Nigerian Research Journal of Biological Sciences **(ISSN: 2971-7116)**
Volume 3, Issue 1, 2025

Dual Evaluation of *Curcuma longa*: *In Silico* Docking and *In Vivo* Comparison with Ginger and Metformin

*[1]Alaebo Prince Ogochukwu, [1]Nwuke Chinedu Paulinus, [1]Egbuonu Anthony Chinedum Cemaluk, [1]Achi Ngozi Kalu, [2]Abalihe Chidera Nnamdi, [1]Nwede Chimaobi Anthony, Okechukwu Kingsley Ifeanyi, Israel Victory Onyedikachi, Okezue Jones David, Chukwu Livinus Chinonso and [1]Enyinna Wisdom Chukwuka

[1]Department of Biochemistry, College of Natural Sciences, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria

[2]Department of Pharmacy, Faculty of Natural Sciences,
Nnamdi Azikiwe University, Awka, Anambra, State, Nigeria

*Corresponding Author: alaebo.prince@mouau.edu.ng

Received 19/9/2025**, Accepted** 3/10/2025**, Published online** 8/10/2025

Abstract

Diabetes mellitus is a chronic metabolic disorder marked by elevated blood glucose due to insulin dysfunction. This study investigates the antidiabetic potential of *Curcuma longa* (turmeric) using in silico and in vivo methods. Initially, 40 phytocompounds from *Curcuma longa* were screened for drug-likeness via Lipinski's Rule of Five, and selected compounds were docked against four key glucose metabolism targets: AMPK (4ZHX), DPP-4 (5Y7H), PPAR-γ (5Y2O), and SGLT2 (8HEZ). Several compounds showed strong binding affinities, comparable to standard antidiabetic drugs. In the in vivo study, antidiabetic effects of *Curcuma longa* and *Zingiber officinale* (ginger) were evaluated in alloxan-induced diabetic rats and compared with Metformin. Fasting blood glucose was measured at baseline and after 14 days. All treatment groups showed significant glucose reductions, with the highest drop observed in the 400 mg/kg curcumin and gingerol group (from 229.75 ± 46.78 to 50.00 ± 0.00 mg/dL), surpassing the Metformin group (from 253.75 ± 16.54 to 66.25 ± 4.73 mg/dL). Both 200 and 400 mg/kg doses significantly ($p < 0.05$) outperformed untreated and Metformin-treated controls. These findings highlight the promising antidiabetic efficacy of *Curcuma longa*, supported by molecular docking and in vivo results, suggesting potential for further therapeutic development.

Keywords: *Curcuma longa*, Antidiabetic activity, Molecular docking, *In silico* analysis, *In vivo* study, Metformin

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, arising from impaired insulin secretion, insulin resistance, or both [1]. Its global burden is escalating rapidly, with over 700 million individuals projected to be affected by 2045 [2]. While conventional antidiabetic drugs such as Metformin remain first-line treatments, their long-term use is frequently

accompanied by side effects including gastrointestinal disturbances, lactic acidosis, and hepatotoxicity [3]. These limitations have prompted a growing interest in alternative therapies that are safer, cost-effective, and readily accessible.

Herbal remedies**,** particularly those derived from traditional medicinal systems, are widely used in diabetes management due to their perceived safety and multitarget efficacy [4–5]. Among these, *Curcuma longa* (turmeric) and *Zingiber officinale* (ginger) have attracted considerable attention for their phytochemical richness and reported antidiabetic effects. *Curcuma longa* contains curcuminoids**,** which exhibit hypoglycemic, antioxidant, and anti-inflammatory properties [6–7], while *Zingiber officinale* is rich in *gingerols* and *shogaols*, known to enhance insulin sensitivity and reduce blood glucose levels [8–9]. These plants are frequently included in commercial herbal formulations, but the efficacy of such crude mixtures remains largely unverified, especially when compared directly with standard pharmaceuticals.

