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Sincerely,
Prof. Dr. Nazım ŞEKEROĞLU
Editor-in-Chief
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Research article
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In Silico Exploration of the Safety Profile of Bioactive Compounds Extracted from Prickly Pear Cladodes (*Opuntia ficus-indica*): Toward Therapeutic Applications

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Abstract

Opuntia ficus-indica, commonly known as prickly pear, is a medicinal plant rich in bioactive compounds such as flavonoids and alkaloids, which have gained increasing interest for their therapeutic potential. This study employs in silico approaches to evaluate the physicochemical properties, bioavailability, and toxicity of ten compounds found in prickly pear cladodes. Molecular modeling tools, including SwissADME, ProTox-II, and Molinspiration, were used to predict their pharmacokinetic and pharmacological profiles. The results indicate that most compounds exhibit favorable aqueous solubility and permeability, supporting good digestive absorption. However, glycosylated flavonoids, such as isoquercitrin and rutin, showed limited membrane permeability but may undergo metabolic transformation into more bioavailable forms, such as quercetin and kaempferol. Toxicity assessments classified most compounds as low risk, though isoquercitrin exhibited a potential genotoxic signal in the Ames test, warranting further investigation. Additionally, molecular docking analysis identified quercetin as a promising inhibitor of GSK-3β, a key enzyme involved in metabolic, inflammatory, neurodegenerative, and oncological diseases. Notably, quercetin demonstrated a stronger binding affinity for GSK-3β than the reference inhibitor IXM, reinforcing its potential for drug development. Overall, these findings highlight the relevance of in silico analyses in early-stage drug discovery and provide a strong basis for further in vitro and in vivo studies to validate the therapeutic potential of these bioactive compounds.

Key Words: *Opuntia ficus-indica*, Cladodes, Safety ,Bioactivity,Quercetin, GSK-3β, In Silico.

Introduction

Opuntia ficus-indica, commonly known as the prickly pear cactus, belongs to the Cactaceae family and has been widely used in traditional medicine to treat various ailments, including diabetes, hypertension, cardiovascular diseases, and inflammation. Its medicinal use dates back several centuries, particularly in Latin America and certain regions of the Middle East, where its antidiabetic, anti-inflammatory, and antioxidant properties have been extensively exploited (Del Socorro Santos Díaz, 2017; Wang, 2023). The cladodes of this plant are particularly valued for their richness in bioactive compounds, whose consumption has been associated with numerous health benefits (Guevara-Figueroa et al., 2010; Martins et al., 2023). Although *Opuntia ficus-indica* is increasingly used for its medicinal properties, the bioactive mechanisms underlying its therapeutic effects remain poorly understood.

This study aims to explore, using in silico approaches, the physicochemical, pharmacological, and toxicological properties of ten bioactive flavonoids extracted from the cladodes of *Opuntia ficus-indica*. We seek to assess their safety as well as their pharmacological potential. In particular, we focus on the inhibition of glycogen synthase kinase-3β (GSK-3β), an enzyme involved in several chronic diseases, including diabetes and cancer (Beurel et al., 2015). We evaluate the efficacy of quercetin, a key metabolite of isoquercitrin, known for its multiple biological activities, as a potential inhibitor of GSK-3β (Valentová et al., 2014).

To achieve this, we use the molecular docking technique, a well-established method for identifying GSK-3β inhibitors, whether natural or synthetic (Benghanem et al., 2023; Benlazar et al., 2024). This work aims to provide a solid scientific basis for the safe and therapeutic exploitation of compounds extracted from the prickly pear cactus (Kashif et al., 2022).

2. Material and Methods

2.1. Molecular Structure Collection and Preparation: The chemical structures of ten bioactive compounds extracted from *Opuntia ficus-indica* cladodes were retrieved from the PubChem database (http://pubchem.ncbi.nlm.nih.gov/) using their respective CID identifiers. (Guevara-Figueroa et al., 2010). Each structure was downloaded in canonical SMILES format to ensure uniform molecular modeling input. The structures were optimized using ChemDraw Professional 22.0 to correct molecular geometry errors and generate high-quality 2D representations. These optimized structures were used as input for in silico prediction platforms, as detailed in Table 1.

2.2. Evaluation of Physicochemical Properties

Each compound underwent QSAR-based prediction analysis, with results expressed as qualitative indicators using a color-coding system for easier interpretation:

- **Red:** High risk of adverse effects
- **Yellow:** Tolerable result
- **Green:** Desired behavior (Kumar et al., 2017)

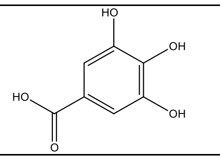
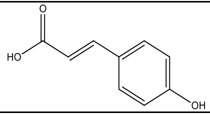
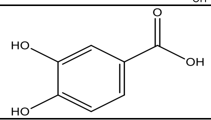
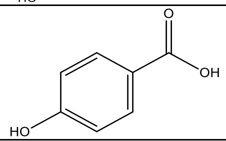
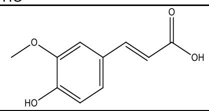
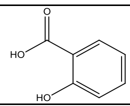
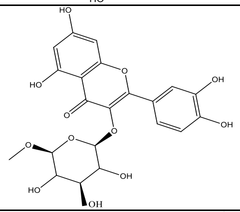
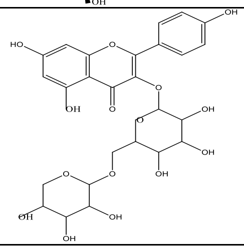
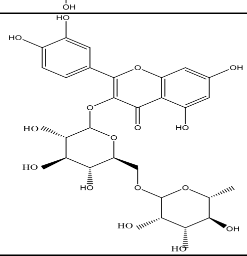
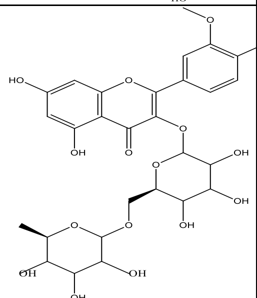
The evaluation followed Lipinski's "Rule of Five," complemented by additional criteria such as aqueous solubility and topological polar surface area (TPSA) (Lipinski et al, 1997).

2.2.1. Molecular Weight (MW): The molecular weight of each compound was calculated using the SwissADME server (http://www.swissadme.ch/). A molecular weight below 500 Da was considered acceptable based on Lipinski's rule (Lipinski et al, 1997). Results are listed in Table 2.

2.2.2. Hydrogen Bond Donors and Acceptors: The number of hydrogen bond donors and acceptors was determined using SwissADME. A maximum of five hydrogen bond donors and ten acceptors was set according to Lipinski's rule (Lipinski et al, 1997). The results are clearly presented in Table 2.

2.2.3. Aqueous Solubility (LogS): Aqueous solubility was determined using OSIRIS (https://www.organic-chemistry.org/prog/peo/logS.html). Values higher than -4 indicated good solubility. Results are presented in Table 2.

Table 1. CID Identifiers, SMILES, and Structures of the Tested Molecules

Ligands	Molécules	CID PubChem	PW	Structures	SMILES
L1	Acide gallique	24721416	188.13		C1=C(C=C(C(=C1O)O)O)C(=O)O
L2	Acide coumarique	1549106	164.16		C1=CC(=CC=C1C=CC(=O)O)O
L3	Acide 3,4-dihydroxybenzoïque	72	154.12		C1=CC(=C(C=C1C(=O)O)O)O
L4	acide 4-hydroxybenzoïque	135	138.12		C1=CC(=CC=C1C(=O)O)O
L5	Acide férulique	445858	194.18		COC1=C(C=CC(=C1)C=CC(=O)O)O
L6	Acide salicylique	338	138.12		C1=CC=C(C(=C1)C(=O)O)O
L7	Isoquercitrine	5280804	464.4		C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)OC4C(C(C(C(O4)CO)O)O)O)O)O
L8	Nicotiflorine	5318767	594.5		C[C@@H]1O[C@@H](OC[C@H]2O[C@@H](OC3=C(OC4=C(C(O)=CC(O)=C4)C3=O)C3=CC=C(O)C=C3)[C@H](O)[C@@H](O)[C@@H]2O)[C@H](O)[C@H](O)[C@H]1O
L9	Rutine	5280805	610.5		C[C@@H]1O[C@@H](OC[C@H]2O[C@@H](OC3=C(OC4=C(C(O)=CC(O)=C4)C3=O)C3=CC=C(O)C(O)=C3)[C@H](O)[C@@H](O)[C@@H]2O)[C@H](O)[C@H](O)[C@H]1O
L10	Narcissine	5481663	624.5		C1CN2CC3=CC4=C(C=C3C5C2C1=CC(C5O)O)OCO4

2.2.4. Topological Polar Surface Area (TPSA): TPSA was calculated using OSIRIS (https://www.organic-chemistry.org/prog/peo/). A TPSA ≤ 140 $Å^2$ was associated with good membrane permeability (Veber et al,2002). Results are shown in Table 2.

2.2.5. Octanol-Water Partition Coefficient (LogP): LogP was calculated using SwissADME (http://www.swissadme.ch/). A value between 0 and 5 indicated a good hydrophilic-lipophilic balance, essential for membrane permeability (Kaiser et al, 1982). Results are detailed in Table 2.

Table 2. Lipinski's Rule of Five from SwissADME, TPSA, and log S from OSIRIS

				Lipinski's Rule of Five				
				Molecular Weight (g/mol)	Lipophilicity (MLogP)	Hydrogen Bond Donors	Hydrogen Bond Acceptors	No. of Rule Violations
N°	CID	Solubility log S	TPSA $Å^2$	Lessthan 500 Dalton	Lessthan 5	Lessthan 5	Lessthan 10	Lessthan 2 Violations
L1	370	-1.07	107.22	170.12	1.28	2	3	0 violation
L2	1549106	-1.7	57.53	164.16	1.28	2	3	0 violation
L3	72	-1.04	77.76	154.12	0.40	3	4	0 violation
L4	135	-1.33	57.53	138.12	0.99	2	4	0 violation
L5	445858	-1.72	66.76	194.18	1.00	3	4	0 violation
L6	338	-1.33	57.53	138.12	0.99	2	3	0 violation
L7	5280804	-2.19	206.60	464.38	-2.59	8	12	2 violations
L8	5318767	-2.69	245.29	594.52	-3.43	9	15	3, violations
L9	5280805	-2.40	265.52	610.52	-3.89	10	16	3, violations
L10	72378	-2.78	62.16	287.31	1.08	2	5	0 violation

2.3. Prediction of Toxicity

2.3.1. Acute Toxicity Prediction (LD50): Acute toxicity was predicted using Protox II (https://tox-new.charite.de/protox_II/). The median lethal doses (LD50) were expressed in mg/kg. The results are presented in Table 3.

