of 5 µg in 10 mL DMSO and 3 µg in 10 mL DMSO. DMSO was used as the control, placed at the center of the agar plates. The zones of inhibition were measured around the extract-containing discs, with the control (DMSO) showing no noticeable antimicrobial effect.

The anti-inflammatory assay, measured at 490 nm and 630 nm, evaluated the radical scavenging activity (% RSA) of methanolic and ethanolic extracts, with NSAID as the standard. At 490 nm, the methanolic extract consistently demonstrated high % RSA, starting at 86.27 %, but decreased to 78.59 % at higher concentrations. In contrast, the ethanolic extract showed significant variation, peaking at 84.97

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% RSA at the third concentration after a sharp drop at the second.

At 630 nm, the methanolic extract displayed higher % RSA than the ethanolic extract, with values of 96.43 %, 95.90 %, and 94.53 % at increasing concentrations. The ethanolic extract started strong at 95.69 % but dropped to 81.40 % at the second concentration before increasing to 96.06 %. Overall, the methanolic extract exhibited stronger and more consistent anti-inflammatory activity, suggesting it may offer greater potential compared to the ethanolic extract.

Table 2: ***The results of Anti-inflammatory activity at various concentrations, along with the corresponding percentage and standard deviation values***

Anti-Inflammatory assay readings at 490nm				
Standard (NSAID)	Methaolic extract	% RSA	Ethanolic extract	% RSA
0.612	0.084	86.274	0.098	83.986
0.612	0.097	84.150	0.532	13.071
0.612	0.131	78.594	0.092	84.967

Anti-Inflammatory assay readings at 630nm				
Standard (NSAID)	Methaolic extract	% RSA	Ethanolic extract	% RSA
1.903	0.068	96.426	0.082	95.691
1.903	0.078	95.901	0.354	81.397
1.903	0.104	94.534	0.075	96.0588

Quantitative analysis of the compounds in the methanol and ethanol fractions of C. cassia extracts was conducted using GC-MS, as presented in Tables 3 and 4. Several compounds were separated and identified in both the methanol and ethanol fractions. Two sulfur-containing compounds were identified in the methanol fraction: 2-(2-Methylvinyl) thiophene and Benzene, (Isothiocyanatomethyl). Previously, only one sulfur-containing compound, an antioxidant sulfur-containing imidazoline alkaloid, was identified in C. *cassia*.

Table 3: ***Compounds detected in the methanolic extract through GC-MS analysis***

Sr	**Compound Name**	**Chemial Formula**	**Molecular Weight (g/mol)**	**Retention Time (min)**	**Peak Percentage (%)**
1	Cyclotetrasiloxane, octamethyl	C14H28O2	120	2.270	1.45
2	Methanamine, N-methoxy	$C_{14}H_{28}O_2$	228.37	2.373	0.72
3	2-Propen-1-ol	$C_{16}H_{32}O_2$	256.42	2.491	0.81
4	2-Hydrazino-4,6-dimethylpyrimidine	C18H34O2	282.47	3.390	0.62
5	Cinnamaldehyde, (E)-	$C_{18}H_{36}O_2$	284.5	4.752	70.48
6	2-Propenal, 3-phenyl	$C_{18}H_{32}O_2$	280.4	4.837	1.77
7	Copaene	$C_{18}H_{30}O_2$	278.4	5.650	1.83
8	Cyclotetrasiloxane, octamethyl	$C_{17}H_{36}$	240.5	6.259	1.48
9	gamma.-Muurolene	$C_{24}H_{50}$	338.7	6.470	0.86
10	Naphthalene, 1,2,4a,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)	$C_{25}H_{52}$	352.7	6.651	5.99

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11	Naphthalene, 1,2,3,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)	$C_{16}H_{28}O$	236.39	6.812	3.11
12	Naphthalene, 1,2,3,4-tetrahydro-1,6-dimethyl-4-(1-methylethyl)	$C_{21}H_{17}NO_2$	315.4	6.849	1.20
13	2-Propenal, 3-(2-methoxyphenyl)	$C_{10}H_{15}BO$	156.04	6.876	3.67
14	Naphthalene, 1,2,3,4,4a,7-hexahydro-1,6-dimethyl-4-(1-methylethyl)	$C_{10}H_9F_3OS$	234.24	6.941	0.31
15	alpha.-Calacorene	$C_{18}H_{35}NO$	281.5	7.018	0.48
16	Naphthalene, 1,2,3,5,6,7,8,8a-octahydro-1,8a-dimethyl-7-(1-methylethenyl)	$C_{16}H_{26}O_3$	266.38	7.704	0.60
17	alpha.-Cadinol	$C_9H_{11}FN_2O_5$	246.19	7.818	2.01
18	1-Cyclohexene, 1,3,3-trimethyl-2-(1-methylbut-1-en-3-on-1-yl)	$C_{12}H_{10}S$	186.27	8.691	0.45
19	Hexadecanoic acid, methyl ester	$C_{12}H_{36}O_4Si_5$	384.84	9.709	0.55
20	Spiro[4.5]dec-6-ene	$C_{12}H_{17}NO_2$	207.27	10.836	0.43