Modern drug discovery has increasingly integrated in silico approaches like molecular docking to screen phytochemicals against key protein targets implicated in diabetes. These include 5′-AMP-activated protein kinase (AMPK) [10], dipeptidyl peptidase-4 (DPP-4) [11], peroxisome proliferator-activated receptor gamma (PPAR-γ) [12], and sodium-glucose co-transporter 2 (SGLT2) [13], all of which regulate glucose homeostasis and insulin sensitivity. However, computational predictions must be validated with in vivo studies to confirm therapeutic efficacy and safety under physiological conditions [14].

Commercially available herbal remedies often utilize crude plant extracts rather than purified bioactive compounds. These crude extracts contain a plethora of secondary metabolites, whose interactions can be synergistic, antagonistic, or neutral. Therefore, the results obtained from crude extract treatments may not reflect the true pharmacological potential of individual compounds like *curcumin* and *gingerol*, necessitating comparative evaluations between pure compounds, plant extracts, and standard drugs.

Although turmeric and ginger are widely used in folk medicine and incorporated into commercial antidiabetic herbal preparations, there is insufficient comparative data on their efficacy versus standard antidiabetic drugs like Metformin**.** Furthermore, there is a lack of clarity on the specific roles of their major bioactive compounds (e.g., *curcumin* and *gingerol*) versus the whole crude extracts**,** particularly in validated diabetic animal models.

This study aims to evaluate and compare the antidiabetic potential of *Curcuma longa* and *Zingiber officinale* (crude extracts and/or compounds) with Metformin in alloxan-induced diabetic rats, and to explore the binding interactions of *curcumin* and *gingerol* with key diabetes-related protein targets using molecular docking. To perform molecular docking of *curcumin* and *gingerol* against key

antidiabetic protein targets including AMPK, DPP-4, PPAR-γ, and SGLT2, evaluate the in vivo antidiabetic effects of *Curcuma longa* and *Zingiber officinale* extracts in alloxan-induced diabetic albino rats, compare the biochemical and physiological outcomes (e.g., fasting blood glucose, liver function, lipid profile, oxidative stress markers) of extract-treated rats with those treated with Metformin, assess possible toxicological effects (e.g., liver enzyme elevation) at different extract doses, to determine safety thresholds. To bridge the gap between commercial herbal use and scientific validation by evaluating whether crude extract mixtures perform comparably to pure bioactives or standard drugs.

In Silico Analysis

a. Selection of Plant and Phytocompounds

Phytocompounds were selected from *Curcuma longa* (turmeric) and *Zingiber officinale* (ginger) based on extensive literature review and phytochemical databases including PubChem**,** ChEMBL, and IMPPAT**.** Key bioactive constituents identified included: Curcumin (PubChem CID: 969516), Demethoxycurcumin (CID: 5469424), Bisdemethoxycurcumin (CID: 5315472), Ar-turmerone (CID: 160611), Gingerol (CID: 442793), Shogaol (CID: 5281794). The 2D and 3D structures of these compounds were retrieved in SDF and PDB formats from PubChem and converted as needed using Open Babel.

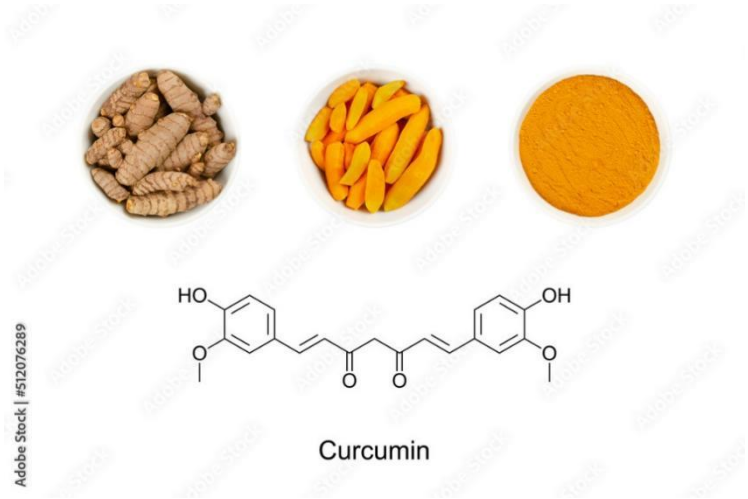


Figure 1: Chemical structures of *curcumin*.