2.3.2. Specific Toxicity: The evaluation of risks related to mutagenicity, hepatotoxicity, and irritation was performed using AdmetSAR (https://lmmd.ecust.edu.cn/admetsar2/), OSIRIS, and Protox. The results are provided in Tables 4 and 5.

2.4. Prediction of Biological Activity Biological activity predictions focused on G protein-coupled receptors (GPCRs), ion channels, kinases, and nuclear receptors, which are crucial in the development of new drugs. The Molinspiration tool (https://www.molinspiration.com/) was used to evaluate the bioactivity scores for the targets. These scores are presented in Table 6.

Table 3. Toxicity Classification of Tested Compounds Based on LD_{50} Values Predicted by Protox-II

Ligands / Classes	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10
Predicted Toxicity Class	4	5	4	5	4	4	5	5	5	3
Classe I : extrêmement toxique (LD50 ≤ 5)	-	-	-	-	-	-	-	-	-	-
Classe II : très toxique (5 < LD50 ≤ 50)	-	-	-	-	-	-	-	-	-	-
Classe III : modérément toxique (50 < LD50 ≤ 300)	-	-	-	-	-	-	-	-	-	+
Classe IV : légèrement toxique (300 < LD50 ≤ 2000)	+	-	+	-	+	+	-	-	-	-
Classe V : non toxique (2000 < LD50 ≤ 5000)	-	+	-	+	-	-	+	+	+	-
Classe VI : sequurise (LD50 > 5000)	-	-	-	-	-	-	-	-	-	-

Table 4. Predicted Toxicity Risks According to OSIRIS and AdmetSAR

serveur	**OSIRIS**	**ADMETSAR**	
Ligands	**Irritant**	**Ames toxicity**	**Carcinogenicity**
L1		Non toxic	Non carcinogenic
L2		Non toxic	Non carcinogenic
L3		Non toxic	Non carcinogenic
L4		Non toxic	Non carcinogenic
L5		Non toxic	Non carcinogenic
L6		Non toxic	Non carcinogenic
L7		Toxic	Non carcinogenic
L8		Non toxic	Non carcinogenic
L9		Non toxic	Non carcinogenic
L10		Non toxic	Non carcinogenic

Table 5. Report on Organ Toxicity, General Toxicity, and Stress Response Pathways by Protox (**A**: Presence of Toxicity , **I**: Absence of Toxicity)

Ligands			L1	**L2**	**L3**	**L4**	**L5**	**L6**	**L7**	**L8**	**L9**	**L10**
	Target											
Classification	Organ toxicity	Hepatotoxicity	0.61 I	I 0.51	I 0.59	I 0.52	I 0.51	A 0.51	I 0.82	**0.80** I	0.88 I	0.87 I
	Toxicity	Mutagenicity	0.94 I	I 0.93	I 0.97	I 0.99	I 0.96	I 0.98	I 0.76	**0.88** I	0.88 I	0.95 I
	Stress response	Nuclear factor (erythroid-derived 2)-like 2/antioxidant	0.85 I	I 0.94	I 0.98	I 1.0	I 0.90	I 0.99	I 0.98	**0.99** I	0.99 I	0.92 I

		responsive element (nrf2/ARE)										
		Heat shock factor response element (HSE)	0.85 I	I 0.94	I 0.98	I 1.0	I 0.90	I 0.99	I 0.98	**0.99** I	0.99 I	0.92 I
		Mitochondrial Membrane Potential (MMP)	0.97 I	I 0.97	I 0.99	I 0.99	I 0.92	I 0.99	I 0.98	**0.97** I	0.97 I	0.79 I
		Phosphoprotein (Tumor Supressor) p53	0.97 I	I 0.95	I 0.99	I 0.99	I 0.92	I 0.99	A 0.5	**0.90** I	0.90 I	0.90 I
		ATPase family AAA domain-containing protein 5 (ATAD5)	0.99 I	I 0.96	I 1.0	I 0.99	I 0.93	I 0.99	I 1.0	**0.99** I	0.99 I	0.78 I
	Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	0.90 I	I 0.96	I 0.96	I 0.96	I 0.94	I 0.98	I 0.92	**0.83** I	0.83 I	0.71 I
		Androgen Receptor (AR)	0.97 I	I 0.87	I 0.84	I 0.99	I 0.83	I 0.99	I 0.90	**0.98** I	0.98 I	0.96 I
		Androgen Receptor Ligand Binding Domain (AR-LBD)	1.0 I	I 0.99	I 1.0	I 1.0	I 0.99	I 1.0	I 0.98	**0.99** I	0.99 I	0.97 I
		Aromatase	**0.99 I**	I 0.99	I 0.99	I 0.99	I 0.99	I 1.0	I 1.0	**0.99** I	0.99 I	0.92 I
		Estrogen Receptor Alpha (ER)	**0.89 I**	I 0.97	I 0.99	I 0.99	I 0.96	I 0.96	I 0.91	**0.95** I	0.95 I	0.80 I
		Estrogen Receptor Ligand Binding Domain (ER-LBD)	**0.9 I**	I 0.97	I 0.95	I 0.98	I 0.96	I 0.98	I 0.99	**0.99** I	0.99 I	0.95 I

Table 6. Predicted Bioactivity Scores for Drug Targets Including GPCR Ligands, Kinase Inhibitors, Ion Channel Modulators, and Nuclear Receptor Ligands (by Molinspiration)

Molinspiration bioactivity	**GPCR ligand**	**Ion channel modulator**	**Kinase inhibitor**	**Nuclear receptor ligand**	**Enzyme inhibitor**	**Protease inhibitor**
L1	-0.77	-0.26	-0.88	-0.52	-0.17	-0.94
L2	-0.56	-0.26	-0.91	-0.12	-0.15	-0.87
L3	-0.88	-0.35	-1.10	-0.58	-0.34	-1.09
L4	-0.98	-0.39	-1.21	-0.62	-0.41	-1.19
L5	-0.47	-0.30	-0.72	-0.14	-0.12	-0.81
L6	-0.98	-0.43	-1.22	-0.79	-0.41	-1.14
L7	0.06	-0.04	0.13	0.20	0.42	-0.06
L8	-0.01	-0.43	-0.09	-0.17	0.18	-0.04
L9	-0.05	-0.52	-0.14	-0.23	0.12	-0.07
L10	0.43	0.25	-0.25	0.10	0.66	0.07

2.5. Molecular Docking Study and Binding Mode

2.5.1. Protein Preparation: The crystal structure of GSK-3β (PDB ID: 1Q5K, Resolution: 1.94 Å) was downloaded from the Protein Data Bank (https://www.rcsb.org/). Chain B was removed, and water molecules were eliminated. The structure was minimized using the OPLS force field.

2.5.2. Ligand Preparation: The deglycosylated metabolite of isoquercitrin, quercetin, was prepared using LigPrep (v4.7, Schrödinger 2019-3). The generated structures were used for docking simulations.

2.5.3. Cross-Docking: A docking test was performed with the reference inhibitor IXM (indurbin), a known GSK-3β ligand. The docking score of quercetin was compared to that of IXM. The results are presented in Table 7, with a detailed analysis of the binding mode of quercetin in the ATP-binding site of the receptor.

Table 7: Docking Scores of Quercetin

Composés	Code CID	Nombre de poses	Glide score	State penalty	Docking score	E model
Quercétine	5280343	7	-10,6	0,03	-10,57	-55,46

3.Results and Discussion

3.1. Evaluation of Physicochemical Properties

3.1.1. Lipinski's Rule Compliance and Accessible Polar Surface Area (TPSA): The evaluation of compounds L1 to L6 and L10 shows that they comply with Lipinski's rule, having molecular weights below 500 Da, a limited number of hydrogen bond donors and acceptors, and a TPSA less than 140 $Å^2$, suggesting favorable oral absorption potential (Veber et al, 2002; Lipinski et al,1997). In contrast, compounds L7 (isoquercitrin), L8 (nicotiflorin), and L9 (rutin) do not meet these criteria, as they have high molecular weights and TPSA values well above 140 $Å^2$, indicating reduced membrane permeability and limited intestinal absorption. This result is consistent with that of Hiremath for isoquercitrin (Hiremath et al., 2021).

3.1.2. Solubility (log S): Adequate solubility is crucial for optimal absorption. Compounds with a log S lower than -4 are considered poorly soluble, which may limit their bioavailability. However, all compounds exhibit moderate log S values, suggesting sufficient solubility for digestive absorption. This result is consistent with that of Hiremath for isoquercitrin (Hiremath et al., 2021) and that of Souza for rutin (Souza et al., 2023).

3.1.3. Lipophilicity (MLogP): Compounds L1 to L6, and L10, and present MLogP values ranging from -0.4 to 5, indicating optimal intestinal absorption. In contrast, compounds L7, L8, and L9 exhibit negative MLogP values (<-2), reflecting excessive hydrophilicity and reduced ability to cross biological membranes.

3.1.4. Reevaluation of Metabolites: Despite initially unfavorable physicochemical properties for optimal absorption, the glycosylated flavonoid derivatives (L7, L8, L9) undergo deglycosylation in the gastrointestinal tract, producing metabolites with improved physicochemical characteristics. For instance, L7 (isoquercitrin) is transformed into quercetin, with a molecular weight of 302.24 g/mol and a TPSA of 131.36 Å^2. L8 (nicotiflorine) is metabolized to kaempferol, with a molecular weight of 286.24 g/mol and a TPSA of 107.22 Å^2, while L9 (rutin) also produces quercetin. These metabolites show molecular weights and TPSA values compatible with good oral absorption. In terms of lipophilicity, quercetin and kaempferol have moderate MLogP values (1.73 and 1.38, respectively), indicating an enhanced ability to traverse lipid membranes and be efficiently absorbed.