Table 4: ***Compounds detected in the ethanolic extract through GC-MS analysis***

Sr	Compound Name	Chemical Formula	Molecular Weight (g/mol)	Retention Time (min)	Peak Percentage(%)
1	1,3-Dioxolane, 4,5-dimethyl-2-pentadecyl	C14H28O2	120	2.593	0.93
2	(4-Hexylbenzene-1,3-diyl)bis(oxy)]bis(trimethylsilane)	$C_{14}H_{28}O_2$	228.37	3.391	3.44
3	hydrazine, (4-butylphenyl)	$C_{16}H_{32}O_2$	256.42	4.634	0.54
4	Cinnamaldehyde, (E)-	C18H34O2	282.47	4.738	14.60
5	4-Hydrazinylpyridin-2(1H)-one	$C_{18}H_{36}O_2$	284.5	4.839	5.06
6	Cinnamaldehyde,(E)-	$C_{18}H_{32}O_2$	280.4	4.927	0.08
7	Copaene	$C_{18}H_{30}O_2$	278.4	5.650	0.28
8	Cinnamaldehyde dimethyl acetal	$C_{17}H_{36}$	240.5	5.781	0.20
9	1-Heptene, 1,3-diphenyl-1-(trimethylsilyloxy)-	$C_{24}H_{50}$	338.7	6.261	2.99
10	Naphthalene, 1,2,3,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-, (1S-cis)-	$C_{25}H_{52}$	352.7	6.469	0.31
11	Benzene, 1,1'-(1-methyl-2-butynylidene)bis	$C_{16}H_{28}O$	236.39	6.650	2.98
12	1-Isopropyl-4,7-dimethyl-1,2,3,5,6,8a-hexahydronaphthalene	$C_{21}H_{17}NO_2$	315.4	6.811	1.57

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13	cis-Calamenene	$C_{10}H_{15}BO$	156.04	6.850	0.60
14	(E)-3-(2-Methoxyphenyl) acrylaldehyde	$C_{10}H_9F_3OS$	234.24	6.880	1.27
15	Naphthalene, 1,2,3,4,4a,7-hexahydro-1,6-dimethyl-4-(1-methylethyl)-	$C_{18}H_{35}NO$	281.5	6.941	0.69
16	4-Isopropyl-6-methyl-1-methylene-1,2,3,4-tetrahydronaphthalene	$C_{16}H_{26}O_3$	266.38	7.017	0.29
17	Perhydro-htx-2-one, 2-depentyl-, acetate ester	$C_9H_{11}FN_2O_5$	246.19	7.556	3.23
18	Naphthalene, 1,2,3,4,4a,7-hexahydro-1,6-dimethyl-4-(1-methylethyl)-	$C_{12}H_{10}S$	186.27	7.704	0.32
19	tau.-Muurolol	$C_{12}H_{36}O_4Si_5$	384.84	7.818	1.05
20	benzenamine, N-[bis(2,4,6-trimethylphenyl) bory]-	$C_{12}H_{17}NO_2$	207.27	8.682	4.14
21	7,9-Di-tert-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione	$C_{14}H_{22}O$	206.32	9.623	0.17
22	5-(p-Aminophenyl)-4-(O-tolyl)-2-thiazolamine	$C_{23}H_{32}O_2$	340.5	9.684	6.24
23	Hexadecanoic acid, ethyl ester	$C_{18}H_{38}$	254.5	10.149	0.15
24	3,6-Dioxa-2,4,5,7-tetrasilaoctane, 2,2,4,4,5,5,7,7-octamethyl	$C_{19}H_{38}O_4$	330.5	10.598	4.28
25	9,12-Octadecadienoic acid (Z,Z)-, methyl ester	$C_{24}H_{38}O_4$	390.6	10.797	0.33
26	9-Octadecenoic acid (Z)-, methyl ester	$C_{12}H_{36}O_4Si_5$	384.84	10.837	1.20
27	Methyl stearate	$C_{12}H_{17}NO_2$	207.27	10.991	1.45
28	3,6-Dioxa-2,4,5,7-tetrasilaoctane, 2,2,4,4,5,5,7,7-octamethyl	$C_{18}H_{37}I$	380.4	11.426	4.04
29	3,6-Dioxa-2,4,5,7-tetrasilaoctane, 2,2,4,4,5,5,7,7-octamethyl	$C_{10}H_{11}N_3O_5$	253.21	12.196	3.77
30	Diisooctyl adipate	$C_{36}H_{74}O$	523	12.552	0.24
31	N-Benzyl-N-ethyl-p-isopropylbenzamide	$C_{24}H_{38}O_4$	390.6	13.054	2.88
32	Bis(2-ethylhexyl) phthalate	$C_{20}H_{34}O_4$	338.5	13.464	9.17
33	N-Benzyl-N-ethyl-p-isopropylbenzamide	$C_{21}H_{42}O_4$	358.6	13.740	2.03
34	N-Benzyl-N-ethyl-p-isopropylbenzamide	$C_{22}H_{32}O_2$	328.5	14.271	1.97
35	1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester	$C_{22}H_{32}O_2$	328.5	14.377	11.48
36	Cyclotrisiloxane, hexamethyl	$C_{22}H_{32}O_2$	328.5	14.504	0.57
37	4-(Aminomethyl)-2-fluorobenzonitrile	$C_{16}H_{31}NO$	253.42	14.817	0.90