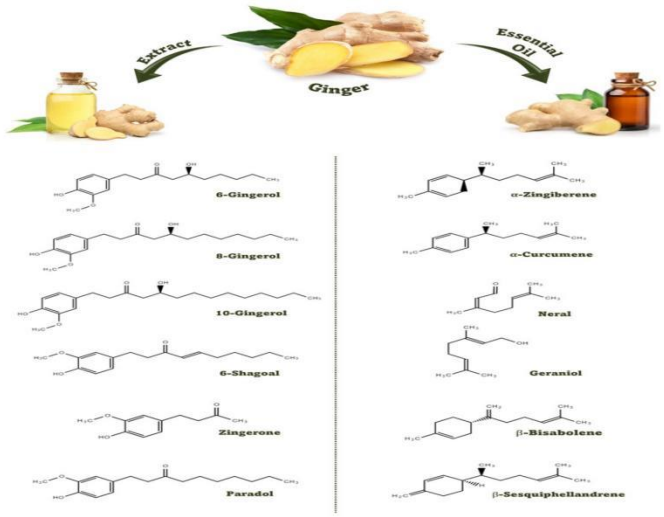


Figure 2: Chemical structures of *gingerol*.

b. Drug-likeness and ADMET Profiling

All selected compounds were screened for drug-likeness using Lipinski's Rule of Five and Veber's Rule, as implemented in DataWarrior v5.5.0 and SwissADME platforms. Compounds with more than one violation of Lipinski's rule were excluded from docking. Further ADMET profiling (absorption, distribution, metabolism, excretion, toxicity) included parameters such as: Blood–brain barrier (BBB) permeability, Gastrointestinal absorption, Hepatotoxicity, Ames mutagenicity and Reproductive toxicity

c**. Selection of Target Proteins**

Four key protein targets relevant to diabetes were selected:

Protein	**Function**	PDB ID
AMPK	Energy metabolism regulator	4ZHX
DPP-4	Degrades incretin hormones	5Y7H
PPAR-γ	Lipid/glucose homeostasis	5Y2O
SGLT2	Renal glucose reabsorption	8HEZ

Their 3D crystal structures were obtained from the RCSB Protein Data Bank and cleaned (removal of water, ligands) using PyMOL and AutoDock Tools.

Molecular Docking

Docking simulations were carried out using AutoDock Vina integrated with PyRx software. Protein structures were prepared by removing water molecules and co-crystallized ligands, and polar hydrogens

were added. Ligands were energy-minimized before docking. Binding affinities (in kcal/mol) were recorded, and top-performing compounds were visualized using Discovery Studio Visualizer.

Reference Compounds

Standard reference drugs for each protein target were docked for comparison:

4ZHX: 5-(5-hydroxyl-isoxazol-3-yl)-furan-2-phosphonic acid

5Y7H: Evogliptin and Sitagliptin

5Y2O: Pioglitazone and Rosiglitazone

8HEZ: Dapagliflozin and Empagliflozin

***In Vivo* Study**

Animals

A total of 30 healthy male albino rats (weighing 150–200g) were obtained from an accredited animal house. The rats were housed under standard laboratory conditions with a 12-hour light/dark cycle and had access to food and water *ad libitum***.**

Ethical Approval

All animal procedures were conducted following institutional ethical guidelines and were approved by the Institutional Animal Ethics Committee (IAEC).

Induction of Diabetes

Diabetes was induced by a single intraperitoneal injection of alloxan monohydrate (150 mg/kg body weight). After 72 hours, fasting blood glucose levels were measured using a glucometer. Rats with glucose levels >200 mg/dL were considered diabetic and included in the study.