3.2. Toxicity Evaluation

3.2.1. Acute Toxicity (LD50): The compounds were classified into five toxicity categories based on the OECD classification system:

- Class I: Extremely toxic (LD50 < 5 mg/kg)
- Class II: Very toxic (5–50 mg/kg)
- Class III: Moderately toxic (50–300 mg/kg)
- Class IV: Slightly toxic (300–2000 mg/kg)
- Class V: Non-toxic (LD50 > 2000 mg/kg)

Compounds with an LD50 greater than 2000 mg/kg were considered safe for potential use. All of the tested compounds fall into Classes III and above. Detailed results are presented in Table 03.

3.2.2. Specific Toxicity

***3.2.2.1. Irritability*: L1 (gallacic acid) and L6 (salicylic acid) were identified as irritants (marked in orange in Table 4), indicating that they could cause skin or mucous membrane irritation. On the other hand, the other ligands (L2 to L5, L7 to L10) showed no irritant properties, which is favorable for potential oral or topical applications.

***3.2.2.2. Genotoxicity*: Ames Test and Mutagenicity:** L7 (isoquercitrin) was classified as toxic in the Ames test, which could indicate a genotoxic potential. However, other studies have shown that isoquercitrin in an inclusion complex (IQC-γCD) does not exhibit genotoxicity in experimental models (Kapoor et al., 2022). The other compounds were considered non-mutagenic according to ProTox-II, indicating a reassuring safety profile for long-term use. Results are shown in Tables 4 and 5. The Ames toxicity and hepatotoxicity results are consistent with those of Souza for isoquercitrin and rutin (Souza et al., 2023).

***3.2.2.3. Carcinogenicity*:** All compounds were classified as non-carcinogenic, which further supports their safety profile for consumption or further development. This is detailed in Table 4.

3.2.2.4. Hepatotoxicity: L6 (salicylic acid) may present a risk of hepatotoxicity. In contrast, other ligands seem to be better tolerated by the liver, as indicated in Table 5.

3.2.2.5. Stress Response Pathways and Nuclear Receptor Signaling Pathways: Interference was observed for L7 concerning the phosphoprotein p53 (tumor suppressor). No other interference with stress response pathways or nuclear receptor signaling pathways was recorded, as shown in Table 5.

3.3. Prediction of Biological Activity

The prediction of biological activity for several compounds extracted from prickly pear cladodes revealed promising therapeutic potential. Molecules such as L7 (isoquercitrin), L10 (narcissine) were predicted to target multiple biological activities. Specifically:

- **L7 (isoquercitrin)** is predicted to interact with G-protein-coupled receptors (GPCRs), act as a kinase inhibitor, bind to nuclear receptors, and inhibit enzymes.
- **L10 (narcissine)** is predicted to modulate ion channels, inhibit proteases, and interact with nuclear receptors. Among these, **isoquercitrin (L7)** stands out for its predicted kinase inhibitory activity, which led to its selection for further investigation, specifically targeting GSK-3β.

3.4. Molecular Docking Study

3.4.1. Scoring Analysis: Molecular docking results, presented in Table 7, show that the best pose was selected based on the docking score, with lower scores indicating higher affinity of the molecule for the receptor. Quercetin achieved a docking score of **-10.57 kcal/mol**, which is lower (indicating higher affinity) than the reference inhibitor **IXM** with a score of **-9.313 kcal/mol**.

3.4.2. Binding Mode: The molecular interactions between quercetin and the reference inhibitor IXM with residues from the active site of GSK-3β (PDB ID: 1Q1K) were analyzed. The 2D interaction diagrams for IXM and quercetin are shown in Figures 1 and 2, respectively.

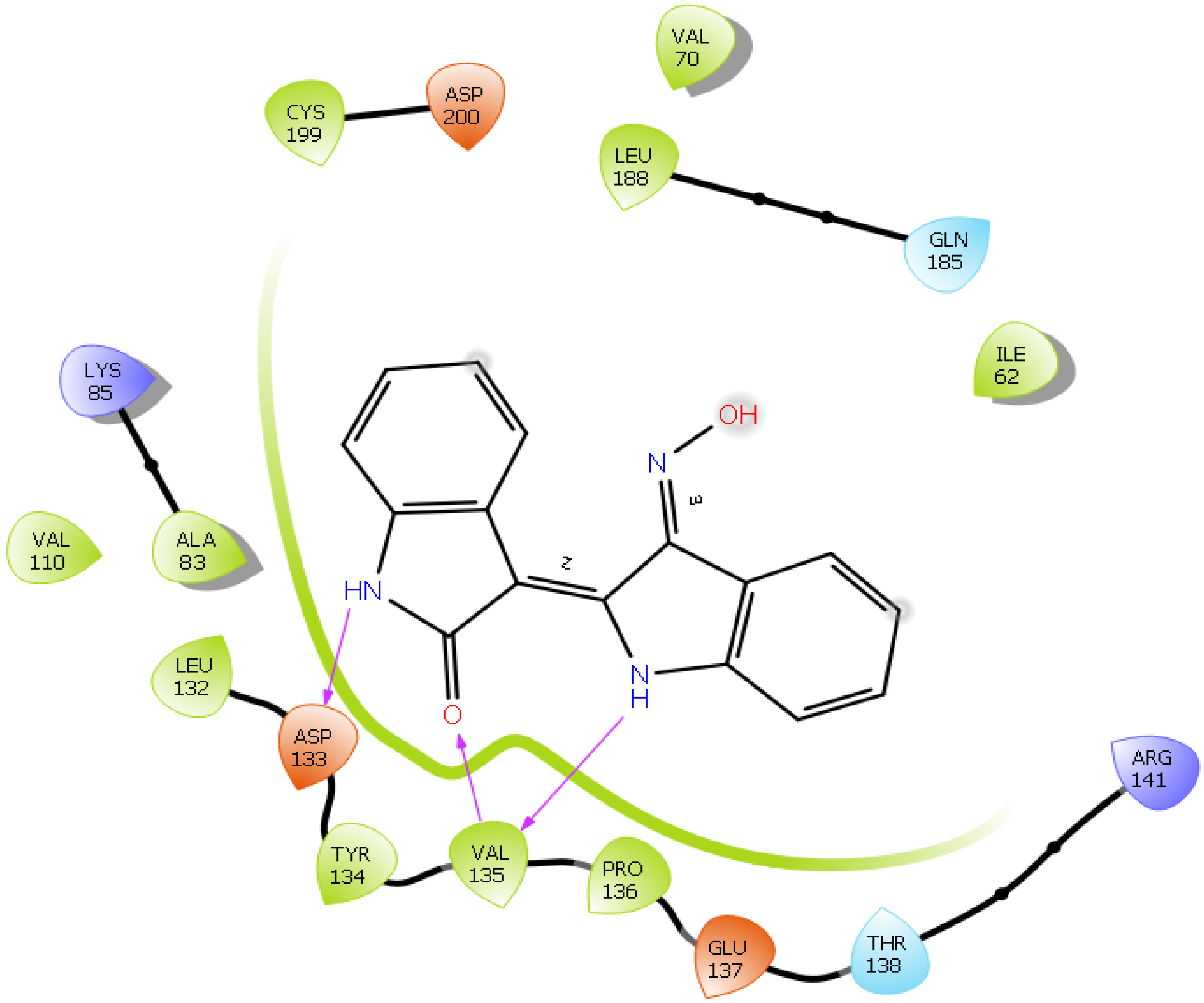


Figure 1. 2D Interactions of IXM (Indirubin) with GSK-3β after Cross-Docking in PDB ID: 1Q5K

