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Unveiling the Anti-Colorectal Cancer Mechanisms of Libyan *Artemisia herba-alba* through Network Pharmacology, DFT, Molecular docking Approaches

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Artemisia herba-alba, colorectal cancer, bioactive compounds, network pharmacology, DFT analysis

A B S T R A C T

Colorectal cancer remains a leading cause of cancer-related mortality worldwide, and natural products have attracted interest as potential multi-target therapeutics. *Artemisia herba-alba*, a traditional medicinal plant in Libya, contains bioactive compounds such as quercetin, caffeic acid, chlorogenic acid, kaempferol, and luteolin, which may exert anticancer effects. This study aimed to investigate the potential mechanisms of these compounds against colorectal cancer using network pharmacology, protein–protein interaction analysis, GO and KEGG enrichment, and density functional theory (DFT) calculations. A total of 148 overlapping targets were identified, with core genes including STAT3, MAPK1, AKT1, EGFR, CDKN1A, CCND1, and TP53, which are involved in pathways regulating cell cycle, apoptosis, and tumor progression. Molecular docking results revealed that quercetin exhibited strong binding affinity with 6GUE (−8.9 kcal·mol^{-1}) through multiple hydrogen bonds and π-interactions, supporting its potential inhibitory role at the active site. DFT analysis of quercetin provided insights into its electronic properties and potential binding sites. Immunohistochemical data confirmed the overexpression of these targets in colorectal cancer tissues. Overall, the findings suggest that the bioactive compounds of *A. herba-alba* may exert multi-targeted anticancer effects by modulating key signaling pathways, highlighting their potential as therapeutic agents for colorectal cancer.

Introduction

Medicinal plants and their derivatives, including herbs, minerals, and natural extracts, have long been valued for their therapeutic, aromatic, and flavoring characteristics. In recent years, reliance on such preparations has grown worldwide, with many people turning to them for the management of different health disorders [1, 2]. These remedies are employed in the prevention and treatment of a broad spectrum of diseases such as cardiovascular problems, metabolic disorders, malignancies, and gastrointestinal inflammations [3, 4]. The global interest in traditional and complementary medicine has risen remarkably, reflecting a renewed appreciation of diverse cultural practices and knowledge systems related to healing and health maintenance. Among these approaches, plant-based therapies remain central, given their historical and ongoing role in combating various illnesses. Although modern medicine has achieved remarkable progress in diagnosis and therapy, traditional practices and home-based nonpharmacological remedies continue to be widely adopted across the globe. According to a 2018 World Health Organization (WHO) survey, the vast majority of its member states reported some level of integration or use of traditional, complementary, and alternative medicine. Interestingly, reliance on herbal treatments is growing in high-income countries such as the United States, while in many developing regions it remains a consistent and parallel approach to conventional healthcare, even within urban populations [5]. The COVID-19 pandemic further

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heightened interest in these practices, with an observable increase in the use of home remedies and herbal formulations. While plant-based therapies demonstrated certain benefits in alleviating COVID-19 symptoms, their use outside formal healthcare frameworks has also raised concerns regarding unregulated self-medication and the potential risks it carries. Throughout history, humans have depended on nature to meet essential needs such as food, shelter, clothing, transport, and medicine. Among these resources, medicinal plants hold a special place, as they continue to play a significant role in healthcare systems worldwide. Their importance is especially evident in regions where traditional healing practices are deeply rooted and access to modern medical infrastructure is limited. For generations, herbal preparations have been used to address a wide range of health conditions, and the preservation of this traditional knowledge remains critical for maintaining community health, particularly in rural and underserved areas. In recent years, there has been a growing global focus on exploring plants as sustainable sources for diverse applications, ranging from pharmaceuticals and nutraceuticals to cosmetics, functional foods, and wellness products. This rising interest is largely driven by the perception that plant-based alternatives may offer safer, more economical, and effective solutions compared to many conventional synthetic options [1]. According to the World Health Organization (WHO), more than 21,000 plant species are recognized as having potential medicinal value. Extensive research has further demonstrated that these plants contain a wide variety of bioactive constituents, which are directly linked to their therapeutic properties and biological activities [6]. *Artemisia herba-alba*, a perennial shrub from the Asteraceae family, is typically found across arid and semi-arid regions such as the deserts and grasslands of North Africa and the Middle East (Scheme 1). In traditional medicine, this species has been widely employed for the management of several ailments, including diabetes, hypertension, bronchitis, diarrhea, and neuralgic disorders. The genus *Artemisia* comprises a group of plants widely recognized for their diverse pharmacological properties [7]. Previous studies have highlighted their antimalarial, anticancer, antibacterial, antifungal, anti-inflammatory, antiseptic, antispasmodic, and antioxidant activities. From the broad range of species within this genus, *Artemisia vulgaris L.* and *Artemisia alba Turra* have been identified in the literature as particularly promising candidates due to their notable medicinal potential. Previous studies have reported that *Artemisia herba-alba* (AHE) possesses notable antioxidant and antitumor properties. In particular, ethanol extracts of the plant demonstrated significant cytotoxic and pro-apoptotic effects against human colon cancer cells, while aqueous extracts showed little or no activity [8]. These findings indicate that AHE may represent a valuable natural source of bioactive compounds with potential therapeutic relevance in colon cancer. Although several studies have highlighted the pharmacological potential of *Artemisia herba-alba*, most reports have focused on its general antioxidant and anticancer activities without providing a detailed mechanistic understanding, particularly in relation to colorectal cancer. Moreover, little attention has been given to Libyan *A. herba-alba*, despite its widespread traditional use in North Africa. To address this gap, the present study aims to explore the anti-colorectal cancer potential of *Libyan Artemisia herba-alba* by integrating network pharmacology and density functional theory (DFT) approaches. This combined strategy is expected to unravel the molecular targets, pathways, and structural features underlying the therapeutic potential of this plant, thereby offering new insights into its possible role in colorectal cancer treatment.