Experimental Design

The diabetic rats were randomly divided into six groups (n=5 per group):

Group I: Normal Control (saline)

Group II: Diabetic Control (alloxan only)

Group III: Diabetic + Metformin (100 mg/kg)

Group IV: Diabetic + *Curcumin*, 100 mg/kg + *Gingerol* 100 mg/kg

Group V**:** Diabetic + *Curcumin*, 200 mg/kg + *Gingerol* 200 mg/kg

Group V**:** Diabetic + *Curcumin*, 400 mg/kg + *Gingerol* 400 mg/kg

Treatment was administered orally once daily for 14 consecutive days**.**

Preparation of Plant Extracts

Rhizomes of *Curcuma longa* and *Zingiber officinale* were shade-dried, powdered, and subjected to ethanol extraction using a Soxhlet apparatus. Extracts were concentrated under reduced pressure and stored at 4 °C until use.

Biochemical Analysis

Fasting blood glucose levels were measured on days 0, 7, and 14. Body weight was monitored weekly. At the end of the experiment, rats were euthanized.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Statistical comparisons were made using one-way ANOVA followed by Tukey's post hoc test. A p-value of <0.05 was considered statistically significant.

Results and Discussion

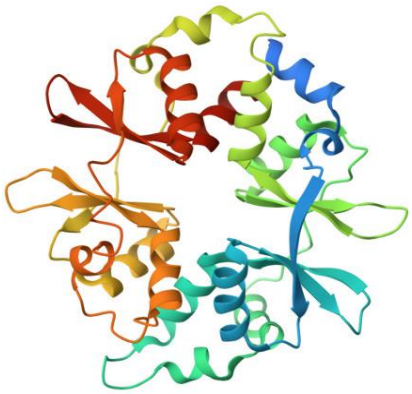
The selected plant for antidiabetic effects:

Curcuma longa: The total of 40 phytocompounds where selected from the plant

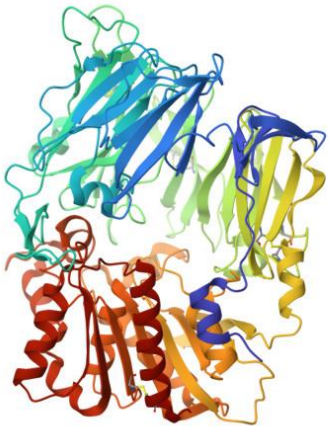
Protein selection

5'-AMP-activated protein kinase (4ZHX), Dipeptidyl peptidase 4(5Y7H), Peroxisome proliferator-activated receptor gamma (5Y2O) and Sodium/glucose cotransporter 2(8HEZ) enzymes were selected as protein targets to be used for molecular docking.

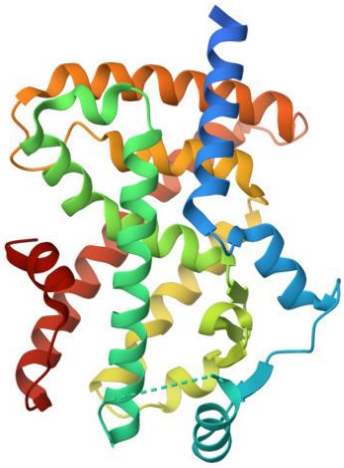
Below are the diagrams showing the selected proteins:



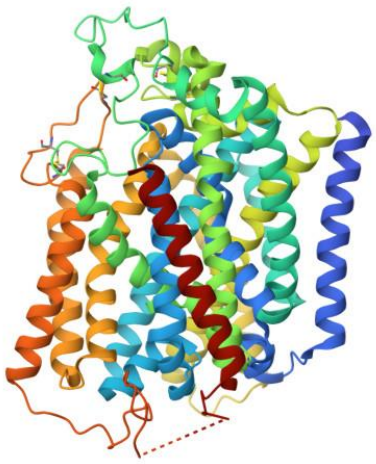
4ZHX_Chain-E



5Y7H_chain-A



5Y2O_chain-A



8HEZ_chain-A

The result from the DataWarrior

The following are the phytocompounds remaining after the application of Lipinski's Rule, rule on the selected phytocompounds:

1. Beta Tumerone
2. Ar-Tumerone
3. Bisacumol
4. Bisacurone
5. Bisacurone A
6. Bisacurone B
7. Bisacurone C
8. Bisdemethoxycurcumin
9. Borneol
10. Cedrene
11. Curcumenol
12. Curcumenone
13. Curcumin
14. Curcumol
15. Cyclocurcumin
16. Dehydrocurdione
17. Demethoxycurcumin
18. Limonene
19. Linalool