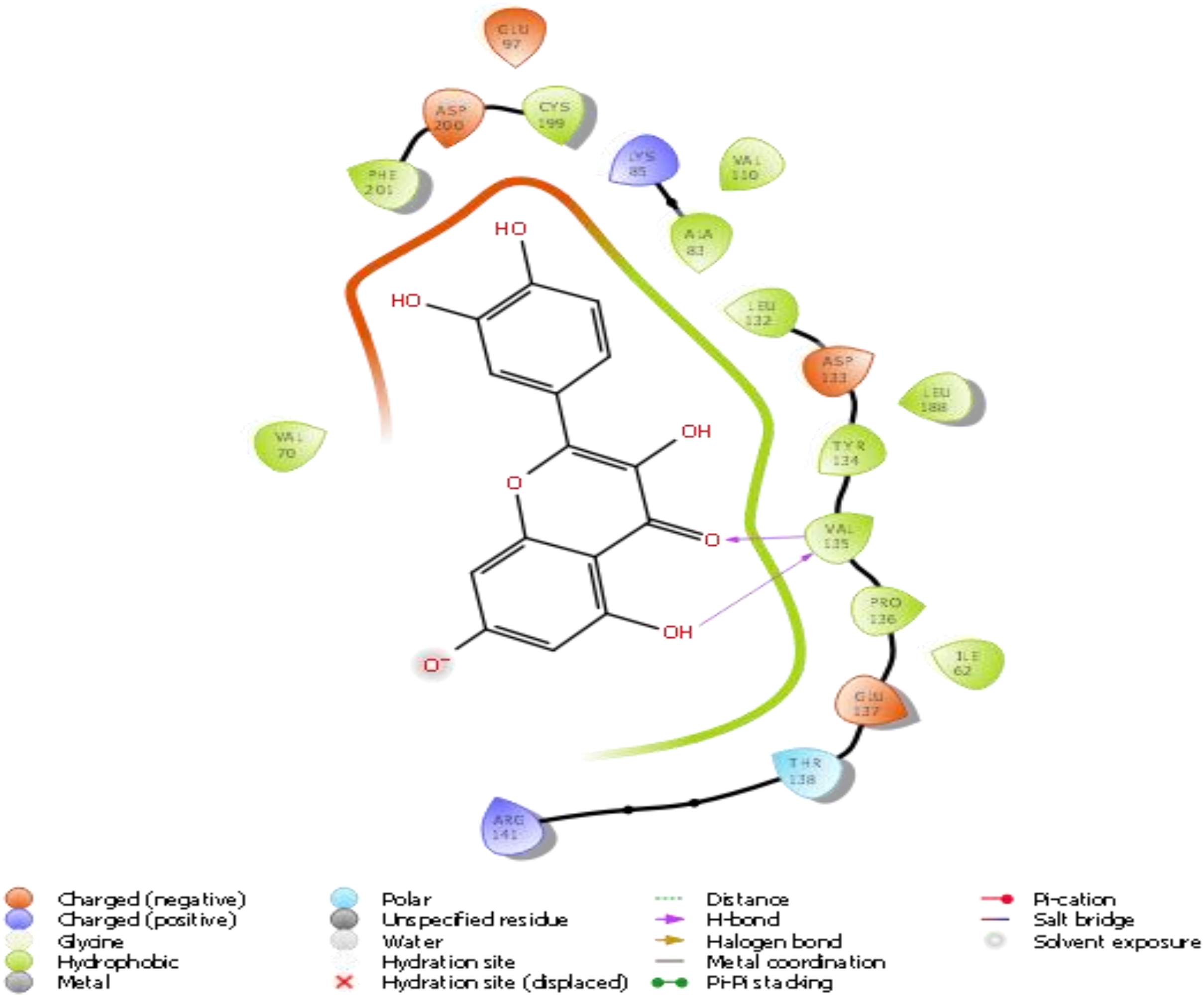


Figure 2. 2D Interactions of Quercetin with GSK-3β after Docking in PDB ID: 1Q5K

Both quercetin and IXM show strong inhibition, mainly due to hydrogen bonding with the **Val135** residue. Notably, while IXM forms an additional hydrogen bond with **Asp133**, quercetin displays a lower binding energy score, indicating a stronger affinity for the active site. This binding mode aligns with the known mechanism of GSK-3β inhibition, where hydrogen bonds with **Val135** and **Asp133** are crucial for effective inhibition, as outlined by Arfeen et al . (Arfeen et al,2016). This result for quercetin is consistent with the findings of Baby et al on quercetin and isoquercitrin, describing their action as inhibitors of serine/threonine kinase, which belongs to the GSK3β superfamily (Baby et al., 2016).

The findings of this study align with previous research on *Opuntia ficus-indica* and its bioactive compounds. Consistent with our results, Hiremath et al. (2021) reported that isoquercitrin exhibits limited membrane permeability. Similarly, Souza et al. (2023) highlighted the low solubility and moderate absorption potential of rutin, further supporting our observations on its pharmacokinetic profile.

In our study, we found that its deglycosylated metabolites, quercetin and kaempferol, formed during metabolism in the small intestine, displayed significantly improved bioavailability. Moreover, molecular docking analysis identified quercetin as a potent GSK-3β inhibitor, exhibiting a higher binding affinity than the reference inhibitor IXM. This is particularly relevant given the involvement of GSK-3β in various diseases, including diabetes, neurodegenerative disorders (e.g., Alzheimer's and Parkinson's), and inflammatory conditions. Our findings align with those of Baby et al. (2016), who previously identified flavonoids as promising regulators of GSK-3β. These results reinforce the potential of *Opuntia ficus-indica* cladodes as valuable sources of bioactive molecules for drug development.

Despite these promising insights, our study has certain limitations. While in silico predictions are valuable for early-stage screening, they require experimental validation through in vitro and in vivo studies. Computational models alone cannot fully assess crucial factors such as metabolic stability, enzymatic transformations, and long-term toxicity. Future research should focus on pharmacokinetic studies and preclinical trials to confirm the bioavailability and therapeutic potential of these cladode-derived compounds.

Overall, this study provides key insights into the pharmacokinetic properties, safety profile, and therapeutic potential of bioactive compounds contained in *Opuntia ficus-indica* cladodes, paving the way for further experimental validation and potential pharmaceutical applications.

4. Conclusion

This study evaluated the physicochemical properties, toxicity, and biological activity of major compounds extracted from prickly pear cladodes. Most compounds exhibited favorable physicochemical properties supporting good oral absorption. However, glycosylated flavonoids (L7, L8, L9) showed reduced permeability, though their deglycosylated metabolites, such as quercetin and kaempferol, demonstrated improved bioavailability. Regarding toxicity, most compounds were classified as low risk, yet isoquercitrin exhibited a potential genotoxic signal in the Ames test, consistent with previous findings, highlighting the need for further investigation. Molecular docking analysis revealed that quercetin displayed a stronger binding affinity for GSK-3β than the reference inhibitor IXM, reinforcing its potential role in targeting this enzyme. Given the involvement of GSK-3β in various pathologies, including diabetes, inflammation, cancer, and neurodegenerative diseases, these findings suggest that quercetin and related metabolites could serve as promising therapeutic candidates.

Overall, this study underscores the importance of in silico assessments in early drug discovery and provides a strong rationale for conducting further in vitro and in vivo studies to validate the therapeutic potential of these bioactive compounds.

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Author Contribution

All authors declare equal contribution to the design and experimental work, interpretation of the results and editing the manuscript.

Conflicts of Interest

The authors declared no conflict of interes.

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Differences Between the Feeding of Hydroponically Grown Curly Vegetables with Postbiotic Free Nutrient Solution and ATAGREEN Postbiotic Supplemented Nutrient Solution with Probiotics

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Abstract

This article presents a comparative analysis of the efficacy of two cultivation methods for curly lettuce crops: one involving the use of a probiotic-derived ATAGREEEN postbiotic-added nutrient solution, and the other relying on a nutrient solution without postbiotic. The analysis is supported by a comprehensive presentation of the experimental design, methodology, and results, as well as illustrative images. This study is discussed in detail under the following headings: basic principles of hydroponic agriculture, curly lettuce growing and its characteristics, the role of postbiotics in agriculture, the use of postbiotics in hydroponic agriculture, experimental design and methods, results and findings, analysis and interpretation of results, presentation of methods and results, discussion and recommendations. The experimental design is centred on the cultivation of curly lettuce plants in a hydroponic environment, with and without the addition of ATAGREEN postbiotic nutrient solutions. The methodology employed in the experiment, the cultivation conditions for the plants, the preparation of the nutrient solutions and the care of the plants were all determined in great detail. Furthermore, the experiment was designed to include a defined duration, measurement intervals, and data collection techniques. The results of the experiment demonstrated that the ATAGREEN postbiotic-supplemented nutrient solution exhibited notable advantages in curly lettuce growth. Plants treated with the ATAGREEN postbiotic solution exhibited accelerated growth, an increased number of leaves, and enhanced root systems. Additionally, plants treated with the ATAGREEN postbiotic solution demonstrated elevated resistance levels and greater resilience to detrimental organisms.

Key Words: Hydroponic farming, probiotic, postbiotic, curly lettuce, vegetables

1. Introduction

Hydroponic farming is a method of plant cultivation that involves the use of water solutions containing nutrients, as opposed to soil, which is the traditional approach. This system has been shown to conserve water and agricultural land (Al Ajmi et al., 2009; Richa et al., 2020; Rakesh and Javakrishna, 2022), whilst reducing the use of chemical fertilisers and pesticides, which are often necessary to combat plant diseases and harmful organisms (Richa et al., 2020). The ability to meet the nutrient requirements of plants in a controlled manner has been demonstrated to increase productivity and enable agricultural production in limited areas (Pandey et al., 2009; Despommier, 2013). The historical development of hydroponic agriculture is a process that extends from ancient times to modern practices. The evolution of hydroponic farming techniques can be traced back to the ancient irrigation canals of the Babylonian and Assyrian civilizations, and has been further refined over time to suit modern agricultural practices. Evidence suggests that in ancient Egyptian and Babylonian times, rock wool and clay were utilised to support the roots of plants in a floating position within water, thus facilitating the cultivation of aquatic flora (Kumar et al., 2023).

The foundations of modern hydroponic agriculture are believed to have been established in the 17th century through studies on the cultivation of plant roots in water (Sabry, 2021). Since the mid-20th century, hydroponic agriculture technology has undergone significant development, primarily driven by NASA's adoption of hydroponic systems for space exploration (Moraru et al., 2004). Subsequent advancements in hydroponic agriculture have been further developed and integrated with contemporary irrigation systems, resulting in the current practices observed today. Since the advent of the 20th century, hydroponic agriculture has emerged as a favoured agricultural modality, particularly in regions characterised by constrained water resources, an outcome that can be attributed to the escalating utilisation of fossil fuels (Pomoni et al., 2023).

1.1. Hydroponic Systems and Their Classification

Surface water technologies constitute a hydroponic system in which the roots of plants are placed on the water surface and are continuously supplied with fresh water and nutrient solution. This system provides plants with easy access to nutrient solutions, but good aeration is necessary to ensure oxygen uptake by the roots. The platforms that support the plant roots must also have an appropriate structure (López-Galvez et al., 2014). Film technologies constitute a hydroponic system in which the roots of plants come into contact with a nutrient solution contained in a thin film. This system necessitates sophisticated control mechanisms to ensure the stability of pH and electrical conductivity (EC) values in the water and nutrient solution. Notably, film technologies have been shown to conserve water by minimising evaporation levels in both water and nutrient solutions (Goddek et al., 2019).

Vertical hydroponic systems, such as cabinet and tower setups, are a notable example of this technological advancement. These systems are particularly well-suited to urban agriculture applications due to their ability to efficiently utilise limited spatial resources. The advantages of these systems include water savings, high productivity and pollution reduction. However, it is imperative to note that ensuring homogeneity in the root zone and the delivery of adequate nutrient solutions are of paramount importance (AlShrouf, 2017). Aquaponic farming is defined as a sustainable agricultural system that combines fish farming and hydroponic plant cultivation. The fundamental principle of this system is predicated on the filtration of the waste produced by the fish, with the process of conversion of the ammonium in the waste into nitrite and subsequently nitrate nutrients, and the development of plants by integrating this nutrient into the system. The nutrients so developed are absorbed by the plants cultivated in the hydroponic environment, thus purifying the water. The purified water is subsequently returned to the fish habitat. The continuous circulation of water in aquaponic farming systems enables the concurrent cultivation of both fish and plants (Goddek et al., 2019).