Materials and Methods

Data collection

The bioactive compounds of *Libyan Artemisia herba-alba* were systematically collected and screened for drug-likeness. Compounds that did not satisfy the established criteria, including Lipinski, Veber, and Pfizer rules, were excluded from further analysis to ensure the selection of promising candidates [9, 10]. The detailed list of compounds is presented in Table 1, while the overall research workflow is illustrated in Figure 1. A comprehensive set of databases and computational tools was utilized to gather information on the chemical properties, predicted targets, gene-disease associations, and biological pathways of the selected compounds. The resources employed included PubChem, SwissTargetPrediction, PharmMapper, OMIM, GEO, GeneCards, UniProt, STRING, DAVID, Venny 2.1, and KEGG Mapper. These platforms facilitated the identification of molecular targets, protein-protein interactions, and functional pathways, enabling an integrated analysis of the potential anti-colorectal cancer mechanisms of *A. herba-alba.*

Colorectal Cancer-Related Target Collection

To identify genes associated with colorectal cancer, the GDS4515 dataset from the GEO database (https://www.ncbi.nlm.nih.gov/geo/) was selected as the primary source for differential expression analysis [11]. Differentially expressed genes (DEGs) were identified using the GEO2R tool with a cutoff of $P < 0.05$ and $|logFC| > 1$. The results were subsequently visualized as volcano plots using TBtools. In parallel, colorectal cancer-related targets were independently retrieved from multiple databases, including OMIM (https://www.omim.org/), DisGeNET (https://www.disgenet.org/), and GeneCards (https://www.genecards.org/) by searching for the term "colorectal cancer." The DEGs obtained from GEO were then intersected with the gene sets from these databases to generate a consolidated list of colorectal cancer-associated target genes, which served as the foundation for subsequent network and functional analyses [12].

Identification of Shared Targets and Construction of Protein-Protein Interaction Network

Potential targets of the selected compounds against colorectal cancer were identified by determining the overlap between compound-associated genes and colorectal cancer-related genes. This was achieved by comparing the two gene sets using an online tool to detect shared biological categories. Genes present in both datasets were consid-

ered as putative targets for therapeutic intervention [13]. The compiled list of overlapping genes was then prepared for protein-protein interaction (PPI) analysis. Relevant information describing the relationships among the proteins encoded by these genes was extracted and formatted for input into online PPI databases and analysis tools. After processing through bioinformatics network software, the interaction relationships among the candidate targets were visualized, allowing for an intuitive interpretation of the potential molecular interactions underlying the anti-colorectal cancer effects of the compounds [14].

Functional Enrichment Analysis of GO and KEGG Pathways

To explore the biological roles and molecular mechanisms of the identified target genes in colorectal cancer, functional enrichment analyses were performed. Gene Ontology (GO) and KEGG pathway analyses were carried out using an online platform for gene functional classification. This approach allowed the determination of the most relevant biological processes, cellular components, and molecular functions associated with the candidate genes. The outcomes were visualized through user-friendly graphical representations, facilitating the identification of key pathways that may mediate the therapeutic effects of the investigated compounds against colorectal cancer [15].

Construction of Compound-Target-Pathway Interaction Network

An interaction network linking the studied compound, its associated target genes, and relevant molecular pathways was constructed using a web-based biological analysis platform [16-19]. By integrating the compound, candidate genes, and their related pathways, a comprehensive network was generated to illustrate the functional relationships among these components. Within this network, nodes represent individual biological entities—such as compounds, genes, or pathways—while edges denote potential functional interactions or associations within the context of colorectal cancer. This network model provides a visual framework to understand better the molecular mechanisms underlying the compound's therapeutic potential [14].

