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RESEARCH ARTICLE

MET-Mediated Drug Resistance in Colorectal Cancer: In Silico Analysis of the Potential of Epicatechin-3-Gallate and Epigallocatechin-3-Gallate as Therapeutic Adjuvants

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Abstract

Background: Colorectal cancer (CRC) is the third most common cancer worldwide by incidence and the second leading cause of cancer-related death. Although chemotherapy has improved survival rates, long-term use often leads to chemoresistance and significant side effects. Therefore, new adjuvant strategies are urgently needed. This study examines the potential of tea catechins (Camellia sinensis), specifically epigallocatechin-3-gallate (EGCG) and epicatechin-3-gallate (ECG), as adjuvants to overcome chemoresistance in CRC.

Methods: We used a computational approach combining network pharmacology and molecular docking.

Results: Protein target analysis showed that ECG and EGCG specifically target four proteins, including the key hub protein c-Met (MET). The MET protein plays a vital role in CRC chemoresistance, especially in response to anti-angiogenic therapy. This potential is supported by patient survival data indicating a poor prognosis for CRC patients with MET overexpression. The molecular docking results suggest that EGCG and ECG bind strongly to c-Met, with binding energies of -9.2 kcal/mol and -9.1 kcal/mol, respectively. This high affinity supports the idea that ECG and EGCG can directly modulate c-Met's various functions.

Conclusion: This in silico study provides a solid molecular basis for developing tea catechins as chemosensitizers to improve chemotherapy effectiveness and reduce chemoresistance in CRC.

Keywords: Chemoresistance, Colorectal Cancer, c-Met, Epigallocatechin-3-Gallate, Ethnopharmacology

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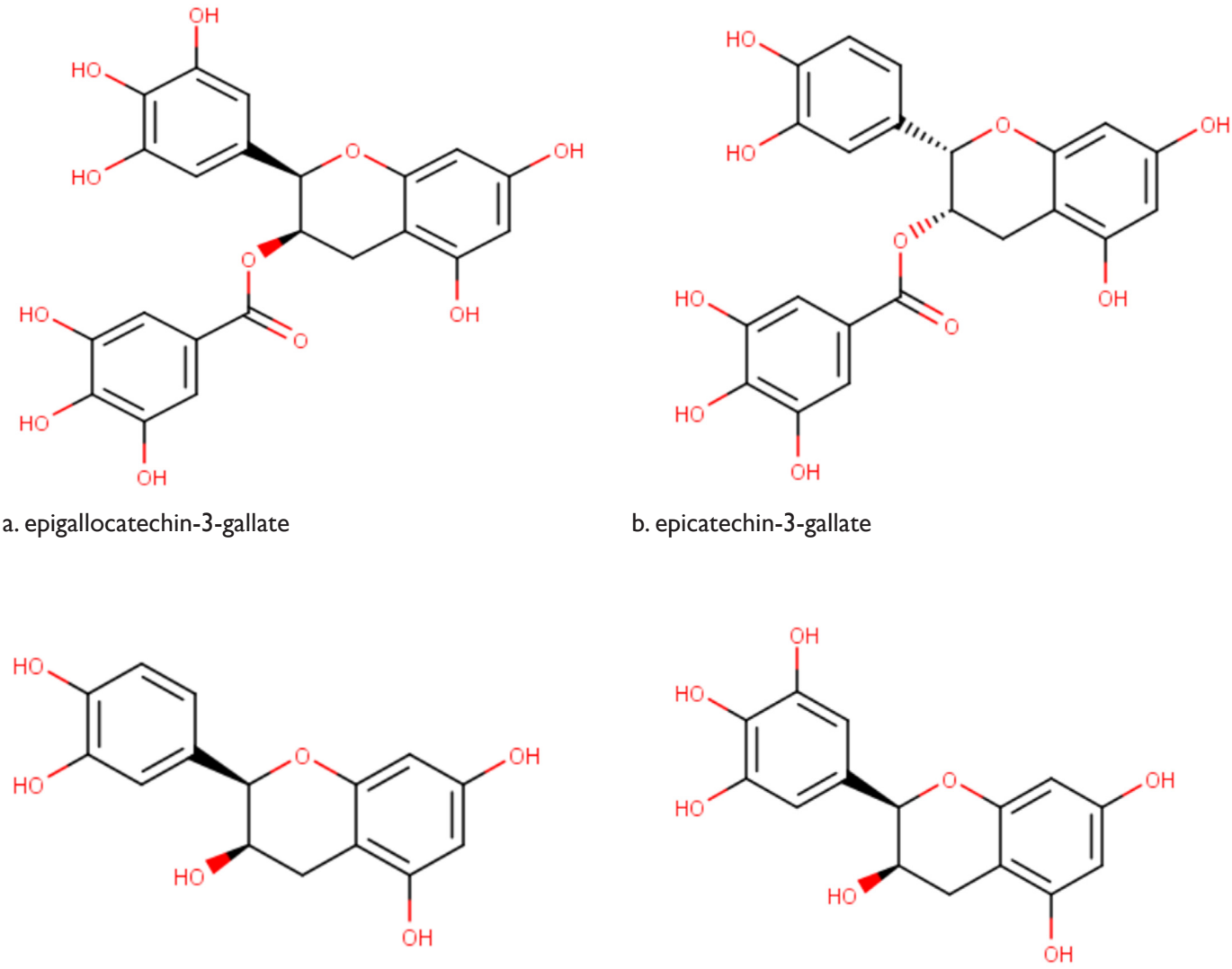
Introduction

Colorectal cancer (CRC) remains a significant global public health challenge; it is currently third in incidence and second in cancer-related deaths [1]. The World Health Organization (WHO) reported about 1.9 million new CRC cases globally in 2020 [1]. In Indonesia, registry data and clinical studies show increasing incidence, geographic differences, and a shift toward younger age groups. Additionally, treatment outcomes in Indonesia are affected by the fact that most patients are diagnosed at an advanced stage [2–4].



a. epigallocatechin-3-gallate

b. epicatechin-3-gallate

c. epicatechin

d. epigallocatechin

Figure 1. Chemical structures of tea catechins: a) epigallocatechin-3-gallate, b) epicatechin-3-gallate, c) epicatechin, and d) epigallocatechin (source: PubChem database).