20. Procurcumadiol
21. Sabinene
22. Terpinolene
23. Tetrahydrocurcumin
24. Turmeronol
25. Zedoarondiol

Table 1: Reference for the selected target proteins

Reference compounds for 4ZHX,.	Reference compounds for 5Y7H,	Reference compounds for 5Y2O	Reference compounds for 8HEZ
5-(5-hydroxyl-isoxazol-3-yl)-furan-2-phosphonic acid	(R)-4-(3-amino-4-(2,4,5-trifluorophenyl)butanoyl)piperazin-2-one(Evogliptin)	(5S)-5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione(Pioglitazone)	(2S,3R,4R,5S,6R)-2-[4-chloranyl-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol(Dapagliflozin)
Benzimidazole	Sitagliptin	Pioglitazone	Dapagliflozin
	Alogliptin	Rosiglitazone	Empagliflozin

Table 1shows the druglike properties of the qualified compounds.

Molecular docking of Reference compounds and phytochemical on the selected protein targets.

After the molecular docking procedure, 5 phytocompounds qualified in 5'-AMP-activated protein kinase (4ZHX), 12 phytocompounds in Dipeptidyl peptidase 4(5Y7H), 5 phytocompounds in Peroxisome proliferator-activated receptor gamma (5Y2O) and 5 phytocompounds in Sodium/glucose cotransporter 2(8HEZ)

Table 2: Molecular Docking Results of Phytocompounds and Reference Drugs on Selected Antidiabetic Protein Targets

Protein Target	PDB ID	Biological Role	No. of Phytocompounds Qualified	Reference Drug(s)
5'-AMP-activated protein kinase (AMPK)	4ZHX	Regulates energy metabolism	5	5-(5-hydroxyl-isoxazol-3-yl)-furan-2-phosphonic acid

Protein Target	PDB ID	Biological Role	No. of Phytocompounds Qualified	Reference Drug(s)
Dipeptidyl peptidase-4 (DPP-4)	5Y7H	Inactivates incretin hormones, reduces insulin	12	Evogliptin, Sitagliptin, Alogliptin
Peroxisome proliferator-activated receptor gamma (PPAR-γ)	5Y2O	Regulates glucose and lipid metabolism	5	Pioglitazone, Rosiglitazone
Sodium/glucose cotransporter 2 (SGLT2)	8HEZ	Mediates renal glucose reabsorption	5	Dapagliflozin, Empagliflozin

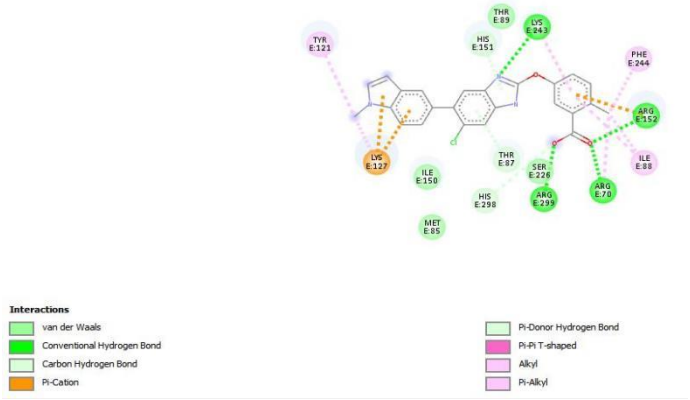
Table 3: The mean binding energy and the standard deviation of the measured binding energies of both the reference compounds and the qualified phytocompounds