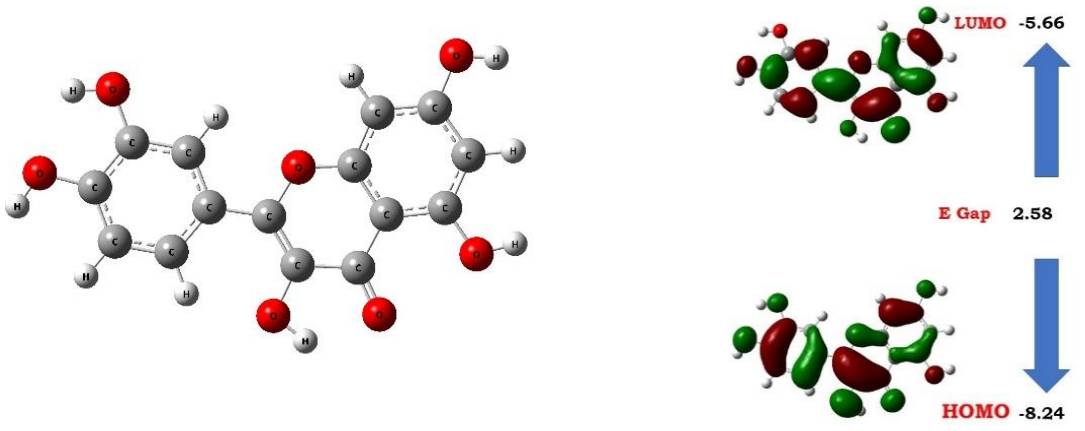
Density Functional Theory (DFT) Analysis

The geometry of quercetin from *Artemisia herba-alba* was optimized using the B3LYP/6-311G(d,p) method [17]. The stability of the optimized structure was confirmed, and the HOMO and LUMO orbitals were analyzed to evaluate electronic properties and chemical reactivity [18-21]. Quantum descriptors such as hardness, softness, and band gap were calculated to provide insights into the potential interactions of quercetin with biological targets [20-23].

RESULTS AND DISSCATION

DFT Analysis

The DFT analysis of quercetin from *Artemisia herba-alba* revealed a HOMO energy of -8.24 eV and a LUMO energy of -5.66 eV, resulting in a band gap of 2.58 eV, which indicates moderate chemical reactivity (Figure 1 and Table 1) [21]. The calculated hardness (1.29 eV) and softness (0.775 eV^{-1}) suggest that quercetin can interact effectively with biological targets, while the electronegativity (6.95 eV) and chemical potential (-6.95 eV) indicate a stable electronic distribution favorable for molecular interactions [22]. These quantum chemical descriptors imply that quercetin possesses sufficient stability and reactivity to act as a bioactive compound, potentially contributing to its anti-colorectal cancer activity. The localization of frontier molecular orbitals suggests possible sites for nucleophilic or electrophilic interactions, which may underlie its biological effects [23-25]. Overall, the DFT results support the potential of quercetin as a promising phytochemical for further experimental evaluation against colorectal cancer [25-29].



(**a**) (**b**)

Figure 1. (a) Optimized molecular structure of Quercetin obtained through DFT calculations.; (b) Frontier molecular orbitals (HOMO and LUMO) of quercetin derived from Artemisia herba-alba

Table 1. Quantum chemical parameters of Quercetin from Artemisia herba-alba calculated using DFT (B3LYP/6-311G(d,p))

Property	HOMO	LUMO	E Gap	η	S	x	μ
Value (eV)	-8.24	-5.66	2.58	1.29	0.775	6.95	-6.95

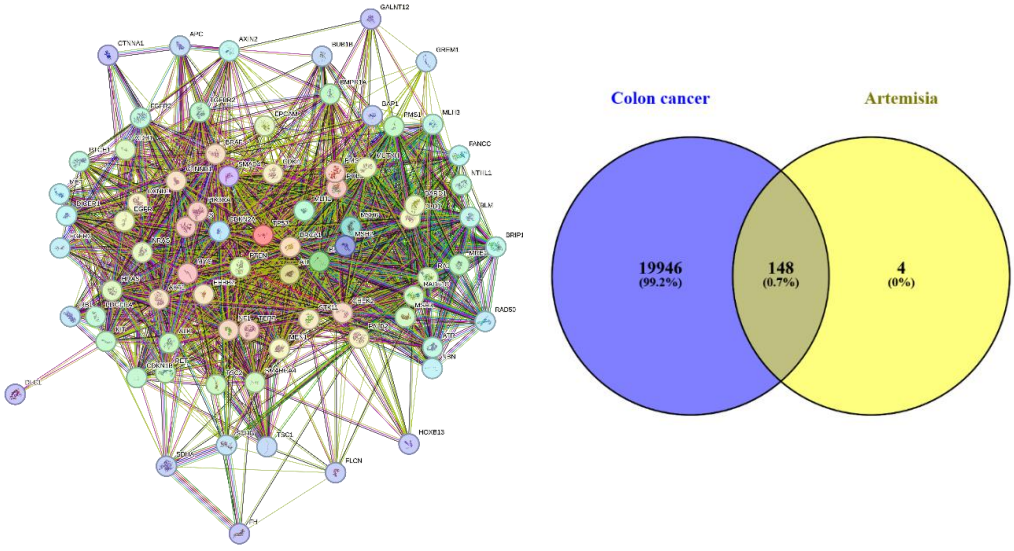
Targets of Quercetin and Colorectal Cancer