Although improved screening and treatment have increased CRC survival rates, 5-fluorouracil (5-FU)-based regimens remain the cornerstone of care in both curative and palliative settings [5,6]. These chemotherapeutic agents are often combined with targeted therapies to extend patient survival. However, prolonged chemotherapy use leads to serious issues, such as systemic toxicity and chemoresistance [7,8]. Resistance to these chemotherapeutic agents poses a major obstacle, resulting in treatment failure, disease recurrence, and a poor clinical outlook [9–11]. Along with clinical obstacles, limited access, and the high cost of targeted therapies, these factors restrict their adoption within Indonesia's healthcare financing system, thereby weakening their cost-effectiveness [12]. Therefore, developing new adjuvant strategies to enhance treatment results and reduce the emergence of chemoresistance has become an essential priority.

Natural products hold great potential as adjuncts in cancer treatment due to their multitarget effects, favorable toxicity profiles of certain compounds, and their abundance in diverse regions, such as Indonesia [13–15]. Various natural compounds have shown anticancer effects against CRC cells in preclinical studies [11,16,17]. Among the promising bioactive substances is catechin, a plentiful component of tea (Camellia sinensis). Catechin derivatives, such as epigallocatechin-3-gallate (EGCG), are known for their wide-ranging anticancer effects, including the ability to inhibit proliferation, induce apoptosis, and exhibit anti-angiogenic and anti-metastatic properties, as well as their established role as effective chemosensitizers in various cancer models [13,18–20].

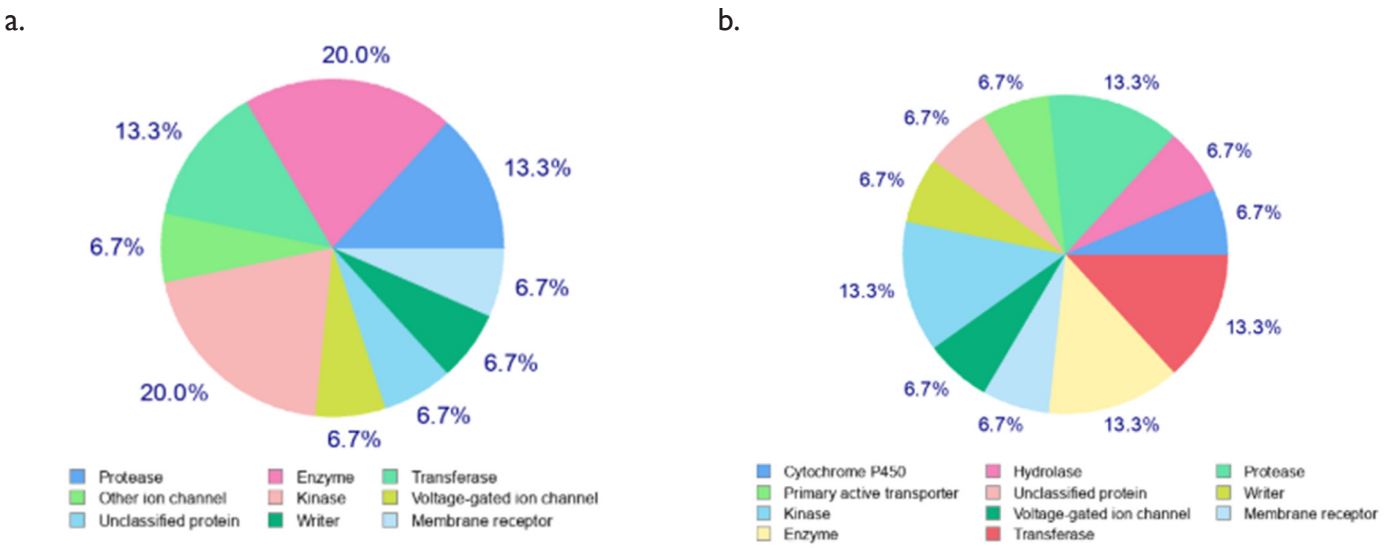


Figure 2. Target prediction results for (a) epicatechin-3-gallate and (b) epigallocatechin-3-gallate. Epicatechin and epigallocatechin did not identify any protein targets in Homo sapiens cells.