	Ligands	Mean binding energy	Standard deviation
AMPK (4ZHX)	Benzimidazole	-9.80	0.00
	Cyclocurcumin	-8.63	0.06
	Demethoxycurcumin	-7.90	0.00
	Tetrahydrocurcumin	-7.87	0.06
	Curcumin	-7.87	0.06
	Bisdemethoxycurcumin	-7.77	0.06
	*5-(5-hydroxyl-isoxazol-3-yl)-furan-2-phosphonic acid	-7.57	0.06
DPP4 (5Y7H)	Sitagliptin	-8.33	0.06
	Curcumin	-7.83	0.12
	*(R)-4-(3-amino-4-(2,4,5-trifluorophenyl)butanoyl)piperazin-2-one(Evogliptin)	-7.83	0.06
	Demethoxycurcumin	-7.77	0.06
	Cyclocurcumin	-7.70	0.00

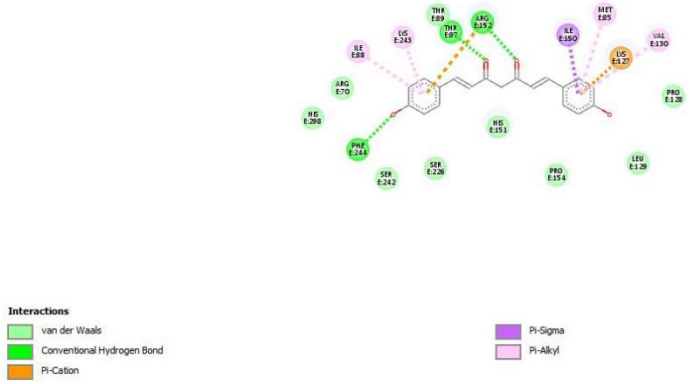
	Bisdemethoxycurcumin	-7.17	0.06
	Bisacurone B	-7.13	0.12
	Turmeronol	-7.13	0.06
	Bisacurone A	-7.07	0.06
	Bisacurone	-6.83	0.06
	Ar-turmerone	-6.80	0.00
	Curcumenol	-6.77	0.06
	Beta Tumerone	-6.73	0.64
	Alogliptin	-6.70	0.17
PPAR(5Y2O)	*(5S)-5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione(Pioglitazone)	-8.83	0.06
	Bisdemethoxycurcumin	-8.73	0.06
	Pioglitazone	-8.63	0.15
	Demethoxycurcumin	-8.37	0.15
	Curcumin	-8.23	0.06
	Cyclocurcumin	-7.87	0.06
	Tetrahydrocurcumin	-7.67	0.06
	Rosiglitazone	-7.40	0.10
SGLT2(8HEZ)	*(2S,3R,4R,5S,6R)-2-[4-chloranyl-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol(Dapagliflozin)	-10.27	0.33
	Curcumin	-9.73	0.26
	Bisdemethoxycurcumin	-9.67	0.25
	Tetrahydrocurcumin	-9.43	0.13
	Demethoxycurcumin	-9.33	0.34
	Cyclocurcumin	-8.83	0.22
	Dapagliflozin	-8.67	0.11
	Empagliflozin	-8.53	0.06
*: The co-crystallized ligand of respective protein target			

The diagrams and tables below show the protein-ligand interactions between the selected target proteins, their reference compounds and the qualified phytocompounds. Key: DB represents the co-crystallized ligand of respective ligand. TARGET: 5'-AMP-activated protein kinase (4ZHX)

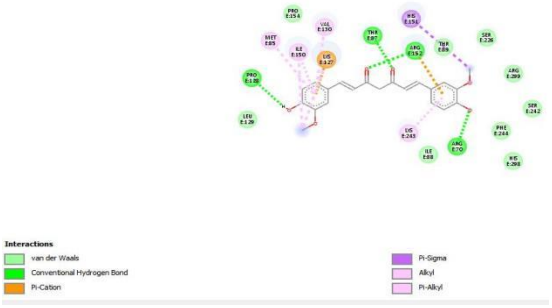
1. Benzimidazole-4ZHX interaction



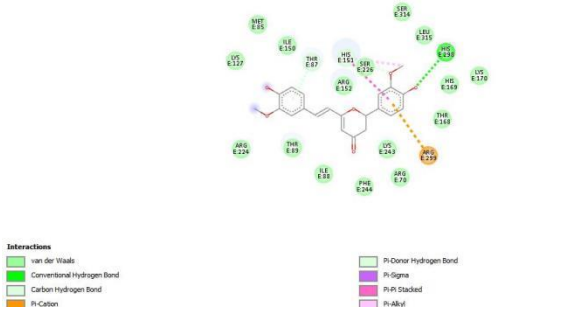
2. Bisedemethoxycurcumin-4ZHX interaction