To explore the therapeutic potential of quercetin from *Artemisia herba-alba*, a total of 152 unique predictive molecular targets were identified for the compound. Analysis of the GDS4515 dataset revealed 19,946 differentially expressed genes associated with colorectal cancer (Figure 2a). Additionally, disease-related genes were collected from multiple databases, including OMIM, DisGeNET, and GeneCards, resulting in a comprehensive list of colorectal cancer-related targets. By intersecting the compound-associated targets with the disease-related gene set, a subset of 152 genes representing potential interactions between quercetin and colorectal cancer was generated and used for subsequent network and functional analyses.

Screening of Overlapping Targets and Protein–Protein Interaction Visualization

Analysis of the Venn diagram revealed 148 overlapping targets (approximately 0.7% of total disease-related genes) through the intersection of the predicted targets of quercetin, caffeic acid, chlorogenic acid, kaempferol, and luteolin with 19,946 colorectal cancer-associated genes (Figure 2B). These shared targets were considered as potential molecular mediators through which the selected compounds may exert therapeutic effects on colorectal cancer.

For protein–protein interaction (PPI) analysis, the overlapping genes were submitted to the STRING database, and the resulting network was visualized using Cytoscape (version 3.10.2). The constructed network included 148 nodes and the corresponding edges, representing interactions among the protein products of the shared genes. Node size and color intensity indicated degree centrality, highlighting the most connected and potentially crucial targets within the network (Figure 3).



(**a**) (**b**)

Figure 2. (a) Protein–protein interaction (PPI) network of overlapping targets constructed using the STRING; (b) Venn diagram illustrating the shared targets between active compounds from Artemisia herba-alba and colorectal cancer.

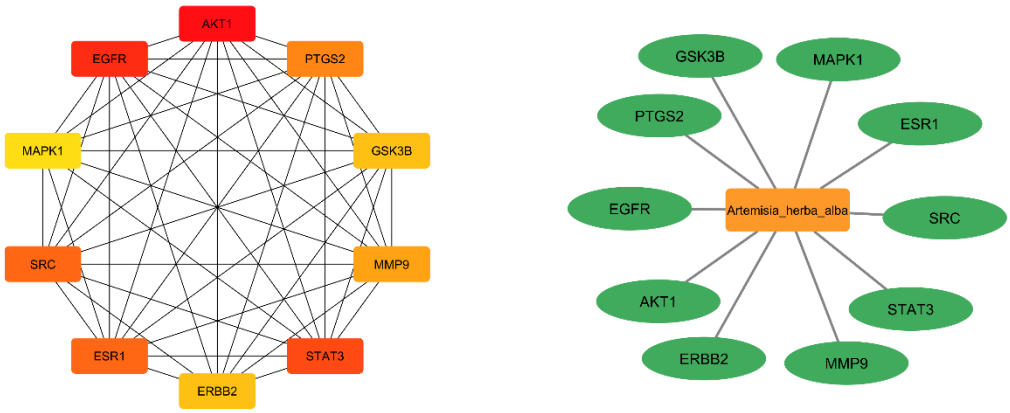
GO and KEGG Enrichment Analysis of Common Targets

The 148 overlapping targets of quercetin, caffeic acid, chlorogenic acid, kaempferol, and luteolin associated with colorectal cancer were subjected to GO and KEGG enrichment analysis using the DAVID platform. The GO analysis revealed enrichment across three domains: biological processes (BP), cellular components (CC), and molecular functions (MF). Key biological processes included cell cycle regulation, stress response, drug stimulus response, and metabolic process regulation. The associated cellular components were mainly exosomes, cytosol, and plasma membrane, while the primary molecular functions involved protein binding, metal ion binding, and enzymatic activities. KEGG pathway analysis highlighted significant enrichment of eight genes within the colorectal cancer-related pathway, including STAT3, ERBB2, MAPK1, MMP9, GSK3B, EGFR, AKT1, ESR1, SRC, and PTGS2, with a

highly significant P-value (<1.0 × 10^{-16}). These genes provide insights into the molecular mechanisms underlying colorectal cancer pathogenesis and suggest that the selected compounds may modulate key biological pathways. The protein–protein interaction (PPI) network constructed from the 148 overlapping targets consisted of 148 nodes and 1,256 edges, with an average node degree of 17, an average local clustering coefficient of 0.553, and an expected number of edges of 492, indicating a highly interconnected network (PPI enrichment p-value < 1.0 × 10^{-16}). This network analysis emphasizes the central role of several hub proteins, suggesting potential targets for therapeutic intervention (Figure 4).