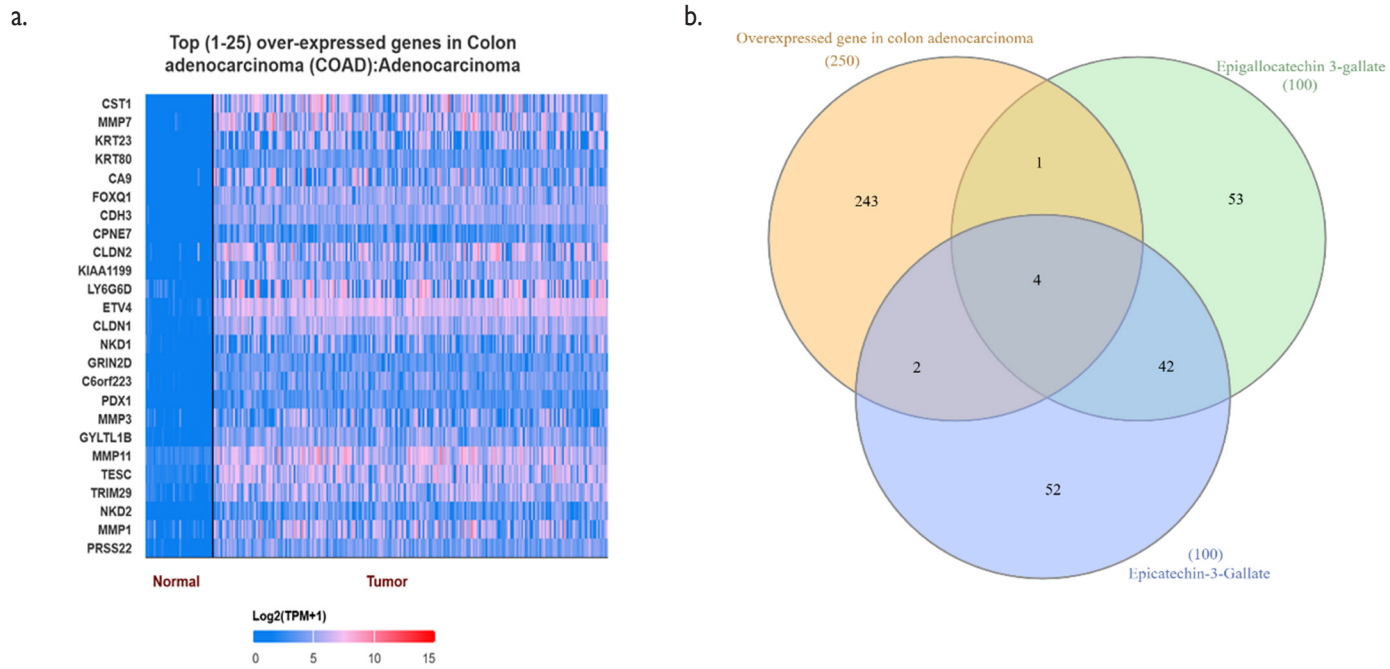


Figure 3. Gene expression analysis in CRC patients (a) revealed that 25 genes, including MMP7, CA9, and FOXQ1, were overexpressed compared to normal tissues. The predicted protein targets of epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate (EGCG) were combined with the overexpressed proteins in CRC to find common target proteins (b).

This study aims to perform a computational analysis and mechanistic review of the potential of tea catechins as adjuvant agents to overcome chemoresistance in colorectal cancer by targeting specific proteins. The results from this in silico analysis are expected to provide a framework for prioritizing relevant molecular targets, thereby supporting the development of more affordable and accessible adjuvant therapy strategies.

Materials and Methods

Structural Acquisition and Pharmacology Analysis

The three-dimensional (3D) structure of tea catechin compounds includes epicatechin (CID:72276), epicatechin-3-Gallate (CID: 65056), epigallocatechin (CID: 72277), and epigallocatechin-3-gallate (CID: 65064) obtained from a public chemical database, PubChem (National Center for Biotechnology Information) at (https://pubchem.ncbi.nlm.nih.gov/) [21]. The physicochemical and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity)

properties of catechin compounds were analyzed using the pKCSM server at https://swissadme.ch/ [22]. The data was accessed in January 2026.

Gene Expression Analysis in Colorectal Cancer Patients

Gene expression data from CRC patients were analyzed to identify clinically relevant protein targets. This data was accessed through the UALCAN website at https://ualcan.path.uab.edu/analysis.html [23], which provides access to The Cancer Genome Atlas (TCGA) data. Proteins that showed overexpression in CRC tissue compared to normal tissue were collected and downloaded as relevant CRC targets. The data was accessed in January 2026.

Target Integration and Protein Interaction Analysis

Potential target proteins of tea catechins in the context of CRC were predicted using a machine-learning-based target prediction server, namely SwissTargetPrediction, available at https://swisstargetprediction.ch [24]. The prediction

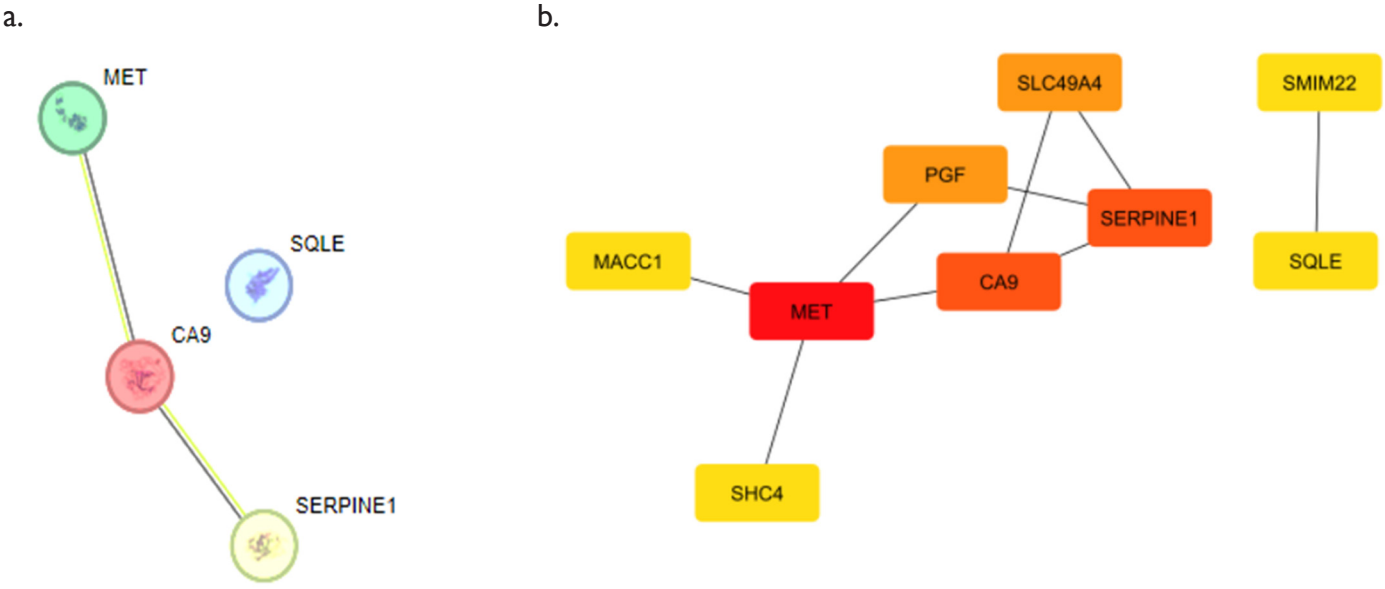


Figure 4. Protein interaction networks created using the STITCH server (a) and Cytoscape software (b).