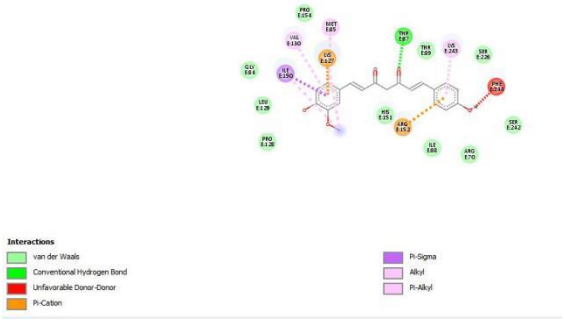
3. Curcumin-4ZHX interaction



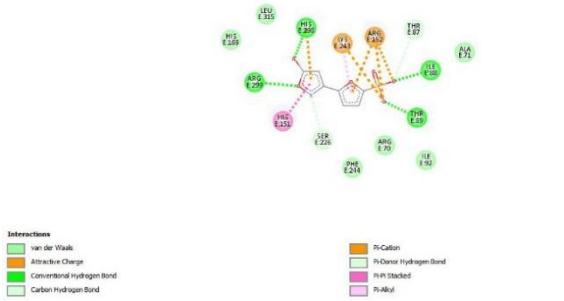
4. Cyclocurcumin-4ZHX interaction



5. Demethoxycurcumin-4ZHX interaction



6. DB-4ZHX interaction



7. Tetrahydrocurcumin-4ZHX interaction

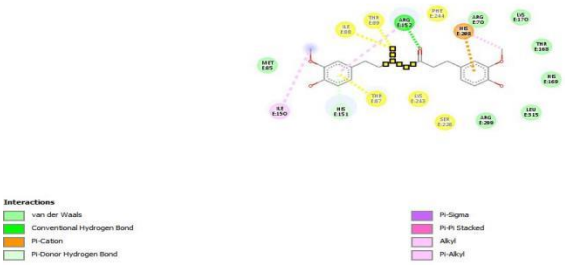


Table 6: Sub-Acute Effects of *Curcumin, Gingerol,* and Metformin on Fasting Blood Glucose Levels in Alloxan-Induced Diabetic Albino Rats.

Group	Mean fasting blood glucose (mg/dL)	
	Week 0	Week 2
Normal control	103.75 ± 4.66[d]	70.50 ± 3.33[a]
Negative control	487.50 ± 27.42[a]	66.00 ± 1.15[a]
Metformin, 100 mg/kg	253.75 ± 16.54[c]	66.25 ± 4.73[a]
Curcumin, 100 mg/kg + *Gingerol* 100 mg/kg	386.00 ± 36.66[b]	56.00 ± 0.00[b]
Curcumin, 200 mg/kg + *Gingerol* 200 mg/kg	268.75 ± 41.79[c]	54.00 ± 0.58[b]
Curcumin, 400 mg/kg + *Gingerol* 400 mg/kg	229.75 ± 46.78[c]	50.00 ± 0.00[b]

Data are expressed as Mean ± Standard Deviation (n = X). Superscripts (a, b, c, d) within each column indicate statistically significant differences between groups at $p < 0.05$ (ANOVA followed by post hoc test). Groups sharing the same superscript letter are not significantly different.

Out of the 40 phytocompounds initially screened from *Curcuma longa*, 25 compounds passed Lipinski's Rule of Five**,** indicating favourable drug-like properties. Compounds such as *curcumin***,** demethoxycurcumin**,** bisdemethoxycurcumin**,** and cyclocurcumin stood out due to their physicochemical compatibility, non-mutagenicity, and suitable molecular weight, all essential parameters for oral bioavailability [19].