Drug–Target–Pathway Network Construction

The significant KEGG pathways identified from enrichment analysis were imported into Cytoscape to construct a comprehensive drug–target–pathway network (Figure 4). In this study, the active compounds of Libyan Artemisia *herba-alb* were connected with their predicted protein targets and the related signalling pathways, while edges indicate potential interactions between nodes. From the intersection of compound-related targets and colorectal cancer-associated genes, 148 overlapping targets were identified. Key genes involved in colorectal cancer pathways—such as STAT3, MAPK1, AKT1, EGFR, CDKN1A, CCND1, and TP53—were highlighted for their central roles in regulating cell proliferation, apoptosis, and tumor progression. Color coding distinguished genes directly implicated in major signaling pathways, emphasizing their functional relevance in disease mechanisms. The network illustrates that the bioactive compounds of *A. herba-alba* may interact synergistically with multiple protein targets, influencing key colorectal cancer-related pathways. This drug–target–pathway network provides mechanistic insights into how the phytochemicals could modulate critical biomarkers, supporting their potential as therapeutic candidates for further experimental validation.



(**a**) (**b**)

Figure 3. PPI network and drug–target–pathway analysis. (a) Protein–protein interaction (PPI) network of overlapping targets related to active compounds from Artemisia herba-alba in colorectal cancer. (b) Drug–target–pathway network constructed in Cytoscape showing the interactions between compounds, target genes, and associated pathways.

Protein Expression Levels of Core Targets

The protein expression profiles of the key targets STAT3, ERBB2, MAPK1, MMP9, GSK3B, EGFR, AKT1, ESR1, SRC, and PTGS2 were evaluated using immunohistochemistry data from the Human Protein Atlas (HPA) (Table 2). The respective antibodies used for detection included CAB068242 (STAT3), CAB000043 (ERBB2), HPA005700 (MAPK1), CAB000348 (MMP9), CAB000341 (GSK3B), CAB080473 (EGFR), HPA002891 (AKT1), HPA000450 (ESR1), CAB004023 (SRC), and CAB080135 (PTGS2). Comparative analysis between normal colon tissues and colorectal cancer samples demonstrated a notable upregulation of protein expression in tumor tissues across all examined targets. For example, STAT3 expression increased in colon cancer tissue from a female patient (age 87) compared to normal tissue from a male (age 83), while similar patterns were observed for MAPK1, ERBB2, MMP9, and other targets. These observations are consistent with previously identified mRNA expression profiles and highlight the potential role of these proteins in colorectal cancer progression. Moreover, these findings support the notion that the bioactive compounds from Libyan *Artemisia herba-alba*, including quercetin, caffeic acid, chlorogenic acid, kaempferol, and luteolin, may modulate these key targets to exert therapeutic effects.