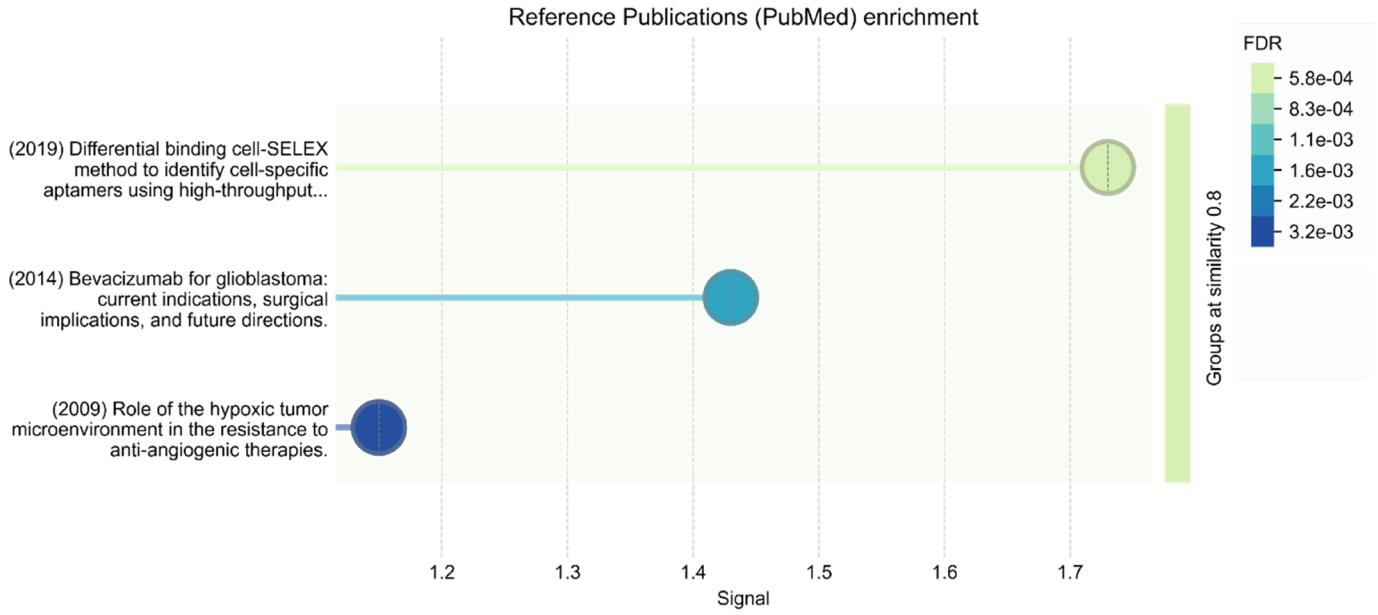


Figure 5. Gene Ontology (GO) and pathway enrichment analyses of the prioritized target proteins.

Table 1. Assessment of the physicochemical properties and drug-likeness of tea catechin derivatives

Description	Compound				
	EC	ECG	EGC	EGCG	Capmatinib
Molecular weight < 500 g/mol	290.271	442.376	306.27	458.375	412.428
Log P < 5	1.54	2.52	1.25	2.23	3.42
Hydrogen bond acceptors < 10	6	10	7	11	6
Hydrogen bond donors < 5	5	7	6	8	1
Rotatable Bonds ≤ 10	1	3	1	3	4
Surface Area Å²	119.662	179.948	124.456	184.742	176.164
Lipinski's Violation	No	1	1	2	No

Table 2. Data on absorption, distribution, metabolism, excretion, and toxicity (ADMET) of tea catechin

Description	Compound				
	EC	ECG	EGC	EGCG	Capmatinib
Huma intestinal absorption (HIA) (%)	68.829	62.096	54.128	47.395	95.104
Caco2 permeability (log pap)	-0.283	-1.264	-0.375	-1.521	1.344
P-gp substrate	Yes	Yes	Yes	Yes	Yes
VDss (L/kg)	10.64	4.61	20.00	6.40	0.39
Fraction unbound (Fu)	0.235	0.158	0.274	0.215	0.216
CYP3A4 inhibitor	No	No	No	Yes	Yes
Total clearance (log ml/min/kg)	0.183	-0.169	0.328	0.292	0.711
AMES toxicity	No	No	No	No	Yes
Max. tolerated dose (log ml/min/kg)	0.438	0.449	0.506	0.441	0.370
Hepatotoxicity	No	No	No	No	Yes
Oral Rat Acute Toxicity (LD50) (mol/kg)	2.5	2.55	2.49	2.52	2.6

results were filtered to include only the species "Homo sapiens" and the highest predicted probability. The list of target proteins was integrated with the list of proteins overexpressed in CRC to identify common targets. Interactions between target proteins were analyzed using the STITCH 5 database (Search Tool for Interactions of Chemicals and Proteins) at https://stitch-db.org/ [25]. The data was accessed in January 2026.

Biological Network Analysis

Protein interaction data were analyzed using Cytoscape software to construct, visualize, and analyze interaction networks. Network topology analysis was performed using the CytoHubba 0.1 plugin in Cytoscape 3.10.3 (https://cytoscape.org/) to obtain protein hubs [26].

Survival Analysis

Survival analysis of colorectal cancer patients expressing specific genes was performed using the GEPIA (http://gepia.cancer-pku.cn/) [27]. The data was accessed in January 2026.