These compounds were docked against four key protein targets involved in type 2 diabetes mellitus (T2DM): AMPK (4ZHX)**,** DPP-4 (5Y7H)**,** PPAR-γ (5Y2O)**,** and SGLT2 (8HEZ)**.** These proteins play critical roles in regulating glucose uptake**,** insulin sensitivity**,** and renal glucose reabsorption**,** making them viable therapeutic targets [20-23].

Table 2 reveals that the highest number of phytocompounds (12) showed significant binding affinity with DPP-4 (5Y7H)**,** suggesting strong inhibitory potential, consistent with the therapeutic actions of known gliptins like Sitagliptin and Evogliptin**.**

In the AMPK pathway (4ZHX)**,** five phytocompounds showed strong binding affinities, with Cyclocurcumin showing the highest binding energy (-8.63 kcal/mol) compared to the standard co-crystallized ligand (-7.57 kcal/mol)**.** This aligns with the findings of Kim et al. [24], who reported curcuminoids as potential AMPK modulators in diabetic models.

Similarly, against PPAR-γ (5Y2O)**,** Bisdemethoxycurcumin (-8.73 kcal/mol) and Demethoxycurcumin (-8.37 kcal/mol) outperformed the standard drug Rosiglitazone (-7.40 kcal/mol), indicating a potentially safer and effective natural alternative. This supports the work of Meng et al. [25], who highlighted *curcumin's* affinity for nuclear receptors related to glucose and lipid metabolism.

Docking against SGLT2 (8HEZ) showed *Curcumin***,** Bisdemethoxycurcumin, and Tetrahydrocurcumin all exhibiting high binding energies (>-9.3 kcal/mol), with curcumin nearly matching the synthetic inhibitor Dapagliflozin (-10.27 kcal/mol)**.** These findings are in line with the computational analysis by Choi et al. [26], who also observed strong SGLT2 binding by polyphenolic compounds.

When compared to standard reference ligands, several *Curcuma longa* phytochemicals demonstrated competitive or superior binding energies, particularly: Cyclocurcumin and Tetrahydrocurcumin against AMPK**,** *Curcumin* and Demethoxycurcumin against DPP-4**,** Bisdemethoxycurcumin against PPAR-γ and *Curcumin* against SGLT2. These results highlight *curcumin* and its derivatives as multi-target ligands an attribute valuable for managing complex metabolic syndromes like diabetes [27-28].

Table 6 presents the effects of curcumin-gingerol combinations on fasting blood glucose (FBG) over a 2-week period. All treated groups exhibited significant ($p < 0.05$) reductions in FBG compared to the diabetic control. The combination of *Curcumin* 400 mg/kg + *Gingerol* 400 mg/kg reduced FBG to 50.00 ± 0.00 mg/dL, which was more effective than Metformin 100 mg/kg (66.25 ± 4.73 mg/dL)**.** The effect was dose-dependent, aligning with earlier studies by Sharma et al. [29] and Al-Amin et al. [30], who reported synergistic effects of *curcumin* and *gingerol* in glycemic control.

This supports the dual-action hypothesis, that *Curcuma longa* not only interacts with multiple diabetic targets in silico, but also ameliorates hyperglycemia in vivo**,** especially when combined with *gingerol,* a known anti-inflammatory and insulin-sensitizing compound from *Zingiber officinale* [31-32].

The combined in silico and in vivo results affirm the therapeutic potential of *Curcuma longa*, particularly its curcuminoid constituents, in targeting multiple diabetes-related proteins. The strong docking scores and hypoglycemic effects in rats suggest that phytochemical synergy, especially with *gingerol***,** may offer a safe, multi-targeted alternative to synthetic drugs. Moreover, *curcumin's* anti-inflammatory**,** antioxidant, and insulin-sensitizing properties may confer added protection against diabetic complications [33-34].

Conclusion

Overall, the findings of this study are in tandem with previous research demonstrating the anti-diabetic efficacy of *Curcuma longa* and extend this knowledge by providing molecular-level evidence of interactions with validated protein targets. The promising performance of *Curcuma longa* compounds, especially in combination with *gingerol*, underscores their potential for further development as natural anti-diabetic therapeutics.

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