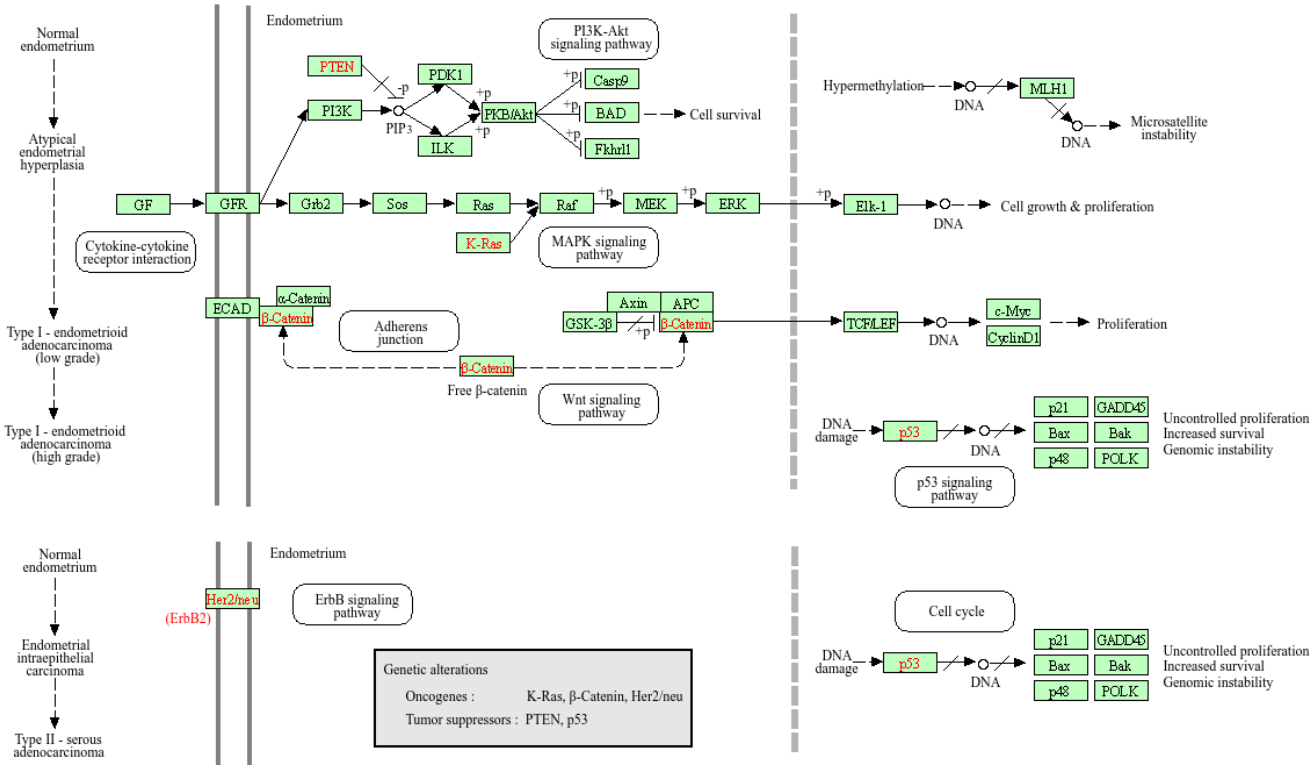


Figure 4. KEGG pathway enrichment analysis of common targets associated with colorectal cancer.

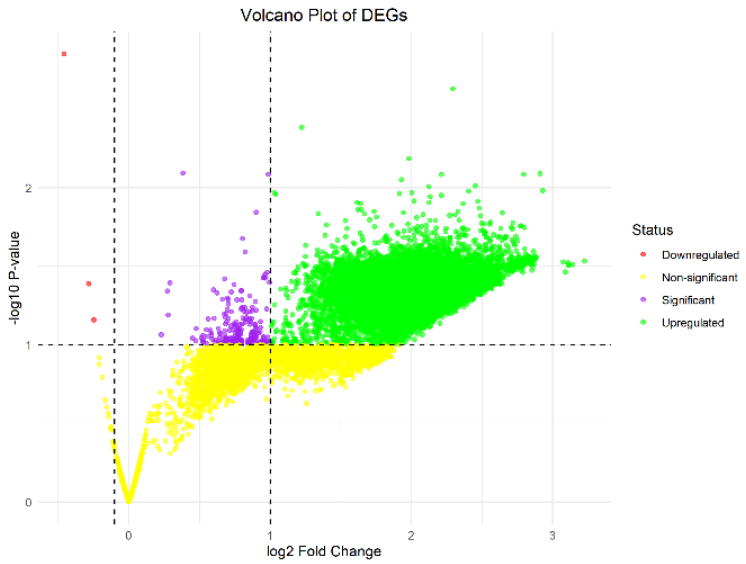
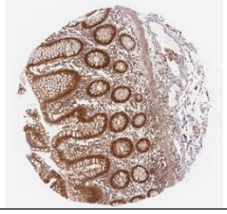
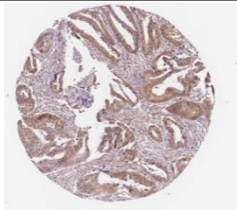
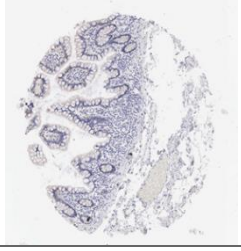
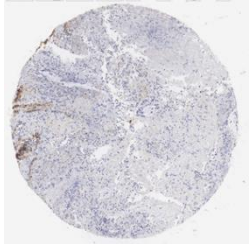
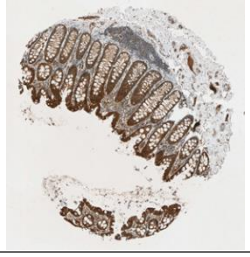
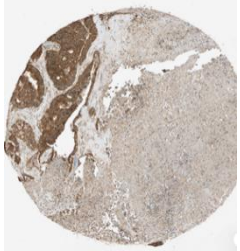
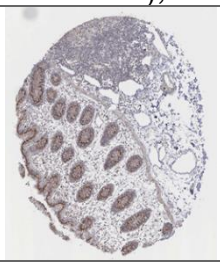
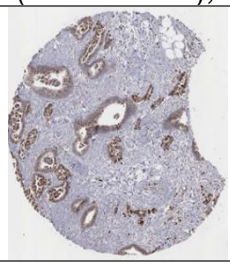
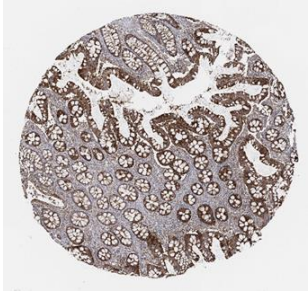
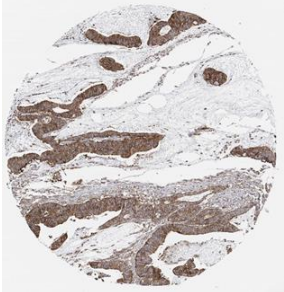
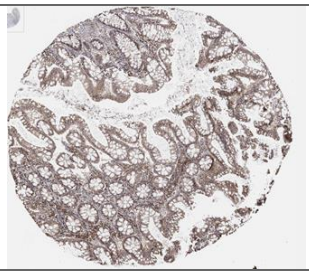
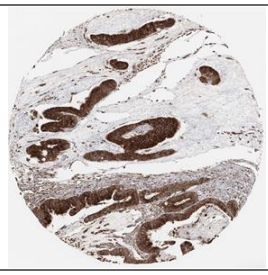
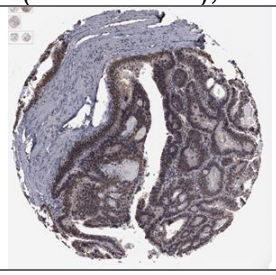
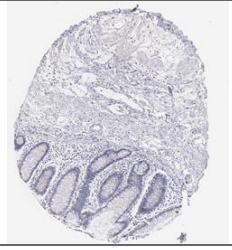
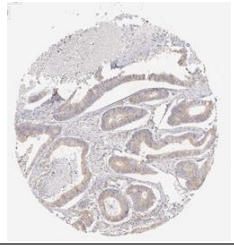
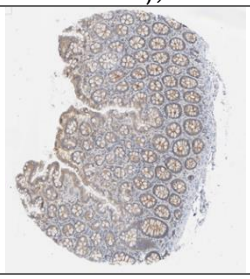
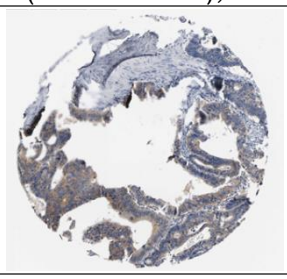
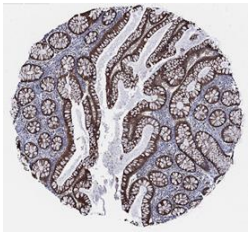
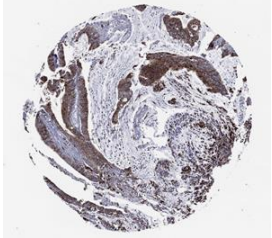