Molecular Docking Analysis

Molecular docking was performed using compounds based on target predictions, namely epigallocatechin-3-gallate (EGCG) (CID: 65064), epicatechin-3-gallate (EGC) (CID: 107905), and capmatinib (control) (CID: 25145656) [28]. These compounds were then optimized using Avogadro 1.2 (https://avogadro.cc/) with the Merck Molecular Force Field 1994 (mmff94) to achieve the lowest score [29]. The structures were converted to the Pdbqt format using Open Babel 2.4.1. The c-Met kinase protein structure was downloaded from the Protein Data Bank (https://www.rcsb.org/) with ID 3RHK, which has a resolution of 1.94 Å—considered good quality as it is below 2 Å—and belongs to Homo sapiens [20]. The protein was prepared using AutoDockTools 1.5.7, in which water molecules were removed, polar hydrogens were added, and Kollman charges were assigned, and then saved in PDBQT format. Docking was performed with AutoDock Vina 1.2.3 at coordinates center_x = -8.266, center_y = 12.334, center_z = -1.420 and box size size_x = 28, size_y = 24, size_z = 26, based on the active site of the protein in ATP binding site attached by ARQ 197, while performing the redocking process of the crystal ligand in the protein structure [30,31]. Redocking and docking analyses were conducted using PyMOL 3.1 to evaluate the Root Mean

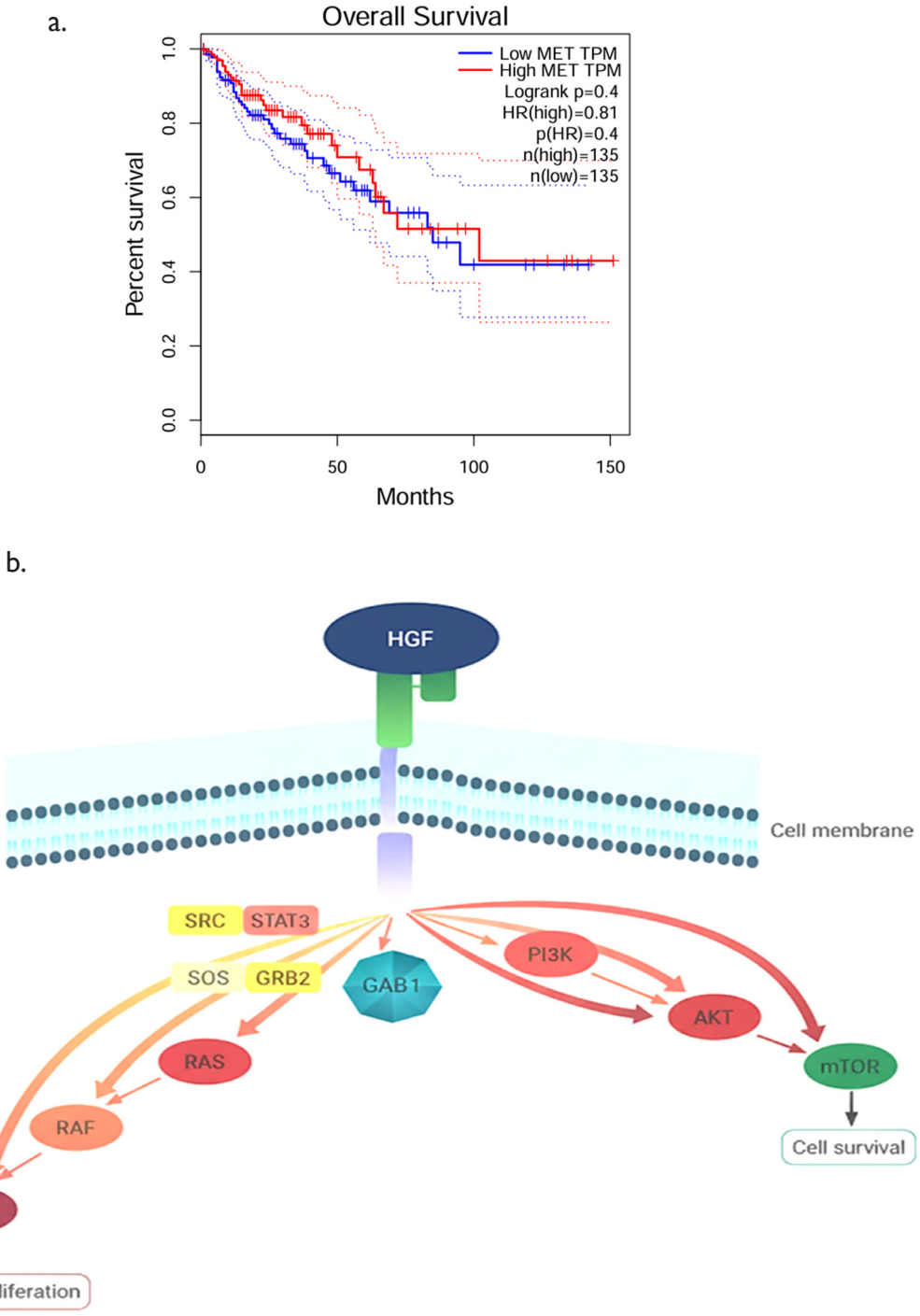


Figure 6. Protein interaction networks created using the STITCH server (a) and Cytoscape software (b).

Square Deviation (RMSD) [32], compound binding values, and interactions, and using Biovia Discovery Studio 2025. The inhibition constant (Ki) calculation was obtained from the binding energy (ΔG), as follows [32]:

$$Ki = \exp\left(\frac{\Delta G}{RT}\right)$$

Note:

$R = 1.985 \times 10^{-3}$ kcal mol^{-1} K^{-1}

T is the temperature (298.15 K)

Results

This study aims to conduct a computational analysis to evaluate the therapeutic potential of tea catechins as adjuvant agents to overcome chemoresistance in colorectal cancer (CRC) by targeting and suppressing key proteins. There are four primary catechins found in tea leaves: epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) (Figure 1a-d).