1.2. Nutrient Solutions and Properties employed in hydroponic Farming

Nutrient solutions utilised in hydroponic farming comprise essential nutrients that are indispensable for the development of plants throughout their life cycle (Trejo-Téllez & Gómez-Merino, 2012). These essential nutrients are defined as elements that are fundamental for the growth and development of plants. Nitrogen, phosphorus and potassium are recognised as essential nutrients, and it is imperative to ensure the appropriate ratios of these elements are present in the nutrient solution to facilitate optimal plant development. These elements are indispensable for various processes, including the formation of plant cells, photosynthesis, root development, seed formation, and general growth (De Rijck & Schrevens, 1999). Macronutrients, meanwhile, are elements required in large quantities for plant growth.

These elements include nitrogen, sulfur, calcium, magnesium, and phosphorus. Micronutrients, meanwhile, are elements that are required in minute quantities by plants. These micronutrients include iron, copper, zinc, manganese, molybdenum and chlorine. These nutrients are vital for the healthy development of plants, and their deficiency can have a detrimental effect on plant growth (Kumar et al., 2021). In hydroponic farming, nutrient solutions containing the essential nutrients required by plants are used. These solutions are formulated to be readily absorbable by the roots of the plants (Li et al., 2020; Ragaveena et al., 2021; Maharana & Koul, 2004).

1.3. The Advantages and Disadvantages of Hydroponic Agriculture

The advantages of hydroponic farming include water savings, labour savings, high productivity, control of nutrient uptake by plants, consistent crop quality, ease of protection from plant diseases and pests, and suitability for urban agriculture (Jones, 2016; Tripp, 2014). However, hydroponic farming also has disadvantages, including high set-up costs, complex maintenance, technical expertise, increased energy consumption, sensitive nutrient solution balance and difficulties in controlling root diseases (Tripp, 2014;Jones, 2016).

1.4. Environmental and Economic Impacts

In comparison with traditional agriculture, hydroponic agriculture is considered to be more environmentally friendly due to its ability to minimise water wastage, reduce erosion and pollution, and decrease chemical pollution (Jones, 2016). This is because the water and nutrients required by plants are supplied directly to the root system. Hydroponic agriculture is distinguished by its reduced reliance on chemical fertilisers and pesticides, making it a commendable method in terms of environmental sustainability. The advantage of soilless farming is that disease and pest organisms can be controlled more easily and chemical interventions can be reduced when necessary (Jones et al., 2020). From an economic perspective, hydroponic agriculture offers a competitive advantage in the market, resulting in high yields per unit area and the production of quality products (Mateus-Rodriguez et al., 2013; Gómez et al., 2019; Emani, 2018; Jafari et al., 2024).

1.5. Application Areas of Hydroponic Agriculture

Hydroponic farming is a favoured method in urban areas where agricultural land is limited. Vertical gardening is employed in urban areas where hydroponic systems are installed on the walls of buildings or on specially constructed platforms. This approach has the potential to establish sustainable agricultural models in urban areas (Michelon et al., 2019;Hamidon et al., 2020). Hydroponic agriculture is a method frequently employed by research and education centres. These centres favour hydroponic farming for the control of plant growth conditions, the study of different nutrient solutions and systems, and the teaching of agricultural practices. This approach facilitates the acquisition of significant insights into future agricultural methodologies (Hamidon et al., 2020).

1.6. New Technologies and Innovation

New technologies and innovations in hydroponic agriculture play an important role in the sustainability and efficiency of agriculture. Aquaponic systems represent a symbiotic integration of aquaculture and hydroponic agriculture. The waste of the fish is used as a nutrient solution for the plants, providing an ideal environment for the plants to grow. This system is highly advantageous in terms of water saving and sustainability. Another innovation is the use of artificial intelligence technologies in agriculture. The utilisation of artificial intelligence has been demonstrated to enhance the efficiency of hydroponic agriculture and to optimise plant-growing conditions. The integration of AI technologies into domains such as plant growth, disease control, and nutrient solution optimization has the potential to enhance agricultural productivity while fostering the development of a more sustainable agricultural model (Mamatha & Kavitha, 2023; Vanipriya et al., 2021).

1.7. Future Perspectives and Research Topics

The present status and future studies of hydroponic agriculture are a significant outcome of research into sustainable agricultural models. The findings, which include high productivity, water conservation, efficient space utilisation and precise control of plant growth conditions, are likely to ensure the preference for hydroponic agriculture in the future. It is anticipated that the research agenda will continue to evolve, with the emergence of novel innovations. The future direction of hydroponic agriculture will be focused on water conservation, sustainability, new technologies and the expansion of application areas. Potential future research topics include plant breeding, nutrient solution optimisation, energy saving and artificial intelligence integration.

2. Hydroponic Agriculture and Curly lettuce Cultivation

The present article analyses the difference between growing lettuce in hydroponic technique with probiotic supplemented nutrient solution and growing lettuce in nutrient solution without probiotic, with the results, methods and pictures to support this analysis. The study methodically explores the fundamental principles of hydroponic agriculture, curly lettuce cultivation, and its distinctive characteristics. It delves into the role of probiotics in agriculture, the utilisation of probiotics in hydroponic agriculture, experimental design and methodologies, results and findings, analysis and interpretation of results, presentation of results, results and discussion, conclusions and recommendations. Curly lettuce is one of the vegetables grown in hydroponic environments and known for its fibrous structure. Curly lettuce is also preferred by consumers for its fast growth, low water use and hygienic production possibilities. Curly lettuce grown in hydroponic environments can be grown in a more controlled environment than in soil farming, which can increase productivity (Dkhar & Bahadur, 2017;Kowalczyk et al., 2014).

2.1. The Role of Probiotics in Agriculture and Effects on Plant Development?

Studies have shown that formulations using probiotics and postbiotics, a type of probiotic product, are significantly more effective on living organisms (Aslan et al., 2023; Gökçe & Aslan, 2024; Tarhan-Celebi et al., 2024, Doğanay et al., 2025). Probiotics found in soil play an important role in promoting plant growth and improving soil health (Hossain et al., 201;John et al., 2020). Probiotics prevent harmful microorganisms from entering the roots of plants and increase nutrient absorption. In addition, they can strengthen plant immunity and provide resistance to diseases. Probiotics can also improve soil structure, increase water retention capacity and provide better nutrition for plants (de Souza Vandenberghe et al., 2017;Song et al., 2012). Some probiotics can promote root development of plants, allowing them to have stronger and deeper roots. Other types of probiotics can support the growth and development of plants by increasing their nutrient absorption. In addition, it is a known fact that probiotics have positive effects on plant growth, so they are increasingly used in agricultural practices (Woo & Pepe, 2018;Hossain et al., 2017).

2.2. Use of Probiotics in Hydroponic Farming

Using of probiotics in hydroponic farming plays an important role in the plant growing process (Kitwetch et al., 2023; Thomas et al., 2024). Probiotics support the development of root systems by containing beneficial bacteria and microorganisms that plants need. In this way, they help plants absorb nutrients more effectively. Probiotics can also increase the resistance of plants to diseases and help them cope with stress (Kim & Anderson, 2018; Hu et al, 2016). Therefore, the use of probiotics in hydroponic farming is of great importance for plant health and productivity.

2.3. Preparation of Probiotic Supplemented Nutrient Solutions

Nutrient solutions with probiotic additives contain beneficial microorganisms, as well as providing the nutrients that plants need. These solutions are typically derived from organic materials and are formulated in such a manner that they are readily absorbed by plants. The preparation of such solutions necessitates the utilisation of specialized equipment and ingredients, in addition to the meticulous measurement and application of the solution components. This ensures optimum utilization of plants (Zhong et al., 2017; Patel et al., 2010).

2.4. Effects of Probiotics on Curly lettuce Breeding

The effects of probiotics on curly lettuce cultivation can significantly improve plant growth and productivity. The use of probiotics has been shown to enhance the strength of plants' root systems, improve nutrient absorption, and augment their resilience to stress (Jones et al., 2019). Furthermore, probiotics have been shown to enhance plant resistance to diseases, thereby providing a protective effect against pathogens. Consequently, the utilisation of probiotics in curly lettuce cultivation has the potential to yield highly favourable outcomes in terms of plant health and productivity.

3. Material and Methods

The experimental design is centred on the cultivation of curly lettuce plants in hydroponics, with and without probiotic supplemented nutrient solutions. The methods employed in the experiment, the growing conditions of the plants, the preparation of nutrient solutions and the care of the plants were determined in detail. The duration of the experiment, the measurement intervals and the data collection techniques were also determined. The primary objective of the experiment was to make a comparison between the growth, development and yield characteristics of curly lettuce plants cultivated with probiotic supplemented nutrient solution and those of plants cultivated without probiotics. The underlying hypotheses posited that the probiotic-supplemented nutrient solution would exert a positive influence on plant growth, enhance plant health and yield, and augment stress tolerance in plants.

To this end, control groups were established and provided with equivalent growing conditions. In order to determine the effects of the probiotic supplemented solution, plants grown with this solution were used as control group. The control groups were maintained under conditions that were analogous with respect to plant growth, solution applications and maintenance.

4. Results and Discussion

The results of the comparison of curly lettuce plants grown with probiotic-supplemented and non-supplemented nutrient solutions revealed that probiotic-supplemented plants exhibited enhanced health and superior growth. The root development of the probiotic-fed plants exhibited enhanced strength, while the leaf coloration displayed heightened vibrancy. In contrast, plants cultivated with the unamended nutrient solution exhibited stunted growth, reduced vigor, and diminished productivity in comparison to those amended with probiotics. This observation lends further credence to the notion that probiotic supplementation exerts a beneficial influence on the development of curly lettuce plants.

Figure 1, Figure 2. the production process for the curly lettuce vegetables

Figures 1 and 2 illustrate the initiation of the production process for the curly lettuce seedlings in question, utilizing the same system and two distinct nutrient solutions.

Figure 3. The image of Curry roots

5. A comparison of Curly lettuce Plants Grown with Probiotic Supplemented and Non-Supplemented Nutrient Solutions, with Analysis and Interpretation of Results

Following analysis of the results of the difference between growing curly lettuce with probiotic-added nutrient solution and growing curly lettuce with probiotic-free nutrient solution by hydroponic technique, it was observed that probiotic-added plants grew faster and healthier. It was determined that the probiotic additive positively affected the root development of the plants and absorbed nutrients more efficiently. Furthermore, it was determined that probiotic supplementation increased the resistance of plants against diseases and positively influenced the overall plant health. This analysis thus demonstrates that probiotic supplementation exerts a substantial influence on the development of curly lettuce plants (Figure 3).