Figure 5. Targets potentially involved in the treatment of colorectal cancer by Artemisia herba-alba phytochemicals. Volcano plot displaying differentially expressed genes (DEGs) linked to colorectal cancer.

Table 2. Immunohistochemical profiles of key hub proteins in normal and colorectal cancer tissues, based on data retrieved from the Human Protein Atlas (HPA) database.

STAT3	
Normal (CAB068242); Male; Age: 83	Colon cancer (CAB068242); Female; Age: 87
	
ERBB2	
Normal (CAB000043); Male; Age: 54	Colon cancer (CAB000043); Female; Age: 65
	
MAPK1	
Normal (HPA005700); Female; Age: 61	Colon cancer (HPA005700); Male; Age: 55
	
MMP9	
Normal (CAB000348); Male; Age: 14	Colon cancer (CAB000348); Male; Age: 82
	
GSK3B	
Normal (CAB000341); Male; Age: 14	Colon cancer (CAB000341); Female; Age: 69
	
EGFR	
Normal (CAB080473); Female; Age: 65	Colon cancer (CAB080473); Female; Age: 69

	
AKT1	
Normal (HPA002891); Female; Age: 67	Colon cancer (HPA002891); Female; Age: 55
	
ESR1	
Normal (HPA000450); Female; Age: 55	Colon cancer (HPA000450); Male; Age: 65
	
SRC	
Normal (CAB004023); Female; Age: 61	Colon cancer (CAB004023); Female; Age: 55
	
PTGS2	
Normal (CAB080135); Female; Age: 65	Colon cancer (CAB080135); Female; Age: 69
	

Molecular docking analysis

Molecular docking of quercetin (C15H10O7) against the colorectal cancer-related target (PDB ID: 6GUE) revealed a highly favorable binding profile (Fig.6). The best-ranked pose exhibited a binding affinity of −8.9 kcal·mol^{-1} with an RMSD of 0.0 Å, indicating a stable and well-fitted conformation within the active pocket. Additional poses showed slightly lower affinities ranging from −8.4 to −7.4 kcal·mol^{-1}, though those with RMSD values exceeding 10 Å were excluded from further structural interpretation due to their instability and spatial deviation (Table 3).

The quercetin–6GUE complex was stabilized through multiple non-covalent interactions, including conventional hydrogen bonds, van der Waals contacts, π–π stacking, amide–π stacking, π–alkyl, and π–anion interactions. Key amino acid residues involved in the binding pocket included ASN B312, MET B334, THR B316, PRO A155, GLN B313, GLY A153, PHE B267, ARG A122, ALA A151, and ARG A150. Notably, π–cation and hydrogen bond interactions with ARG A122, THR B316, and PHE B267 were significant contributors to the ligand stability. These interactions suggest that quercetin's planar aromatic system and multiple hydroxyl groups enable both π and hydrogen-bonding networks, which may account for its high affinity and potential inhibitory effect [30-31].
Overall, the docking data support a strong and specific interaction between quercetin and the 6GUE protein, highlighting quercetin as a promising bioactive compound from *Artemisia herba-alba* with potential anti-colorectal cancer properties. Further validation using molecular dynamics simulations and binding free energy calculations (e.g., MM-GBSA) is recommended to confirm the stability and energetic favorability of the complex under physiological conditions.