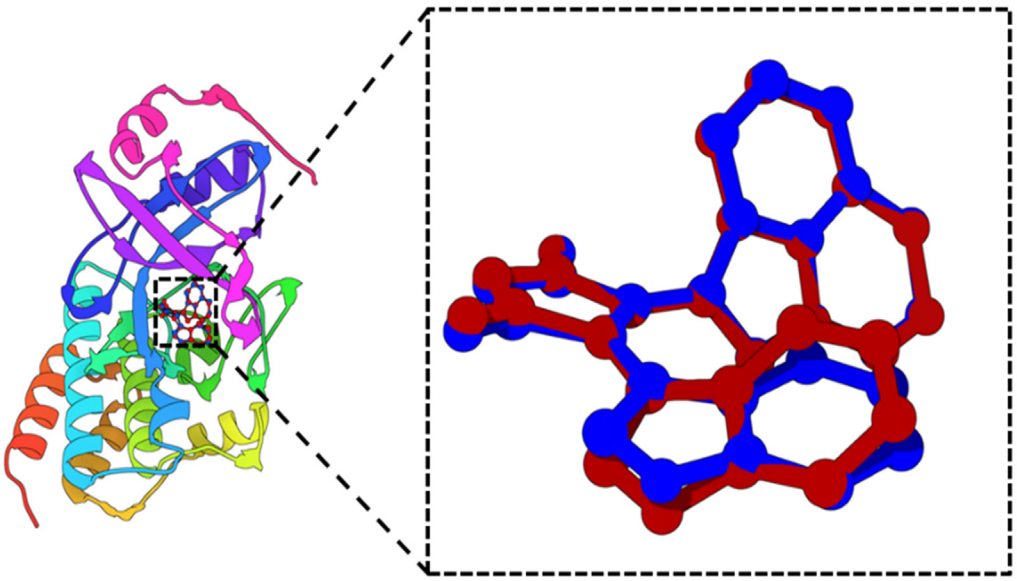


Figure 7. Visualization of the comparison results for re-docking the native ligand (ARQ 197) with protein c-Met. Note: red line (after) and blue line (before).

Physicochemical and ADMET analyses using pkCSM indicate that all evaluated catechins have potential as drug candidates [22]. However, some parameters deviate from Lipinski's Rules of Five (RO5), including molecular weight, Log P, hydrogen-bond acceptors, and hydrogen-bond donors (Table 1). ECG and EGC each have one violation, EGCG has two, and capmatinib has none. The violation from RO5 does not always determine the final result of the compound, but it is just an indicator [33]. In comparison, EC had no violations. ADMET analysis focused on several indicators (Table 2). The highest absorption was observed for capmatinib (95.10%) and EC (68.82%), and the lowest for EGCG (47.39%). This result shows that every compound has good absorption, greater than 30% [34].

Caco-2 permeability ranged from -1.521 to 1.344; this indicator correlates with HIA: the higher the value, the better the result [35]. The P-gp substrate results showed that all compounds are P-gp substrates, indicating that they are recognized by P-gp and actively effluxed from cells, thereby reducing intracellular absorption [45]. The steady-state distribution volume (VDss) ranged from 0.39 to 20.00 L/kg. EGC showed the highest value, whereas capmatinib had the lowest. VDss values greater than 2.8 L/kg indicate that a compound can effectively reach tissues, while values above 3.5 L/kg suggest an even greater capacity for tissue distribution [28].

Human unbound fraction (Fu) ranged from 0.158 to 0.274, a value lower than 0.7, indicating that a moderate proportion of the compounds remains unbound in plasma. These values suggest a considerable level of plasma protein binding while still allowing sufficient free drug to distribute into tissues [35]. CYP3A4 inhibitors identified include EGCG and capmatinib. When a compound acts as a CYP3A4 inhibitor, it can deactivate other CYP3A4 substrates. This mechanism is especially important because CYP3A4 is highly expressed in colon cancer, where it contributes to drug resistance during chemotherapy [36]. EGC had the highest value, and ECG the lowest, with a compound range of -0.169 to 0.328; however, capmatinib showed the highest value. Total clearance indicates how efficiently a drug is eliminated from systemic circulation through metabolic and excretory processes. Compounds with higher total clearance values are generally eliminated more quickly from the body, which may decrease systemic accumulation but can also shorten the duration of pharmacological activity [28].

The maximum tolerated dose (MTD) for all compounds ranges from 0.370 to 0.506; values below 0.477 are considered low, while the highest is EGC. The high MTD value indicates that the compound is better tolerated at higher doses [37]. All compounds tested showed "No" for Ames' toxicity (potential to cause mutagenicity in bacteria) and hepatotoxicity, except capmatinib. Lethal Dose (LD_{50}) values ranged from 2.49 to 2.6, suggesting that all compounds are low-toxicity [28,37].

Epicatechin-3-gallate (ECG) is predicted to target mainly proteins from the enzyme and kinase categories. Meanwhile, epigallocatechin-3-gallate (EGCG) is expected to target a wider range of proteins, mainly kinases, transferases, membrane receptors, and enzymes (Figure 2).