5.1. Analysis of the Data Obtained and Statistical Analyses

A thorough examination and statistical analysis of the data obtained during the experiment revealed clear differences in the development of curly lettuce plants grown with and without probiotic supplementation. Statistical analysis indicated that probiotic supplementation significantly augmented plant height, leaf growth, root length, and total yield. Furthermore, in comparison with the control groups, probiotic supplementation led to a marked enhancement in the general health status of the plants and optimized nutrient utilization.

5.2. A comparison of Curly lettuce Plants Grown with Probiotic Supplemented and Non-Supplemented Nutrient Solutions

Following analysis of the results of the difference between growing curly lettuce with probiotic-added nutrient solution and growing curly lettuce with probiotic-free nutrient solution by hydroponic technique, it was observed that probiotic-added plants grew faster and healthier. It was determined that the probiotic additive positively affected the root development of the plants and absorbed nutrients more efficiently. Furthermore, it was determined that probiotic supplementation increased the resistance of plants against diseases and positively influenced the overall plant health. This analysis thus demonstrates that probiotic supplementation exerts a substantial influence on the development of curly lettuce plants.

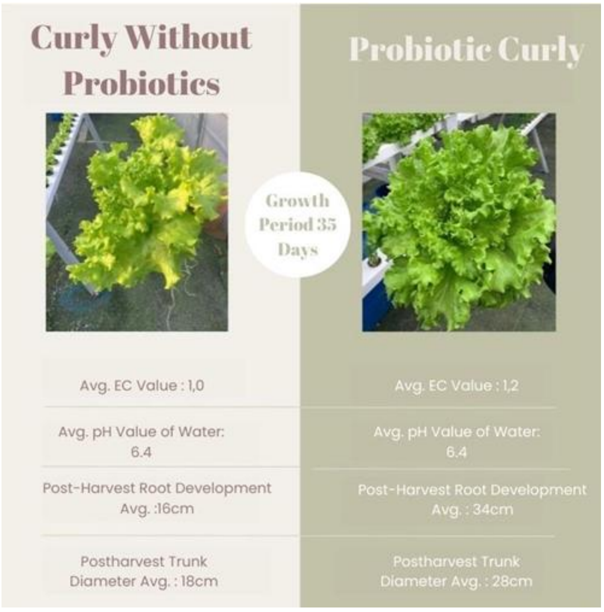

Figure 4. Measurement of some physical values in the growth stage of curly lettuce vegetable

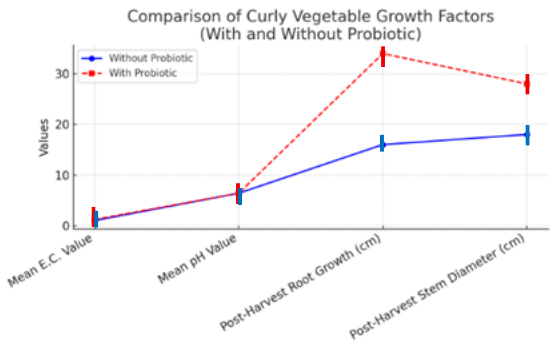

Figure 5. Graph of some physical changes of curly lettuce vegetable during growth stage

The experiment yielded results indicating that lettuce cultivated in a hydroponic technique using a nutrient solution fortified with probiotics exhibited superior growth characteristics in comparison with lettuce cultivated in the absence of probiotics. The experiment revealed that plants cultivated with the probiotic solution exhibited accelerated growth, an increased number of leaves, and healthier root systems. Furthermore, plants treated with the probiotic-amended solution exhibited enhanced resistance levels and greater resistance to harmful organisms.

The positive and beneficial effects of probiotic and postbiotic formulations on life forms have been documented (Aslan & Celebi, 2023; Aslan et al., 2025). The potential of probiotics in agricultural applications is significant. These microorganisms have been shown to enhance productivity by promoting plant growth, increasing plant resistance to harmful organisms, and enhancing plant resistance to diseases. Probiotics have been shown to play a significant role in improving plant growth and soil health (Hossain et al., 2017; John et al., 2020). They have been shown to enhance soil structure and increase water retention capacity, thereby ensuring optimal plant nutrition (de Souza Vandenberghe et al., 2017; Song et al., 2012). Furthermore, it has been documented that probiotics have a favorable impact on plant growth (Hossain and colleagues, 2017; Woo & Pepe, 2018).
The utilization of probiotic-enhanced nutrient solutions in the cultivation of curly lettuce plants has been demonstrated to yield several notable advantages. These include the provision of effective microorganisms that stimulate plant growth, facilitate nutrient absorption, and enhance plant resistance to harmful organisms. It has been observed that the general health status of plants improves and their productivity increases with the use of probiotic-added solutions. Further research is required to ascertain the full potential of probiotics in agricultural applications (Figure 4, Figure 5).

5. Conclusion

Following a comprehensive analysis of the outcomes, methodologies and images obtained from experiments conducted in a hydroponic environment, it was determined that the utilization of a nutrient solution augmented with probiotics exerted a favorable influence on the cultivation of curly lettuce plants. Observations revealed that the probiotic nutrient solution promoted faster growth, healthier plants and increased productivity. The findings of this study demonstrate that probiotic supplementation has significant advantages on curly lettuce cultivation. Future studies should focus on a detailed investigation of the effects of different probiotic strains, optimization of application dosages and evaluation of environmental effects. A detailed examination of the effects of different probiotic strains is recommended for future studies. In addition, optimizing probiotic application dosages and evaluating environmental effects are also important issues. In addition, investigating the long-term effects of probiotic-added nutrient solution and examining its effects on other plant species are among the suggested topics for future studies.

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Author Contribution
All authors shared equal tasks at all stages of the study.

Conflicts of Interest
Authors declare no conflicts of interests.

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Can Black Tea and Green Tea Prevent Cancer? Novel Drug Delivery Approaches

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Abstract

Green tea and black tea, derived from *Camellia sinensis*, are polyphenol-rich beverages known for their health benefits. Green tea is abundant in epigallocatechin gallate (EGCG), a potent antioxidant with anticancer properties, while black tea, produced through fermentation, contains theaflavins and thearubigins, which helps reduce oxidative stress and support DNA repair. Both teas contain polyphenols that regulate tumor initiation, progression, and metastasis. Green tea has shown protective effects against esophageal, colorectal, and gynecologic cancers, while black tea exhibits anti-angiogenic and chemo-preventive properties. Combining both teas may enhance their anticancer potential, though factors like preparation methods, dosage, and genetic variability influence their efficacy. Various studies based on drug delivery systems using *Camellia sinensis* components have been added to this article to provide examples of approaches for future studies. Advances in nanotechnology are improving the bioavailability of tea polyphenols, facilitating their integration into cancer prevention and treatment strategies. Further research is needed to establish optimal consumption guidelines.

Key Words: *Camellia sinensis*, cancer prevention, anti cancer, drug delivery

1. Introduction

1.1.Green tea and black tea properties

Green tea and black tea, derived from the *Camellia sinensis* plant, are among the most consumed beverages worldwide (Khan & Mukhtar, 2019; Cabrera et al., 2006). Widely enjoyed in many countries, *Camellia sinensis* boasts numerous health benefits attributed to its rich composition of bioactive compounds (Bursalioglu, 2019). Green tea is a non-fermented type of tea and contains higher levels of catechins compared to black tea (Cabrera et al., 2006). These catechins have been shown to possess strong antioxidant properties in both cell culture and animal studies (Khan & Mukhtar, 2019). EGCG (Epigallocatechin gallate) is the most extensively studied polyphenol in green tea, known for its antioxidant and antiviral properties (Khan & Mukhtar, 2019; Mhatre et al., 2021) . Moreover, the polyphenol content of green tea has been associated with various health benefits, including support for oral health, weight management, and anti-inflammatory effects (Cabrera et al., 2006; Xing et al., 2019). Figure 1 presents a photograph of several active ingredients found in *Camellia sinensis*.

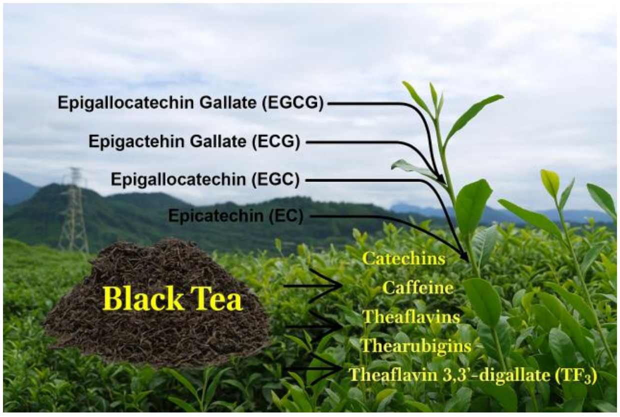

Figure 1. The image is associated with certain contents of the *Camellia sinensis* plant. This figure was originally drawn by the authors.

Black tea, on the other hand, contains unique bioactive compounds such as theaflavins and thearubigins, which are formed through the oxidation of polyphenols during fermentation (Tenore et al., 2015; Khan & Mukhtar, 2019). The composition of black tea makes it particularly effective in reducing oxidative stress caused by radiation and lowering blood pressure (Korystova et al., 2021; Mahdavi-Roshan et al., 2020). Additionally, black tea exhibits stronger antibacterial properties and a greater impact on reducing oral biofilms compared to green tea (Fernández et al., 2022). Polyphenols like theaflavin-3,3'-digallate (TF3) in black tea have shown potential antiviral effects, particularly against SARS-CoV-2 (Mhatre et al., 2021). Furthermore, black tea's fermentation products are effective in reducing cholesterol and triglyceride levels, making it a promising option for addressing conditions related to metabolic syndrome (Tenore et al., 2015).

Both green tea and black tea have been found to reduce the negative effects of obesity on male reproductive health, with black tea demonstrating a stronger impact in this regard (Han et al., 2020). Additionally, the antihypertensive effects of green tea have been observed to be more pronounced compared to black tea, especially with regular consumption (Mahdavi-Roshan et al., 2020). The distinct bioactive properties of catechins in green tea and fermentation-derived compounds in black tea highlight their complementary health benefits (Xing et al., 2019; Korystova et al., 2021).