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38	1,1,1,3,5,5,5-Heptamethyltrisiloxane	$C_{19}H_{24}O_4$	316.4	15.421	0.36

***In-Silico* analysis**

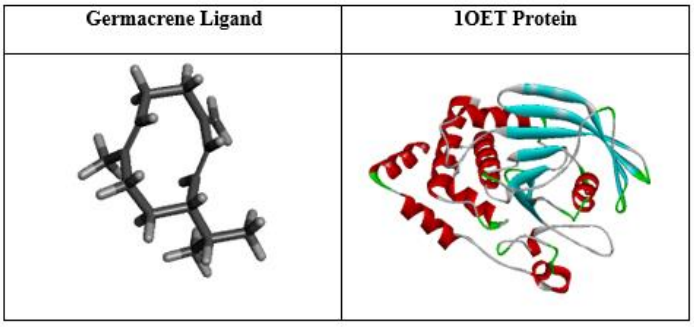

Figure 5: **The molecular visualization represents the ligand's three-dimensional conformation and the protein's ribbon structure**

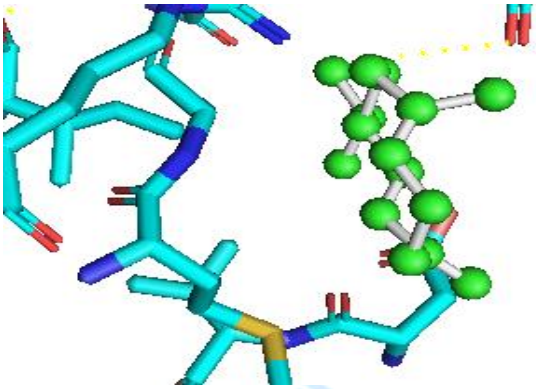

Figure 6: Molecular docking interaction of Germacrene ligand with the 1OET protein active site The image depicts the docking interaction of the Germacrene ligand (green) within the active site of the 1OET protein. The visualization highlights key atomic interactions, including hydrogen bonding (yellow dashed lines) and van der Waals forces, indicating the binding stability. This interaction is crucial for understanding the ligand's potential bioactivity and its role in modulating protein functions.

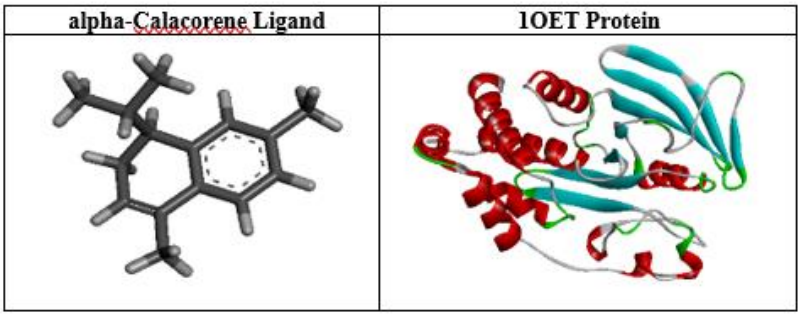

Figure 7: **Molecular structures of alpha-Calacorene ligand (left) and 1OET protein (right) used in docking analysis**

The left panel illustrates the three-dimensional structure of the alpha-Calacorene ligand, showcasing its aromatic and aliphatic groups, essential for binding interactions. The right panel displays the

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ribbon representation of the 1OET protein, highlighting its secondary structure elements, including alpha-helices (red) and beta-sheets (cyan). These molecular representations are fundamental for visualizing potential binding interactions and assessing the ligand's compatibility with the protein's active site.