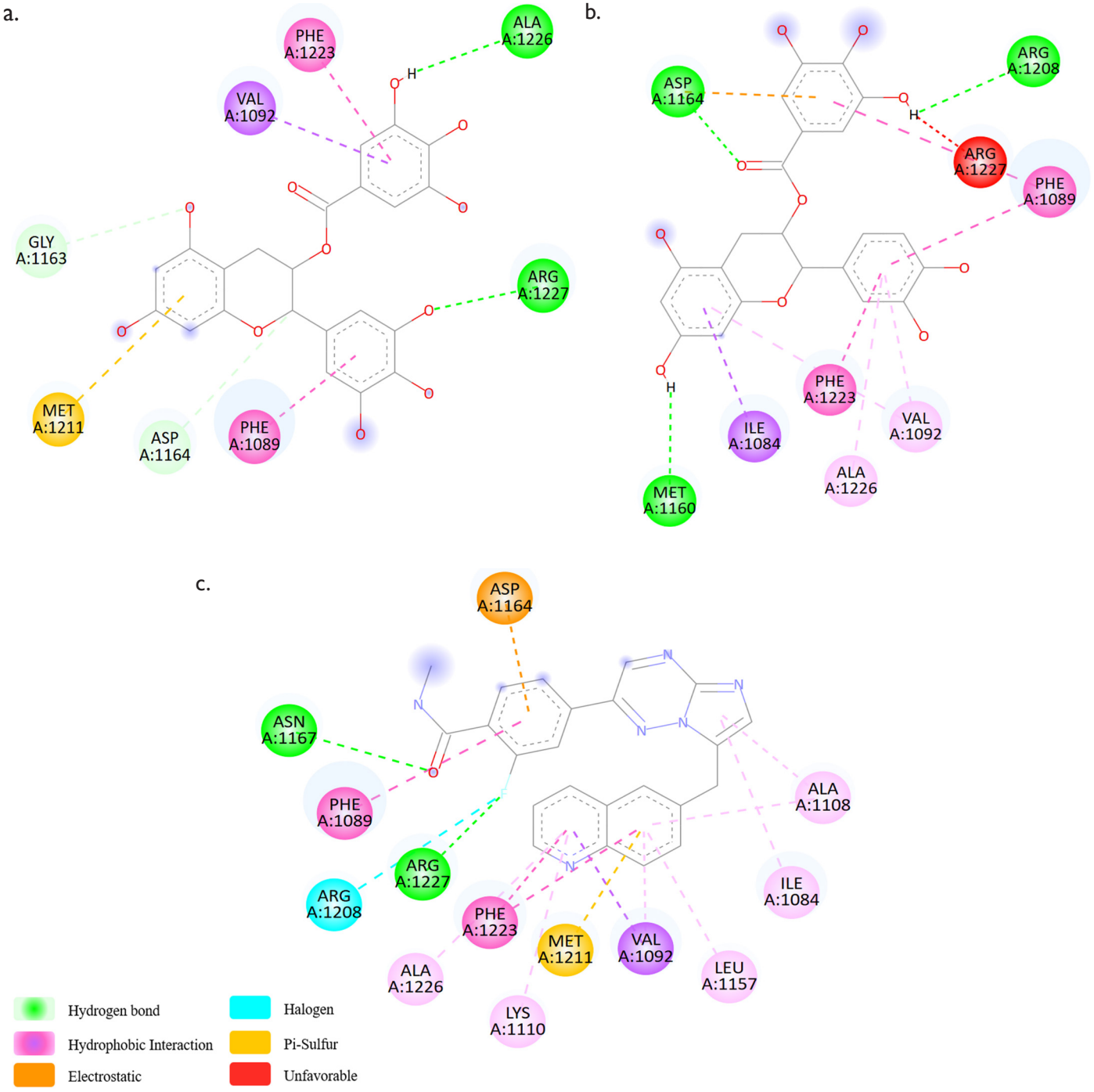


Figure 8. 2D visualization of the molecular docking results for (a) EGCG and (b) ECG with the c-Met protein. Red highlights indicate interactions within the protein's active site that are consistent with those of the native ligand.

Results show that 250 genes are overexpressed in CRC patients, and four common target proteins were identified: CA9, SERPINE1, MET, and SQLE (Figure 3). Protein-protein interaction (PPI) analysis further indicated that MET acts as a central hub within the interaction network. (Figure 4; Table 3).

Functional enrichment analysis reveals that the target proteins significantly contribute to chemoresistance, particularly against anti-angiogenic agents, which are crucial for colorectal cancer progression (Table 3; Figure 5). This result is further supported by survival analysis, which indicates that patients with MET protein overexpression have a poorer prognosis and significantly lower overall survival (Figure 6a). Additionally, the MET protein functions not just as an isolated target but as a central hub that integrates multiple signaling pathways essential for cancer cell survival (Figure 6b). For further analysis, the MET protein was docked with the compounds. The docking validation was performed by re-docking the ligand from the crystal structure (Figure 7), yielding a result of 0.285 Å, whereas valid re-docking results range from 0.0 to 2 Å [32].

Molecular docking results showed that capmatinib and EGCG have the highest binding energies, at -11.3 kcal/mol

Table 3. Network topology analysis using CytoHubba and functional annotation of target proteins

Rank	Gene Symbol	Protein Name	Biological Function
1	MET	MET proto-oncogene, receptor tyrosine kinase	A critical component of signalling pathways regulating cell proliferation, motility, invasion, and angiogenesis.
2	CA9	Carbonic anhydrase 9	An enzyme that catalyses the hydration of carbon dioxide; it maintains intracellular pH homeostasis under hypoxic environments.
2	SERPINE 1	Serpin family E member 1 (PAI-1)	The primary inhibitor of tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA); it plays a key role in fibrinolysis.
4	PGF	Placental Growth Factor	A member of the Vascular Endothelial Growth Factor (VEGF) family, it functions as a potent growth factor that stimulates neo-angiogenesis.
4	SLC49A4	Solute Carrier Family 49 Member 4	A solute carrier protein involved in the transmembrane transport of metabolites and nutrients.
6	MACC1	Metastasis-Associated in Colon Cancer 1	A transcription factor that acts as a key regulator of MET signalling.
6	SMIM22	Small Integral Membrane Protein 22	A small integral membrane protein.
6	SQLE	Squalene Epoxidase	A rate-limiting enzyme in the cholesterol biosynthesis pathway.