2. Method

2.1. Examples from the literature on the anti-cancer effects of green tea and black tea

Tea is one of the three most consumed nonalcoholic beverages, and its global consumption has increased significantly in recent years (FAO 2019). These drinks, which are a beautiful gift of nature, play a beneficial role in health as well as flavor and pleasure. Green and black tea, derived from *Camellia sinensis*, have been extensively studied for their potential health benefits, particularly in cancer prevention. These teas contain polyphenols such as catechins and theaflavins, which have demonstrated potent antioxidant and anti-inflammatory properties, crucial in inhibiting cancer progression (Beltz et al., 2006; Chung, 1999; Farhan, 2022; Filippini et al., 2020). Epigallocatechin gallate (EGCG), a key catechin in green tea, has been shown to interfere with cancer cell proliferation as well as to induce apoptosis and regulate signaling pathways associated with tumor growth and metastasis (Almatroodi et al., 2020).

Epidemiological studies suggest that regular green tea consumption is linked to a reduced risk of esophageal, colorectal, and gynecologic cancers (Abe & Inoue, 2021; Zhao et al., 2021; Ohishi et al., 2022). These protective effects are attributed to green tea polyphenols targeting pathways involved in tumor initiation, promotion, and progression. They modulate gene expression by downregulating oncogenes and upregulating tumor suppressor genes, thereby creating an inhospitable environment for cancer cell growth (Zhao et al., 2014).

Black tea, while less researched compared to green tea, contains unique polyphenolic compounds, including theaflavins and thearubigins, which exhibit significant antioxidative and chemo-preventive properties. These compounds help reduce oxidative stress, suppress angiogenesis, and inhibit matrix metalloproteinases, which play roles in tumor invasion and metastasis. Black tea polyphenols also support DNA repair mechanisms and protect against carcinogen-induced DNA damage, making them valuable in cancer prevention strategies (Singh et al., 2017; Bag & Bag, 2018; Sharma, et al., 2018; Kager, et al., 2010).

Studies combining green and black teas have shown complementary effects in preclinical and clinical research. Green tea catechins have been linked to delayed cancer onset and reduced recurrence rates, particularly in colorectal adenomas, while black tea polyphenols exhibit preventive effects against oral cancers through molecular pathways like the epidermal growth factor receptor (EGFR) pathway (Khan & Mukhtar, 2019; Nimbalkar, et al., 2022; Yoon, et al., 2012). These findings highlight the importance of integrating different tea types into dietary interventions for comprehensive cancer prevention. The anticancer mechanisms of tea polyphenols are diverse. They act as both antioxidants and pro-oxidants depending on the microenvironment, selectively targeting cancer cells while sparing normal cells (Yang & Wang, 2016; Rogovskii, et al., 2019; Lambert & Forester, 2013). Cell cycle, apoptosis and angiogenesis constitute the main points of the process in tumor development. Additionally, tea polyphenols induce cell cycle arrest, promote apoptosis, and inhibit angiogenesis all of which are critical processes in preventing tumor growth and metastasis (Khan & Mukhtar, 2010; Beltz, et al., 2006; Daniel et al., 2005). Epigenetic modulation is a process that regulates gene expression without changing the DNA sequence, through mechanisms such as DNA methylation, histone modification and non-coding RNAs. Epigenetic modulation by tea polyphenols, including alterations in DNA methylation and histone modification, further enhances their chemo-preventive potential (Nandakumar et al., 2011; Meeran et al., 2010). Emerging evidence suggests that tea polyphenols enhance the efficacy of conventional cancer therapies. For example, combining green tea catechins with chemotherapy drugs has demonstrated synergistic effects in reducing tumor size and improving patient outcomes (Rahmani et al., 2015; Fujiki et al., 2012).

Despite these promising findings, several challenges remain. Factors such as variations in tea preparation methods, individual genetic differences, and optimal dosages significantly influence the effectiveness of tea polyphenols in cancer prevention. High-temperature brewing has been associated with enhanced catechin bioavailability, but excessive consumption may lead to adverse effects, including hepatotoxicity in sensitive individuals. Addressing these variables is essential for maximizing the benefits of tea in cancer prevention. (Wang et al., 2010; Lambert & Forester, 2013; Yang, et al., 2009; Fujiki, et al., 2018; Chow et al., 2005; Sarma et al., 2008). These studies are also given in Table 1.

Table 1. The protective effects of green tea and black tea against cancer.

Tea Type	Active İngredient	İmpact of Cancer Prevention	References
Green tea/black tea	catechins theaflavins	these teas possess significant antioxidant and anti-inflammatory properties, which renders them of considerable importance in the prevention of cancer progression.	Beltz et al., 2006; Chung, 1999; Farhan, 2022; Filippini et al., 2020
Green tea	EGCG	induces apoptosis and may be involved in regulating signalling pathways associated with tumour growth and metastasis	Almatroodi et al., 2020
Green tea	polyphenols	they affect tumor initiation, promotion, and progression pathways by gene modulations.	Zhao et al., 2014
Black tea	polyphenols	support DNA repair mechanisms and protect against DNA damage	Bag & Bag, 2018; Sharma, et al. 2018;
Green tea	catechins	protection colorectal adenomas	Khan & Mukhtar, 2019
Black tea	polyphenols	preventive effects against oral cancers	Nimbalkar, et al. 2022; Yoon, et al. 2012
Green tea /black tea	polyphenols	preventing tumor growth and metastasis.	Beltz, et al. 2006; Daniel et al. 2005
Green tea /blac k tea	polyphenols	chemo-preventive effects due to epigenetic modulation	Nandakumar et al. 2011; Meeran et al. 2010
Green tea	catechins	using with chemotherapy drugs has synergistic effects	Rahmani et al., 2015; Fujiki et al., 2012

3. Novel drug delivery approaches

Drug delivery systems are innovative approaches developed to ensure effective and controlled delivery of therapeutic agents to target areas. Overcoming the limitations of traditional methods, these systems enable drugs to overcome biological barriers, target-specific release, and reduce side effects through carriers such as liposomes, nanoparticles, and biocompatible polymers. For example, the liposomal formulation of *Rosmarinus officinalis* (rosemary) extract significantly increased skin permeability compared to conventional forms, providing a high absorption rate in a short time of 160 minutes (Aslan & Kurt, 2021). Similarly, liposome-gel systems containing Estradiol/Estriol developed for women in menopause offered ease of transdermal application with their alcohol-free structures and low toxicity, while ensuring homogeneous distribution to the skin

(Aslan & Aytekin, 2023). The therapeutic potential of liposomes is not limited to skin permeability. The utilisation of liposome carrier systems has been demonstrated to reduce the toxicity of certain volatile oils (Özdemir et al., 2018) and to increase the antifungal activities of some essential oils (Yazıcı et al., 2011) Furthermore, the employment of herbal formulations has been documented to accelerate wound healing (Gunal et al., 2019; Gunal et al., 2021)) and enhance the kinetic stability of plants obtained by maceration(Kurt et al., 2025), as in nanoemulsion formulations (Kurt & Aslan 2025).

They also hold promise in neurological diseases thanks to their ability to cross the blood-brain barrier. Liposomal resveratrol's more effective suppression of penicillin-induced epileptic seizures compared to the free form is an example of this (Ethemoglu et al., 2017). In addition, chitin, a natural polymer, provides the advantage of use in wound healing carrier systems with its antimicrobial properties and biocompatibility (Mehrabani et al., 2018), while liposomes modified with terpenes have increased treatment sensitivity by improving GLUT1 receptor targeting in cancer cells (Wang et al., 2021). Nanotechnology-based systems have created an important turning point in cancer treatment. Although nanoparticles accumulate in tumor tissues with enhanced permeation and retention (EPR) effect, they are weak in reaching metastatic lymph nodes. Dual-target nanosystems such as enzyme-sensitive DMSN@Pla-Lipo developed to solve this problem both increase penetration in the primary tumor and optimize drug delivery to lymphatic metastases (Yuan et al., 2025). In breast cancer treatment, PTX-loaded nanostructured lipid carriers (NLC) have increased treatment safety by reducing normal cell toxicity while showing target-specific effect (Attar et al., 2025). The use of natural components plays a critical role in drug delivery systems in terms of both stability and efficacy. Herceptin complexes with (-)-Epigallocatechin-3-O-gallate (EGCG) have shown promising results in cancer treatment, while tannic acid and therapeutic protein combinations have shown promising results in cardiovascular diseases (Chung et al., 2014; Shin et al., 2018). In addition, gel formulations of liposomal postbiotics have created a new perspective in pharmaceutical applications by providing ease of use while maintaining antimicrobial activity (Gokce & Aslan, 2024).

A number of studies have indicated the potential of green and black tea to offer protection against cancer, thereby raising hopes that they may also possess therapeutic properties and reduce side effects. A significant number of studies have evaluated the components of the *Camellia sinensis* plant in terms of their therapeutic efficacy, with a view to identifying cancer-protective properties. The search for new methods of cancer treatment has also led to a growing interest in substances with anti-carcinogenic properties, with various studies being conducted using different drug delivery systems. The potential for these studies to inform the development of new treatment modalities is significant. Advances in nanotechnology, such as nanodelivery systems, have further improved the bioavailability and therapeutic efficiency of tea polyphenols, paving the way for their clinical application in cancer treatment (Jiang et al., 2021; Almatroodi, et al., 2020). Xiong and colleagues conducted a study to ascertain the efficacy of delivering anticancer proteins (e.g. Herceptin) using micellar nanocomplexes (MNCs) containing green tea catechin derivatives. The MNCs demonstrated significant toxicity towards breast cancer cells by inducing apoptosis, while showing no toxicity towards normal human cells. Furthermore, MNCs are unlikely to induce kidney toxicity (Xiong et al., 2023). Bae and colleagues reported the findings of research conducted on micellar nanocomplexes. These nanocomplexes, which consist of a conjugate of hyaluronic acid and EGCG, in addition to cisplatin, have been shown to facilitate targeted drug delivery in ovarian cancer via CD44 receptors. The antioxidant property of EGCG has been demonstrated to reduce the organ toxicity of cisplatin, while the core-structured design of the nanocomplex has been shown to allow for high drug accumulation in the tumour. The basis of this system being a safe and effective chemotherapy strategy is attributable to its green tea catechin composition (Bae et al., 2017). Chung et al., 2014) reported that micellar nano-complexes formed by the gradual self-assembly of EGCG derivative and anticancer protein Herceptin can solve traditional problems associated with drug carriers by demonstrating both carrier and therapeutic effects. This structure, with Herceptin-EGCG oligomers in the core and PEG-EGCG in the shell, provides longer blood circulation, targeted tumour accumulation and effective tumour shrinkage compared to free Herceptin in mouse models. The anticancer and protective properties of EGCG enhance therapeutic efficacy while eliminating carrier toxicity concerns, thus demonstrating the potential of 'bifunctional' nanotherapeutics in cancer treatment (Chung et al., 2014).