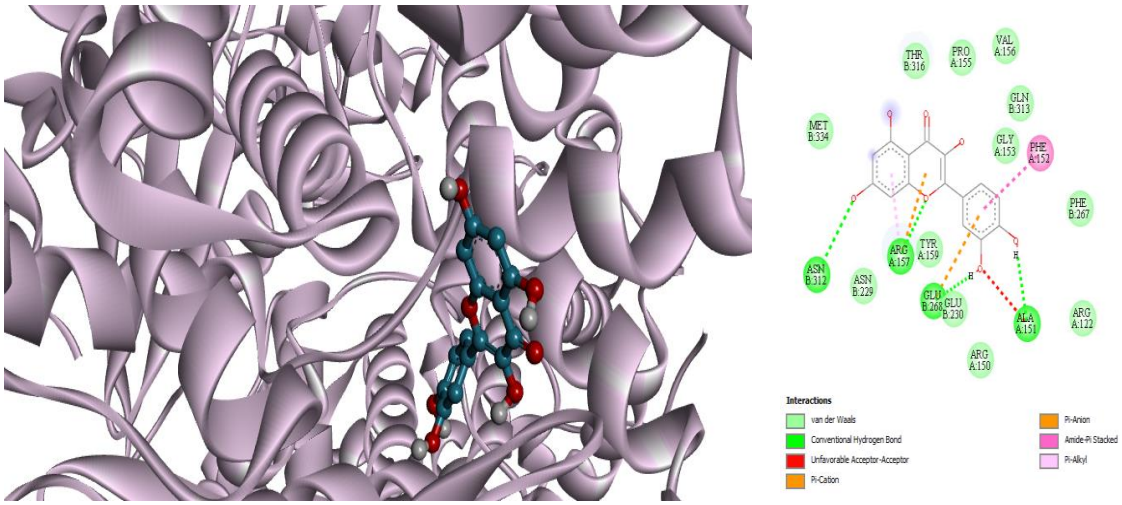


Figure 6. D2 and D3. 3D and 2D binding interactions of quercetin with 6GUE showing hydrogen bonds, π–π stacking, and hydrophobic contacts within the active site.

Table 1. Binding affinities and key interactions of quercetin with 6GUE obtained from molecular docking analysis.

rmsd/lb	rmsd/ub	Binding Affinity	Ligand
0	0	-8.9	6GUE_C15H10O7_uff_E=229.77
2.716	4.755	-8.4	6GUE_C15H10O7_uff_E=229.77
51.924	56.355	-8.3	6GUE_C15H10O7_uff_E=229.77
54.318	58.747	-8.3	6GUE_C15H10O7_uff_E=229.77
3.502	9.028	-7.9	6GUE_C15H10O7_uff_E=229.77
2.052	3.74	-7.5	6GUE_C15H10O7_uff_E=229.77
1.589	2.331	-7.4	6GUE_C15H10O7_uff_E=229.77
60.023	61.309	-7.4	6GUE_C15H10O7_uff_E=229.77
57.357	60.491	-7.4	6GUE_C15H10O7_uff_E=229.77

Conclusion

In this study, the therapeutic potential of Libyan *Artemisia herba-alba* and its main bioactive compounds—quercetin, caffeic acid, chlorogenic acid, kaempferol, and luteolin—against colorectal cancer was systematically investigated. Network pharmacology analysis identified 148 overlapping targets associated with colorectal cancer, highlighting key genes such as STAT3, MAPK1, AKT1, EGFR, CDKN1A, CCND1, and TP53 as central regulators in tumor-related pathways. Functional enrichment analyses revealed that these targets are involved in critical biological processes, including cell cycle regulation, apoptosis, and metabolic control, and participate in signaling pathways relevant to tumor progression. DFT calculations of quercetin provided insights into electronic properties, chemical reactivity, and potential interaction sites, supporting its capability to interact with protein targets. Fur-

thermore, immunohistochemical analysis confirmed the overexpression of core targets in colorectal cancer tissues compared to normal colon tissues, corroborating their role in disease progression and suggesting their potential modulation by the compounds. These findings suggest that quercetin exhibits a strong and specific interaction with 6GUE, supporting its potential as an effective anti-colorectal cancer agent derived from *Artemisia herba-alba*.

Overall, this integrative approach demonstrates that the bioactive compounds of *A. herba-alba* may exert multi-targeted anticancer effects, providing a mechanistic basis for their potential development as therapeutic agents for colorectal cancer. Future experimental validation is warranted to confirm these findings and explore their pharmacological applications.

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Conflicts of Interest

The authors declare no conflicts of interest.

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