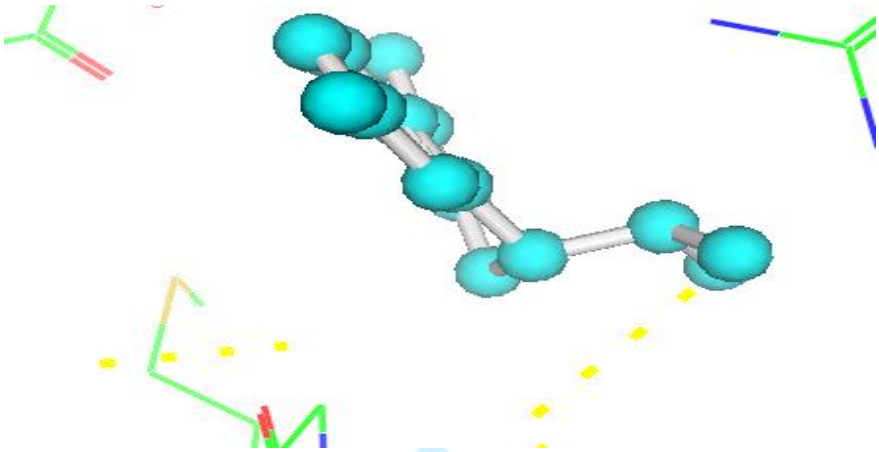

***Figure 8*: Docking interaction of alpha-Calacorene ligand within the active site of 1OET protein**

The figure illustrates the binding conformation of the alpha-Calacorene ligand (cyan) in the active site of the 1OET protein. Key interactions, such as hydrogen bonds (yellow dashed lines) and other non-covalent forces, are visualized. This representation highlights the ligand's orientation and potential binding stability within the protein's active pocket, providing insights into its bioactivity.

DISCUSSION

The therapeutic potential of *Cinnamomum cassia* is attributed to its synergistic blend of bioactive compounds such as tannins, alkaloids, saponins, flavonoids, phenols, and terpenoids, which exhibit antioxidant, antimicrobial, anti-inflammatory, and antidiabetic properties (Ahamed, 2013; Cong et al., 2007). Methanolic, ethanolic, and aqueous extracts show higher phytochemical concentrations and notable pharmacological effects. GC-MS analysis identified 20 compounds in the methanolic extract, including heptadecanoic acid ethyl ester, hexadecanoic acid, and 9,12,15-octadecatrienoic acid, which showed antioxidant, antimicrobial, cholesterol-lowering, and anticancer activities. *C. cassia* extracts improved insulin levels in STZ-induced diabetic rats, similar to *Psidium guajava* (Manikandan, 2013), and clinical studies reported no toxicity at doses up to 6 g/day (Dugoua et al., 2007). Flavonoids and polyphenols in the extract enhance insulin secretion, restore β-cell function, and reduce oxidative stress (Hasanzade et al., 2013; Al-Waili et al., 2017). Compounds like 9-octadecenoic acid showed strong binding with PPARα and PPARγ, supporting their role in managing diabetes and cardiovascular diseases (Mangelsdorf et al., 2007; Huttada, 2016). In silico docking revealed stable binding of Germacrene and alpha-Calacorene with 1OET protein, suggesting potential for modulating metabolic processes (binding affinities -4.4 and -4.3 kcal/mol, respectively), reinforcing their antidiabetic prospects.

CONCLUSION

This study highlights the therapeutic potential of *Cinnamomum cassia* extracts in diabetes management. The methanolic extract, rich in cinnamaldehyde and flavonoids, showed superior glucose-lowering and antimicrobial effects, while the ethanolic extract demonstrated strong antioxidant activity at lower doses. Both extracts inhibited α-amylase, reduced oxidative stress, and displayed significant antimicrobial properties, particularly against *S. aureus* and *P. aeruginosa*. These results suggest that *C. cassia* offers a natural, effective, and multi-targeted approach to managing diabetes and its complications.

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