Bae et al., 2022) reported the findings of a study on the design of bone marrow-targeted nanotherapeutics based on green tea catechins. Green tea catechins-based bone marrow-targeted micellar nano-complexes have been shown to enhance the anti-leukaemic effect of sorafenib in the treatment of acute myeloid leukaemia (AML) by targeting mTOR, the survival signal of leukaemic cells. The nanocomplex demonstrated a 11-fold higher accumulation in the bone marrow compared to free sorafenib, effectively clearing leukaemic cells in the bone marrow in a mouse model derived from an AML patient. (Bae et al., 2022). The investigation by Haratifar and colleagues sought to ascertain whether the antiproliferative effect of EGCG, the main component of green tea, would be preserved through its nanoencapsulation with casein micelles. The study revealed that EGCG encapsulated in casein micelles exhibited a comparable level of inhibition of HT-29 cancer cell proliferation to that of free EGCG, thereby confirming that bioaccessibility was not diminished. of EGCG (Haratifar et al., 2014). A study on Sunitinib-loaded micellar nanocomplex (SU-MNC) was reported by Yongvongsoontorn and colleagues.SU-MNC was constructed using poly(ethylene glycol)-conjugated epigallocatechin-3-O-gallate (PEG-EGCG) as a carrier. The study concluded that SU-MNC specifically inhibited vascular endothelial growth factor-induced proliferation of endothelial cells and exhibited minimal toxicity against normal kidney cells (Yongvongsoontorn et al., 2019). Almatroodi and colleagues conducted a study on the potential to overcome poor bioavailability through nanotechnology-based strategies such as encapsulation, liposomes, micelles, nanoparticles and various other formulations. Although EGCG, the main component of green tea, has antioxidant and anticancer properties, it suffers from low bioaccessibility; therefore, nanoencapsulation methods play an important role in overcoming this problem by increasing the effectiveness of clinical doses and increasing its potential in cancer treatment (Almatroodi et al., 2020).

The interaction between green tea and liposomes was conducted by Andrade and colleagues. The study found that green tea extract (GTE) increased membrane fluidity by binding to biomembranes through hydrophobic and electrostatic interactions in liposome models. However, the presence of cholesterol reduced this interaction and limited the anti-lipid peroxidation effect, which may affect the effectiveness of GTE (Andrade et al., 2021). A study was conducted on the subject of skin penetration of catechins. The process of skin penetration of catechins is challenging due to their lipophilic nature. However, the use of carriers such as liposomes, micelles and polymeric nanoparticles has been shown to improve bioavailability by increasing skin hydration and supporting follicular transport. This is promising in terms of applications in skin cancer and anti-aging (Aljuffali et al., 2022). Liang et al. reported the development of micellar nanocomplexes (MNC) with high stability (88% drug loading) by combining doxorubicin (DOX) and polyethylene glycol (PEG)-EGCG conjugate. This approach addressed the problems of low drug loading and instability in the bloodstream, which hindered the success of nanomedicine in the clinic. In mouse models of liver cancer, MNCs showed significant tumour suppression effect even at low doses while minimising unwanted side effects, compared to free DOX and liposomal DOX (Liang et al., 2018). In the study by Jin et al., a nano-micelle composite was developed, consisting of a cationic lipopolymer functionalised with catechin and serum albumin. Cationic liposomes have been shown to increase the bioavailability of catechins by accumulating in the lung microvasculature due to electrostatic effects. Albumin contributes to long-term in vivo retention as a biocompatible anti-plasma sorbent.

The physicochemical and antitumour properties of the nano-micellar complexes have been confirmed by detailed analyses, suggesting that this system could be a promising tool in the treatment of lung diseases (Jin et al., 2024). Fang and colleagues was reported that liposomes with added anionic components (deoxycholic acid) accelerated drug release but did not significantly increase skin deposition when applied topically. However, liposomes provided greater drug delivery to solid tumours compared to catechins in free form. The gallic acid ester in the structure of EGCG significantly improved tissue uptake, while (+)-catechin and (-)-epicatechin isomers differed in their accumulation in skin and tumour (Fang et al., 2005). De Pace and colleagues developed the EGCG encapsulated chitosan-coated nanoliposomes (CSLIPO-EGCG) system, which consists of chitosan-coated nanoliposomes. This system was developed to address the problems of instability and poor absorption in the body of EGCG, the main component of green tea. The CSLIPO-EGCG system has been shown to induce apoptosis in MCF7 breast cancer cells by providing higher intracellular uptake compared to free EGCG. The biocompatible and degradable nature of the system offers an innovative strategy for breast cancer treatment by providing chemoprevention at doses where conventional EGCG is ineffective (De Pace et al., 2013).

A liposome-based system to enhance the intra-tumour distribution of EGCG, the main component of green tea, was developed by Fang and colleagues. The accumulation of EGCG in basal cell carcinoma (BCCs) tissue was increased 20-fold by liposomes containing deoxycholic acid (DA) and 15% ethanol compared to the free form, resulting in a marked improvement. The liposomes, in addition to their protective effect against EGCG degradation, exhibited the capacity to induce BCCs cell death even at low concentrations.The efficacy of this system was further demonstrated through its application in melanoma and colon tumours, thereby substantiating the potential of modified liposomes as a targeted therapeutic agent through intra-tumour injection (Fang et al., 2006).

As a result, drug delivery systems have the potential to further increase treatment success when integrated with personalized medicine and combination therapies. The use of biocompatible materials allows for the development of sustainable and safe formulations, while multifunctional nanosystems open the door to a new era in metastasis control. Research in this area will continue to shape the future of the pharmaceutical industry and provide transformative solutions for treating diseases. A description of all stages of this compilation work is shown in figure 2.

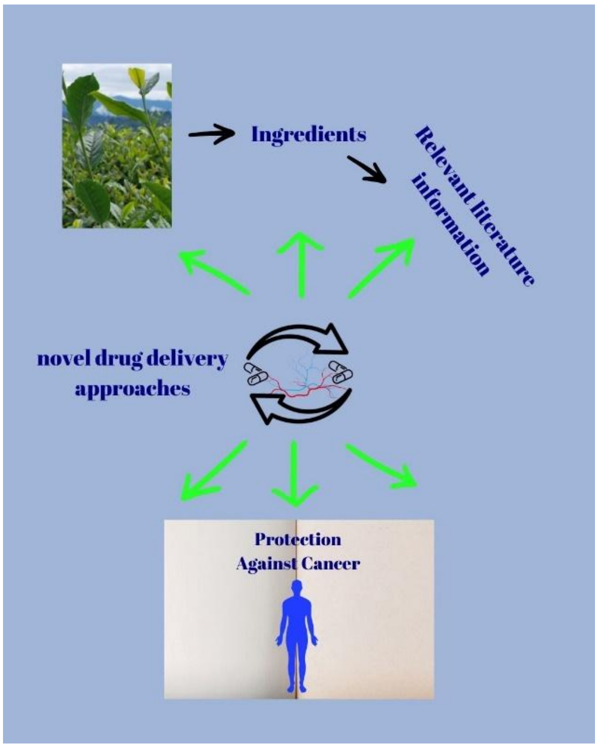

Figure 2. visualisation of the basic stages of the study on the anticancer content of the *Camellia sinensis* plant ingredients and next generation drug transport systems approach**.** This figure was originally drawn by the authors.

4. Conclusion

Green and black teas represent valuable natural resources for cancer prevention. Their polyphenolic compounds, particularly catechins and theaflavins, modulate key processes involved in carcinogenesis, including tumor initiation, progression, and metastasis (Beltz et al., 2006; Chung, 1999; Farhan, 2022; Filippini et al., 2020). Green tea, rich in EGCG, has shown protective effects against esophageal, colorectal, and gynecologic cancers (Abe & Inoue, 2021; Zhao et al., 2021; Ohishi et al., 2022), while black tea's theaflavins and thearubigins exhibit antioxidative, anti-angiogenic, and DNA repair-supporting properties (Bag & Bag, 2018; Sharma, et al., 2018). Combining both teas may enhance their anticancer potential, as their complementary mechanisms target multiple pathways in cancer development (Beltz et al., 2006; Chung, 1999; Farhan, 2022; Filippini et al., 2020; Daniel et al., 2005; Nandakumar et al., 2011; Meeran et al., 2010). Advances in nanotechnology, such as nanodelivery systems, are improving the bioavailability and therapeutic efficiency of tea polyphenols, facilitating their integration into cancer prevention and treatment strategies (Jiang et al., 2021; Almatroodi, et al., 2020). However, factors like preparation methods, dosage, and genetic variability significantly influence their efficacy. High-temperature brewing may enhance catechin bioavailability, but excessive consumption could lead to adverse effects, including hepatotoxicity in sensitive individuals (Almatroodi et al., 2020; Chung et al., 2014; Bae et al., 2022). Continued research is essential not only to establish optimal consumption guidelines but also to understand individual variability and improve delivery mechanisms. By addressing these knowledge gaps, researchers can unlock the full therapeutic potential of green and black teas, making them an integral part of dietary recommendations for comprehensive cancer prevention and treatment (Almatroodi et al., 2020; Chung et al., 2014; Bae et al., 2022; Ohishi et al., 2022).

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Author Contribution
All authors shared equal tasks at all stages of the study.

Conflicts of Interest
Authors declare no conflicts of interests.

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