Table 4. Molecular docking analysis results

Protein	Ligand	Binding affinity (kcal/mol)	Inhibition Constant (μM)	Binding Interactions
c-Met	EGCG	-9.2	0.188	Hydrogen bonds: Pro1158, Met1160 Hydrophobic bonds: Ile1084, Phe1089, Val1092, Ala1108, Lys1110, Leu1157, Phe1223, Ala1226, Arg1227 Electrostatic bonds: Met1211
c-Met	ECG	-9.1	0.221	Hydrogen bonds: Met1160, Asp1164, Arg1208 Hydrophobic bonds: Ile1084, Phe1089, Val1092, Phe1223, Ala1226 Unfavourable bonds: Arg1227
c-Met	Capmatinib (control)	-11.3		Hydrogen: Asn1167, Arg1227 Hydrophobic: Ile1084, Phe1089, Val1092, Ala1108, Lys1110, Leu1157, Phe1223, Ala1226 Electrostatic: Aps1164 Pi-Sulphur: Met1211

and -9.2 kcal/mol, respectively, along with estimated inhibition constants of 0.0051 μM and 0.18 μM (Table 4). Meanwhile, epicatechin-3-gallate (ECG) exhibited a binding free energy of -9.1 kcal/mol and an estimated inhibition constant of 0.221 μM. These negative, thermodynamically favorable values indicate that the ligand-protein interactions occur spontaneously and are highly stable. Further analysis of the ligand-protein complexes revealed that the compounds interact with the active site of c-Met kinase via multiple intermolecular interactions. Important interactions include hydrogen bonding, hydrophobic interactions, and electrostatic interactions, although minor unfavorable interactions were also observed (Table 4; Figure 8). EGCG and EGC bind in the ATP-binding pocket, stabilized by AR 197, as demonstrated by the control capmatinib, with residues Phe1089, Met1211, Phe1223, and Arg1227 playing crucial roles in the protein [28,38]. This interaction profile strongly supports the hypothesis that ECG and EGCG can modulate MET's pleiotropic functions in CRC. Furthermore, these findings provide a molecular basis for the potential chemosensitizing effects of these compounds

on CRC cells during chemotherapy.

Discussion

The MET proto-oncogene encodes the receptor tyrosine kinase (MET), whose activity is regulated by its ligand, hepatocyte growth factor (HGF). Dysregulation or uncontrolled activation of MET in colorectal cancer (CRC) triggers downstream signalling cascades that involve vital pathways such as PI3K/Akt, MAPK, and STAT3 [17,20,39]. These pathways play a crucial role in driving oncogenic processes, including uncontrolled cell proliferation, migration, invasion, and chemoresistance (Figure 6b).

MET overexpression is a primary mechanism of CRC cell resistance to conventional chemotherapy, particularly to cytotoxic agents such as 5-fluorouracil (5-FU) and oxaliplatin [5,6,11,16]. Enhanced MET signalling tends to protect cancer cells from apoptosis, typically induced by cytotoxic drugs, often by promoting the epithelial-mesenchymal transition (EMT) or activating anti-apoptotic proteins [9,20,39]. Furthermore, MET activation—via either ligand-dependent induction by HGF or ligand-independent crosstalk with factors such as EGF and IGF-1—promotes the maintenance of cancer stemness, thereby driving aggressive oncogenic phenotypes and metastatic progression [19,40]. Consequently, suppressing MET signalling is a necessary strategy to overcome treatment failure and improve prognosis in patients with CRC.

Our in-silico results identify MET as a key hub in the CRC signaling network, supporting the development of MET-targeted compounds. Epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate (EGCG), the main bioactive components of tea (Camellia sinensis), show promise as MET-targeted therapies (Figure 4). Mechanistically, EGCG inhibits MET activation and downstream signaling. In vitro studies confirm EGCG's ability to block these pathways, reducing CRC cell proliferation, invasion, and metastasis. Moreover, EGCG's potential as a chemosensitizing adjuvant is particularly important; combining EGCG with first-line CRC chemotherapeutic agents, such as 5-fluorouracil (5-FU), has been shown to produce synergistic effects [5,6,11]. This combination markedly promotes apoptosis, increases cellular sensitivity to 5-FU, and inhibits cancer cell growth and colony formation by modulating apoptotic pathways and inducing cell-cycle arrest [10,17,20,39].

Although epicatechin-3-gallate and epigallocatechin-3-gallate show promising therapeutic potential, their clinical use faces major hurdles, particularly their low oral bioavailability and rapid breakdown in the gastrointestinal tract, especially at neutral or alkaline pH [11,41,42]. As a result, the therapeutic dose that reaches the MET target within tumor tissues remains insufficient. Future research should focus on creating new nanotechnology-based drug formulations. Preclinical strategies—such as encapsulating tea catechins in pH-responsive nanoparticles, liposomes, or lipid-polymer hybrids—have been demonstrated to improve the stability and bioavailability of these compounds [10,11,41,42].

While the current in silico analysis offers a solid initial framework for identifying epicatechin-3-gallate and epigallocatechin-3-gallate as potential therapeutic adjuvants against MET-mediated drug resistance, certain limitations must be recognized. Primarily, the molecular docking and binding affinity predictions presented here represent a static computational environment; the study lacks molecular dynamics simulation (MDS) data, which is crucial for assessing the structural stability, conformational flexibility, and time-dependent behavior of the protein-ligand complexes under simulated physiological conditions. As a result, although the current findings are enough to generate a prioritized list of candidate phytochemicals, they should be considered a foundational step. Future research will involve conducting high-nanosecond MDS to dynamically validate these interactions, followed by rigorous in vitro and in vivo experimental tests to confirm the biological effectiveness of these compounds in overcoming resistance in colorectal cancer cell lines.

Conclusion

Our in-silico findings identify epicatechin-3-gallate and epigallocatechin-3-gallate as promising colorectal cancer chemosensitizers targeting the c-Met (MET) receptor. Molecular docking simulations showed strong binding affinities (EGCG: -9.2 kcal/mol; ECG: -9.1 kcal/mol), providing a molecular basis for using tea catechins as multitarget inhibitors to block MET-mediated signaling and reduce chemoresistance in CRC.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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